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412 The evolving science of cancer: emerging approaches to prevention and early detection, & more

Guest: Siddhartha Mukherjee
Date: 2026-10-19 · Duration: 2:04:53
URL: https://www.youtube.com/watch?v=xKB5GTsaKKs

KEYPOINTS

• Fifteen years after The Emperor of All Maladies, the picture splits into prevention, early detection and treatment—with real progress in each, but big gaps in prevention.

Mukherjee says overall US cancer mortality is falling, so 'cancer is exploding' is nonsense. But colorectal cancer in young people is rising, breast cancer's mortality gains have plateaued, and esophageal cancer is climbing. Endometrial cancer's rise is most likely obesity; the colorectal trend is 'a complete mystery.' Trends lag exposures by roughly 5–10 years.

• The 'bad luck' model of cancer is early, not wrong: the 5% hereditary figure is too low, and random mutations need a second push to become tumours.

Attia recalls Vogelstein's 2015/2017 Science papers: roughly 5% of mutations hereditary, ~30% environmental, ~two-thirds random. Mukherjee argues single-gene counts miss much of hereditary breast cancer—known single genes cover only about a third to a quarter of it—with the rest from hundreds of small-effect variants. 'Bert is not wrong. He is just early.'

• Think of hereditary risk as 'shove' mutations versus 'nudge' mutations.

BRCA1/2 are shoves: they push you off the cliff at roughly 9–10× baseline risk of early breast cancer. Polygenic nudges each add a little, combining with environment until you tip over. Because the categories overlap, quantifying where someone sits could route them into prevention programmes or trials.

• Healthy tissue is full of dormant 'sleeper' cells carrying cancer mutations; inflammation can be what wakes them.

Biopsy every lung cell in two non-smokers and you'd likely find thousands of cells with cancer-hallmark mutations, citing work including Charlie Swanton's lab. The real difference between people may be a particular inflammatory response converting one sleeper into a tumour. Mukherjee stresses 'inflammation' is still a loose word, like 'energy' before Newton.

• Chronic 'insulinemic tone' sustains cancers and their resistance to therapy—shown for treatment, hypothesised for causation.

His Nature paper with Lou Cantley found in animals that insulin and its downstream cascade, not obesity itself, drove resistance to therapy. He chooses words carefully: extending this to cancer initiation is an extrapolation and a 'fussy' but doable experiment nobody has run. Attia cites Mitch Lazar's two-by-two showing cardiometabolic disease tracked hyperinsulinemia rather than adiposity.

• Osteoarthritis is not simply an obesity or wear-and-tear disease; it reflects inflammation suppressing cartilage stem cells.

Mukherjee's lab discovered the first osteoarthritic stem cells. Cartilage is constantly made and destroyed; disease appears when genesis falls while destruction holds or rises. Lean women get it in non-weight-bearing hands and necks. In young mice, injecting an immune activator such as LPS into a joint stops stem cells making cartilage and almost exactly mimics osteoarthritis. Why stem cells respond this way is unknown—'teleology is not biology.'

• Tumours carry many recognisable neoantigens, but dozens of 'don't eat me' checkpoint flags keep T cells away.

Attia cites Steve Rosenberg: ~80% of solid tumours have neoantigens. Mukherjee argues the ~100 point mutations don't explain this; Tyler Jacks' lab shows dysregulated gene decoding produces cryptic proteins as the real source. Normal cells display many 'I'm normal' flags, which is why we don't have devastating autoimmunity; cancers that survive evolve the same flags.

• CAR-T works in blood cancers because it kills an entire lineage we can live without—so solid-tumour CAR-T needs an expendable tissue target.

CD19 CAR-T kills all B cells, not just malignant ones; humans tolerate that. The same logic could apply to ovary, prostate, endometrium or even pancreas, but not brain. Ovarian cancer (really fallopian-tube in origin) has known antigens and several CAR-T attempts. Pancreas lacks good unique antigens, and most KRAS sits inside the cell, making it a small-molecule target instead.

• Pancreatic cancer survival depends heavily on anatomy, and new KRAS drugs may be most valuable after surgery.

Tail tumours are often found incidentally and are anatomically separate; head tumours sit in 'the traffic intersection of everything,' presenting with pain or jaundice. Mukherjee has patients alive 10 years after tail cancers. The KRAS inhibitor daraxonrasib extends life in metastatic disease despite skin side effects; adjuvant trials after a Whipple are 'in the works in 1,000 ways.'

• Preventing the big killers may not equal longevity; the next frontier is 'regenerative failure.'

Supercentenarians tend not to die of cancer but of skin, bone, blood and immune failure. Attia counters that atherosclerosis can be made nearly an 'orphan disease' with known drivers—no smoking, insulin sensitivity, very low apoB, treated blood pressure—but cancer can't be eliminated that way. Both agree on a parallel strategy: remove proximal diseases while systematically studying regeneration.

• Aging science lacks its 'cholesterol'—a validated biomarker—and finding one is a decades-long Manhattan Project.

Cardiology moved fast once blood pressure and cholesterol served as proxies. A longevity biomarker study could take 15–30 years prospectively, perhaps 15 with AI; Attia suggests mining metabolomes and proteomes of Interventions Testing Program winners. Echoing David Sabatini, they argue funding must anchor in basic science rather than rushing to drug discovery, and likely sits outside the NIH's illness-focused mandate.

EXAMPLES

• Oxford's croton-oil mouse experiment (1950s)

Painting a carcinogen (DMBA) on a mouse's back produced about four tumours; adding an inflammatory agent, croton oil,

produced about 80. Mukherjee uses it to argue for publishing unexplained observations, as Osler urged.

- **Allan Balmain's staples**
  Genetically cancer-prone mice developed a few tumours; a simple cut did little, but wherever wounds were stapled—triggering ongoing inflammation—massive cancers grew.
- **AI reading of CT scans flagged the thymus**
  A Harvard group scanned tens of thousands of CTs and found people retaining a thymus had fewer autoimmune diseases and cancers. Correlative only; the next step is thymus transplants in older animals, then finding thymic growth factors. Attia calls a growth-hormone/metformin/DHEA regeneration study 'kitchen sink,' and Mukherjee agrees random cocktails are a mess.
- **Vogelstein's 'three zeros' on tumour burden**
  Cutting a billion cancer cells to a million lowers the odds of a pre-existing resistant clone a thousandfold—why debulking plus adjuvant therapy usually works better.
- **Low-cost CAR-T in India**
  Mukherjee co-founded one of India's first CAR-T companies, selling therapy at about 1/20th the US price and treating roughly 150–200 patients. Some US CAR-T patients are 15 years out.
- **Dennis Burkitt's fibre observation**
  Burkitt found virtually no colorectal cancer in fibre-rich African populations who evacuated about twice a day, versus once every 2–3 days in the US.
- **Manifold and the napkin trial**
  Manifold trains AI on medicinal chemists' rules to design 'keys' for wriggling protein 'locks.' Separately, a sushi-dinner napkin sketch with Cantley became Faeth Therapeutics, whose early metabolism-targeting trials in endometrial and breast cancer look promising.

OTHER RELEVANT

- **Mukherjee's colorectal advice**
  Double or triple fibre, cut exposure to 'forever chemicals,' and—by his own admission on no evidence—eat cheap live yogurt at least weekly. Attia argues screening should start at 40 for average-risk adults, earlier with hereditary drivers; guidelines moved from 50 to 45.
- **Use blood-based early-detection tests selectively**
  Applied to the general population they likely bring false positives and extra biopsies without lowering mortality; in high-risk people, such as gene carriers or survivors, they may be valuable.
- **A trial worth funding: GLP-1s as cancer adjuvants**
  Both endorse randomising patients with endometrial, ovarian or breast cancer to standard care with or without a GLP-1, tracking insulin versus weight effects. They prefer this over observational studies because of confounding.
- **Be sceptical of peptide 'hacks'**
  With 20 amino acids per position, the odds of finding the right peptide at the right dose randomly are effectively zero. Regenerative failure needs systematic science, not shortcuts.
- **Mukherjee's writing process**
  Spend 'dream time' on narrator, place, mood, reader, structure before writing; then write fast and edit slowly. He is now writing a book on death and longevity.

410 The biology of pregnancy: physiologic adaptation, childbirth, and long-term maternal health

Guest: Dr. Kathryn (Katie) Gray
Date: 2026-10-05 · Duration: 2:01:48
URL: https://www.youtube.com/watch?v=KIFD0Y6UVE0

KEYPOINTS

• Pregnancy is a combined cardiovascular and metabolic stress test that can unmask a woman's future disease risk.
Dr. Katie Gray, a high-risk obstetrician and maternal-fetal medicine specialist at the University of Washington, frames pregnancy as an abrupt load on the heart (plasma volume expands dramatically) and on metabolism (insulin resistance rises in the second half). Women who 'fail' these tests often carry an underlying predisposition that pregnancy simply reveals early, which is why obstetric history matters for decades afterwards.

• Plasma volume rises about 50% by roughly 28 weeks, creating a relative anemia and a load some hearts can't tolerate.
Red cell mass doesn't keep pace, so hemoglobin concentration falls. Women with severe cardiac or pulmonary disease may be advised not to become pregnant at all, because standard heart-failure tools like diuretics would themselves endanger the pregnancy. Gray notes that around half of pregnancies are unplanned and the sickest patients often lack insurance and access, so disease can stay hidden until pregnancy exposes it.

• Severe pregnancy nausea appears to be driven by the GDF-15 gene, not hCG as long assumed.
Genetic studies of hyperemesis gravidarum flagged GDF-15, which is now being explored as a drug target. Fewer than 1% of pregnancies need IV fluids or nutrition, but for those women it's severe and tends to recur in later pregnancies. The main risk is maternal dehydration and malnutrition, since the fetus generally takes what it needs. Standard anti-nausea drugs can be used but often aren't enough.

• Folic acid matters before conception, because the neural tube closes before most women know they're pregnant.
Folate deficiency raises the risk of neural tube defects, and by the time a pregnancy is recognized it's too late to correct levels. Gray's referral center still sees neural tube defects monthly and saw two cases of anencephaly this year. A balanced diet plus fortified foods covers many women, but a prenatal vitamin before conception is the standard advice. Selected cases of spina bifida can now be repaired in utero, which can improve walking and bowel and bladder function.

• Gestational diabetes is an adaptive insulin resistance that overshoots, and screening is universal because risk factors missed half of cases.
Gray agrees with Attia's framing: every pregnancy shifts toward insulin resistance to route fuel to the fetus, and genes plus environment (sleep, stress, nutrition) amplify it in some women. High maternal glucose makes the fetus overgrow (macrosomia), raising the risk of C-section, shoulder dystocia, preeclampsia and newborn hypoglycemia, since the baby's own insulin keeps running after birth. Diagnosing it earlier than 24–28 weeks hasn't been shown to improve outcomes.

• Preeclampsia comes from a placenta that hasn't invaded deeply enough releasing sFlt-1, which mops up VEGF.
Normally trophoblast cells remodel the mother's spiral arteries into wide, low-pressure vessels. If that falls short, the oxygen-starved placenta releases sFlt-1, an anti-angiogenic factor that soaks up VEGF and damages endothelium in both blood vessels and kidney glomeruli. That links the hypertension and the protein in the urine. It affects about 5–7% of US pregnancies; first pregnancies and very young or older mothers are at highest risk. Untreated, it historically progressed to seizures, stroke, organ failure and death.

• Delivery is the only cure for preeclampsia, so management balances maternal risk against fetal maturity.
Blood-pressure drugs (mainly nifedipine and labetalol, chosen for safety data; ACE inhibitors and ARBs are known to harm the fetus but are used after delivery) can buy weeks. The timing of delivery depends on how severe the disease is, liver enzymes, platelets and fetal testing, not on the protein in the urine. At 37 weeks or later even mild hypertension means delivery. HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) isn't managed expectantly: give betamethasone for the baby's lungs, wait about 48 hours, deliver.

• Pregnancy complications forecast lifelong risk: about 50% of women with gestational diabetes later develop type 2 diabetes.
Preeclampsia raises later cardiovascular and kidney risk, and its strongest genetic overlap is with essential hypertension; the top hits in the first maternal genome-wide study of preeclampsia matched known blood-pressure genes. Postpartum hypertension can take 6–12 weeks to settle, may persist, or may return within 5–10 years. The pregnancy exposure itself may add risk on top of genetics, which is still being researched.

• US C-section rates have roughly tripled, and multiple C-sections raise the risk of a placenta that grows into the uterus.
Rates went from around 10% to about 30% at academic centers. Drivers include higher-risk pregnancies, repeat C-sections, maternal obesity and larger babies, and continuous fetal monitoring. Placenta accreta spectrum, where the placenta invades and won't detach, rises with each prior C-section. A low transverse incision carries under 1% rupture risk in a later labor; a vertical 'classical' incision, often needed for very premature deliveries, carries about 10%, so those women shouldn't labor.

EXAMPLES

• The sFlt-1 discovery came from a nephrologist collecting placentas.
Dr. Ananth Karumanchi at Beth Israel in Boston ran gene-expression microarrays on placentas from preeclamptic pregnancies and found sFlt-1 massively upregulated, then showed it could drive the disease. Gray, his former mentee, and Attia use it as a case for physician-scientists, and Attia links it to Judah Folkman's anti-VEGF cancer work.

• The old Down syndrome screen had a 5% positive predictive value.
Serum protein screens flagged many women, but only 1 in 20 positives actually carried a fetus with trisomy 21, which pushed many into amniocentesis. Cell-free DNA from a maternal blood draw at 9–10 weeks is far more sensitive and specific for

trisomies 21 and 18 and fetal sex, so invasive procedures have dropped.

- **Stillbirth occurs in about 1 in 160 US pregnancies.**
  Attia was startled. Stillbirth means any fetal death after 20 weeks. Even with placental pathology, autopsy and genetics, roughly half stay unexplained. A cord around the neck shows up in about a third of normal births and usually causes no harm.
- **About 20% of planned vaginal deliveries convert to C-section.**
  Gray uses this to explain why she recommends hospitals or birthing centers over home births: hemorrhage and other emergencies can arise in seconds, far from surgical backup.

OTHER RELEVANT

- **Tell every future doctor about your pregnancy complications.**
  Gestational diabetes or hypertension in pregnancy should trigger regular glucose and blood-pressure screening for life, plus serious lifestyle work. A 2-hour glucose test at the six-week postpartum visit is recommended. Primary care often never asks, so bring it up yourself.
- **Gestational diabetes treatment: diet first, then insulin quickly.**
  Targets Gray cited are fasting under 95 and 1-hour post-meal under 140 mg/dL. If more than half of readings are above target, insulin is first-line because its safety data and newborn outcomes are best; metformin is considered fairly safe but less proven. Lifestyle gets days to a couple of weeks, not months.
- **Keep exercising during pregnancy if it's going well.**
  Bed rest is bad. Don't start an intense new program, but established runners and lifters can usually continue, avoiding fall and abdominal-trauma risks like downhill skiing or riding. Women with a short cervix or threatened preterm labor may get lifting limits. Late in pregnancy, avoid lying completely flat; waking on your back isn't an emergency.
- **Don't treat breastfeeding as birth control or C-section as a microbiome failure.**
  Missing one feed can end the suppression of ovulation. Gray thinks the gut-microbiome benefits of vaginal birth are overhyped and says it shouldn't be a source of guilt.

409 Inside modern drug development: the science, economics, and regulatory hurdles

Guest: Lloyd Klickstein
Date: 2026-09-28 · Duration: 2:35:05
URL: https://www.youtube.com/watch?v=GoNjdK-I0Bc

KEYPOINTS

• Real innovation starts from unmet medical need, not from a 'seventh statin'.
Klickstein, who spent about 20 years at the Novartis Institutes for BioMedical Research, describes starting with patients and indications: his team listed roughly 7,000 clinical indications that were unmet. Incremental drugs are commercially attractive and low risk, so the industry is biased toward them; first-in-class drugs for conditions that may not even have diagnostic codes require educating doctors, patients, payers and regulators from scratch.

• Drug-development risk compounds multiplicatively, so killing failures early is the core skill.
A new target in a new indication carries perhaps 20 separate risks (target, format, bioavailability, toxicity and so on). Even if each has a 90% chance of going right, multiplying them out leaves very little. Klickstein says he has personally killed programs and has never seen one that couldn't be stopped for some reason; big companies run two to four formal checkpoints, small companies run more frequent, faster ones tied to fundraising.

• Patent economics shape which drugs get made.
A patent runs 20 years from filing, but practically a drug gets 10–15 years of exclusivity after launch to recover costs Peter compares to building the Burj Khalifa—thousands of people, many years, more than a billion dollars. Companies extend life by layering patents on process steps, doses and routes. The old '10 years and $1 billion' estimate is now considered low; Klickstein cites the Tufts center's much higher figures.

• Falls were the target Klickstein most wanted, but they proved unmeasurable.
He frames falls as having roughly 11 causes; healthy people stumble constantly but catch themselves with reactive foot speed. In a study with geriatrician Lou Lipsitz in frail residents aged 80 to over 100, a wearable detected only about 17% of real falls (of 117 events found), and older people under-report falls for fear of losing independence. Without a measurable endpoint, the falls program was stopped.

• Bimagrumab blocks activin type II receptors to unlock muscle growth.
The rationale came from myostatin-deficient 'double-muscled' animals (mice, cattle, dogs). Rather than chase myostatin alone, the Novartis team led by Chris Lu and David Glass built an antibody (code BYM338) against the activin type II receptor, preferring IIB but also hitting IIA, blocking signaling from several ligands. Follistatin, the gray-market favorite, would cost on the order of a million dollars a month at effective doses and has a short half-life.

• Modern antibodies are made human from the start, which complicates animal work.
Klickstein says for 15–20 years antibodies have not been made in mice; they come from human libraries. Bimagrumab turned out to be immunogenic in mice (not rats), so the team 'murinized' it (CDD866) for mouse studies. Mice showed roughly 30% muscle-mass increases and were stronger and faster; humans get about 4–8%.

• First-in-human design is governed by a 'lightning strike' safety threshold.
Klickstein's framework: if the risk of a serious adverse event exceeds roughly 1 in 100,000—about the annual U.S. lightning-strike risk—you should not use healthy volunteers but patients who might benefit. Serious harm to healthy volunteers happens about once a decade industry-wide; the TGN1412-type CD28 antibody disaster, which caused a cytokine storm at a tiny dose, is why trials now dose sentinel participants first.

• Phase 1 doses go as high as safely possible, but never above animal exposures.
Bimagrumab went up to roughly 50–100 mg/kg in early testing to learn what overdose would look like, then multiple monthly doses to see pharmacodynamic effects (muscle by MRI/DEXA, blood muscle proteins like CK). Japan and China require ethnic-sensitivity phase 1 data; China's notification-based process is making it increasingly popular for early trials.

• More muscle did not reliably mean better function.
Novartis ran around 16 phase 2 studies. The drug reliably increased muscle size, but older adults' 4–8% gain yielded only about a 9-meter improvement in six-minute walk—neither Peter nor Klickstein thinks that prevents falls. In rodents, function improved because mass rose 20–30%.

• The surprise was fat loss and improved glucose control.
A 48-week study in type 2 diabetics at 10 mg/kg monthly for 12 doses produced substantial fat loss and HbA1c reductions of about 7–8% (relative), with only standardized dietary advice. That pivoted the program toward obesity.

• A new cancer-prevention idea: find what drugs that cause cancer are inhibiting.
If a drug causes cancer, it probably inhibits a protective pathway. Sorafenib, a multikinase inhibitor for kidney and liver cancer, causes skin cancers in about 10% of older patients. Klickstein's company is developing a compound to activate that pathway, testable in people 50+ with prior skin cancer, who have about a 50% chance of another within a year—so 100–120 people could show prevention in phase 2.

EXAMPLES

• Versanis and investor skepticism
Bimagrumab spun out of Novartis in 2021 into Versanis, with Klickstein as founding CEO. Pitched for sarcopenia, almost no investors were interested; after Novo's semaglutide obesity data, the company repositioned around adding muscle-sparing fat loss on top of GLP-1s. The drug is named for Bhima, a mythological figure 'as strong as 10,000 elephants'; development continues at Eli Lilly.

• The BELIEVE trial
Originally a 24-week sarcopenic-obesity study, it became a roughly 500-person, nine-arm trial (low/high bimagrumab IV, low/high open-label semaglutide, combinations, placebo), 72 weeks of treatment with a 48-week primary endpoint, for around $70

million. High-dose combination lost 22–23% of body weight, but about 45.7% of body fat, with lean mass better preserved; published in Nature Medicine.

- **Protein study**
  In a bimagrumab trial at three protein-calorie intakes, people at half the recommended intake lost muscle, but the drug prevented that loss. Peter notes twice the RDA is only 1.2 g/kg and suspects 1.6–2 g/kg would have shown more hypertrophy.
- **Peter's student guinea-pig days**
  Peter recalls joining paid trials as a student—any study paying $1,000 he'd do—illustrating that 'healthy volunteers' are often economically motivated, one reason protection rules matter.
- **Gray-market peptides**
  Both are skeptical of gray-market peptides; Klickstein contrasts them with GMP manufacturing required for an IND, though Peter puts BPC-157 'on the podium' of interesting compounds despite wellness-industry grift.

OTHER RELEVANT

- **Judge muscle drugs by function, not scans.**
  Mass gains of 4–8% may not translate to walking speed or fall prevention; grip strength was chosen in BELIEVE because it best links to clinical outcomes.
- **GLP-1 users should think about lean mass.**
  The combination data suggest muscle-preserving agents may matter; meanwhile adequate protein and resistance training remain the tools available today. Klickstein envisions combination injectables to move people out of obesity, then oral maintenance therapy.
- **Watch LDL on activin-pathway drugs.**
  Klickstein acknowledges unfavorable LDL effects but argues they can be monitored and treated with existing drugs.
- **Be cautious on mTORC1 'geroprotection'.**
  He expects modest effect sizes in humans, says rapalogs lose selectivity with sustained exposure (mTORC2 suppression), and calls for a truly mTORC1-selective inhibitor before conclusions.

407 Preventing cardiovascular and Alzheimer’s disease: lowering LDL early, APOE4, and more

Guest: Michael Davidson
Date: 2026-09-14 · Duration: 2:19:15
URL: https://www.youtube.com/watch?v=EuPcbF9YVTo

KEYPOINTS

• Atherosclerosis is driven by cumulative LDL exposure—the '8 gram rule'.
Davidson, a lipidologist whose father died of a heart attack at 47, frames risk as lifetime cholesterol burden: roughly 200 mg/dL for 40 years, 100 mg/dL for 80 years, or 80 mg/dL for 100 years all add up to the same exposure that produces heart disease. Plaque forms relatively rapidly in the 20s–40s, so that decade is when the most effective treatment matters.

• Prevention should target causal drivers, not 10-year risk scores.
Peter credits Allan Sniderman with reframing the argument: instead of treating 5-, 10- or 15-year risk, treat the causes of disease. A 30-year-old's 10-year risk is low by any calculator, but Davidson says the goal is preventing heart disease at 80 or 90. He notes extra care around pregnancy for women.

• HDL-raising was a seductive hypothesis that failed repeatedly.
Observational data suggested every 1% rise in HDL cut risk about 3%, so CETP inhibitors—which raise HDL 50–75%—looked like a cure. Pfizer's torcetrapib failed (~2006) with off-target harms; Roche's dalcetrapib raised HDL ~30–40% with no LDL effect and no MACE benefit; Lilly's evacetrapib was stopped for futility after about two years despite ~75% HDL increases. Niacin on top of statins (HPS2-THRIVE) also failed.

• Merck's REVEAL proved the benefit tracks LDL, not HDL.
In about 30,000 patients, anacetrapib lowered LDL-C ~17% (~11 mg/dL absolute), and the modest event reduction matched what LDL lowering predicts: about 22% relative risk reduction per 1 mmol/L (38.7 mg/dL). Mendelian randomization similarly says HDL-C is not causal; some high-HDL genes such as SR-B1 variants raise risk.

• Obicetrapib is a far more potent, low-dose CETP inhibitor.
Earlier CETP inhibitors were dosed at 100 mg-plus; obicetrapib at 5–10 mg lowered LDL 40–50% and raised HDL ~150% in the short TULIP study (8–12 weeks). NewAmsterdam, which raised $200 million in its Series A in early 2021, ran phase 3 and the PREVAIL outcomes trial in parallel.

• The phase 3 program shows consistent additional LDL lowering.
ROSE and ROSE2: ~45–50% as monotherapy, ~55% with ezetimibe. BROOKLYN in familial hypercholesterolemia: about 40% further reduction, roughly 100 to 60 mg/dL at 12 months. BROADWAY in ASCVD patients on maximal statins (70% high-intensity): ~35% at 12 weeks, sustained to 52. TANDEM with ezetimibe: ~50%. PREVAIL, at 400+ sites globally, would support approval for secondary prevention.

• ApoB and LDL-P may move less than LDL-C on CETP inhibition.
Davidson acknowledges discordance among LDL-C, LDL particle number and apoB with CETP inhibitors—relevant for clinicians tracking apoB. Obicetrapib also lowers Lp(a), similar to PCSK9 inhibitors' 15–20%, though the reason is unclear.

• APOE4 is a lipid gene, and HDL is the lipoprotein that touches the brain.
About 20–25% of people carry one E4 and ~2–3% are homozygous, with roughly 10x Alzheimer's risk. Davidson's model: E4 impairs astrocyte cholesterol clearance; excess cholesterol leaves only as 24- or 27-hydroxycholesterol, becomes toxic and inflammatory, and amyloid and tau follow. HDL may deliver antioxidants and remove cholesterol and amyloid. He argues statins don't cause Alzheimer's.

• Biomarkers suggest an effect, especially in E4 homozygotes.
A pilot of about 13 E4 patients with MCI showed CSF 24- and 27-hydroxycholesterol falling (not seen with statins) and stable cognition, though it was open-label and unpowered. In a prespecified BROADWAY substudy (2,500 patients), p-tau217 rose less overall; in E4/E4 participants it was over 20% better than placebo, with p-tau181, A;#C"óC Â t`AP and neurofilament light all improving.

• Davidson argues high-dose statins are outdated.
80 mg atorvastatin made sense 25 years ago when nothing else existed; now ezetimibe, PCSK9 inhibitors, bempedoic acid and others allow combinations. He calls pricing PCSK9 inhibitors at $16,000 a year a blunder that slowed adoption.

• Small companies can take risks big pharma won't.
Davidson argues biotech's nimbleness—no corporate hierarchy, willingness to start an outcomes trial alongside phase 3—is why obicetrapib was revived after big companies abandoned the class. NewAmsterdam bet on starting PREVAIL early, and phase 3 success then let it raise the cash to finish. He also notes competitive pressure from China, where he says chemists vastly outnumber those in the U.S.

EXAMPLES

• Two brothers
Davidson started a statin early; his brother started later and fared differently—an n of one he finds persuasive for early treatment. His wife's grandfather also died at 47.

• Longevity genetics
The Bronx aging study of Ashkenazi centenarians found CETP loss-of-function among the most common variants, supporting the Alzheimer's hypothesis.

• p-tau217 as a future endpoint
GLP-1 trials (EVOKE, EVOKE+) showed no cognitive benefit and no p-tau217 change, while Lilly's TRAILBLAZER anti-amyloid trials showed cognition tracking p-tau217—why Davidson thinks it could become a regulatory endpoint.

• Omega-3 lesson

High-dose omega-3s lower triglycerides, but some raised LDL about 9–10%, which he says changed how he thinks about them.

- **Compliance and AI**

  Peter asks how many trial participants were truly adherent; Davidson suggests compliant-only trials could shrink a 10,000-person study to 2,000, and hopes AI can cut drug costs from ~$4 billion and 10 years.

OTHER RELEVANT

- **Lower LDL/apoB early and keep it low.**

  The cumulative-exposure model argues for action in the 30s–40s rather than waiting for 10-year risk to rise.

- **Combination therapy beats maxing one drug.**

  Moderate statin plus ezetimibe or other agents may achieve deep lowering with fewer side effects.

- **Treat high HDL with skepticism.**

  A very high HDL-C does not reliably protect and isn't a treatment target.

- **E4 carriers: watch this space, not off-label hype.**

  Obicetrapib's Alzheimer's data are early biomarker signals; a prevention trial of conversion to MCI is still planned.

- **Ask how a drug's benefit compares with its LDL drop.**

  The REVEAL lesson is a useful rule of thumb: expect roughly a 22% relative event reduction per 38.7 mg/dL of LDL lowering sustained over years. A therapy that claims more than that via HDL or other effects deserves skepticism until outcome trials such as PREVAIL report.

Blood pressure: how to measure, manage, and treat high blood pressure (AMA #48 rebroadcast)

Date: 2026-09-07 · Duration: 1:16:49
URL: https://www.youtube.com/watch?v=n42zMaH2Jgc

KEYPOINTS

• Blood pressure is one of three main drivers of atherosclerosis, along with apoB and smoking, because it mechanically damages the endothelium.

Peter frames them as complementary attacks: hypertension is a mechanical injury to the vessel lining, smoking is a chemical one, and apoB is the particle that gets through the damaged wall. All three are 'area under the curve' problems that compound over decades, so a 35-year-old with untreated hypertension is accruing risk for 40 years, not the 3 years of a typical trial.

• Current US categories: normal is below 120/80, elevated is 120–129/<80, stage 1 is 130–139 or 80–89, stage 2 is "e140 or "e90.

Tightened in 2017 after SPRINT. Note 120/83 is stage 1 despite a normal systolic. Peter would be happy with 119/78 but won't rush to medicate a borderline 123/79 average, because unlike apoB, pressure can go too low and overtreatment causes orthostasis, fainting and falls.

• SPRINT showed intensive control below 120 systolic cut cardiovascular events by about 25% and all-cause death by 27%.

About 9,400 high-risk, non-diabetic adults with systolic pressure of 130 or higher were treated to below 120 or below 140. After one year they averaged 121.4 versus 136.2. The trial was stopped early at a median of a little over 3 years. The composite outcome had a hazard ratio of about 0.75 (roughly 0.54% absolute reduction per year), cardiovascular death halved, and all-cause mortality fell 1.2% in absolute terms, including fewer kidney and even accidental deaths. Peter calls it about as conclusive as trials get.

• Hypertension mostly damages three small-vessel organs: heart, brain and kidneys.

Meta-analyses of 40–70-year-olds show each 20 mmHg rise in systolic (or 10 diastolic) doubles the risk of death from stroke, heart disease or vascular disease, so 140/90 carries about twice the risk of 120/80. The kidneys are 1–2% of body weight but get 20–25% of cardiac output, which makes them highly pressure-sensitive. In SPRINT MIND, intensive lowering cut dementia risk by about 16% in relative terms.

• About 46% of US adults have hypertension, and it's largely silent.

Prevalence is roughly 30% in men and just under 20% in women aged 20–44, about half of men at 45–55, and over 80% for both sexes at 75 and older. It's highest in African Americans (about 59% of men, 56% of women). There are no reliable symptoms; the only way to know is to measure accurately.

• Sloppy technique can move a reading by 10–30 mmHg, so home measurement under protocol beats office readings.

The errors Peter lists: wrong cuff size or measuring over clothing; unsupported back or feet (5–10 mmHg); crossed legs (5–8); skipping a 5-minute silent rest (10–20); talking (10–15); pain (10–30); a full bladder (10–15); and about 2 mmHg for every inch the arm sits above or below the heart. He ignores his own office readings. Before judging anything he wants two weeks of readings taken two or three times a day.

• Manual readings are the gold standard, and automated cuffs read 10–15 mmHg high for Peter.

He describes the manual method: inflate about 30 mmHg past the point where the pulse disappears, then release slowly; the first tapping sound is systolic and the point where the sound vanishes is diastolic. His two expensive automated cuffs consistently read high systolic against several manual checks. His guess is that automated devices estimate from mean arterial pressure. Automated cuffs are still fine for most people if they're used correctly.

• Pressure should dip 10–20% at night; during exercise systolic rises normally, but a rising diastolic is a red flag.

Lying down and parasympathetic tone should lower nighttime pressure, which is what 24-hour ambulatory monitors look for. Stress alone can push Peter over 140. During VO2 max testing a systolic of 180–200 is normal, because widening arterioles lower vascular resistance and keep diastolic flat. People with dilated aortas may need to avoid heavy breath-holding lifts that spike pressure.

• About 10% of hypertension has a fixable underlying cause (secondary hypertension).

Clues include resistance to medication, readings over 180, sudden onset, or high pressure in a young person with no risk factors. Causes to rule out include kidney disease, narrowed renal arteries, thyroid disease, excess aldosterone and adrenal tumors. 'Primary' hypertension, Peter says, is really code for 'we don't know the cause.'

• Lifestyle moves blood pressure far more than it moves lipids, and might let about half of hypertensives avoid drugs.

Each kilogram lost lowers systolic by a little over 1 mmHg and diastolic by nearly 1. Aerobic training of 90–150 minutes a week at 65–75% of max heart rate (zone 2) lowers systolic by up to 8 and diastolic by about 5 within weeks. Dynamic resistance training lowers it by about 2/3, and isometric work by about 6/3. Insulin resistance raises pressure by reducing nitric oxide availability (ADMA and SDMA are markers). Sleeping under 5 or over 10 hours is linked to up to 40% higher hypertension risk.

EXAMPLES

• An athlete friend's 190/120 turned out to be an adrenal tumor.

Around 2013–14, a friend's very high morning pressure didn't respond to several drugs. Peter suspected a pheochromocytoma; the friend's doctor refused the urine catecholamine test. An earlier chest MRI showed an adrenal nodule the radiologist hadn't flagged. Testing elsewhere confirmed the tumor, and after surgery his pressure normalized.

• STEP trial (2021): replicating SPRINT in older Chinese adults.

About 8,500 people aged 60–80 with isolated systolic hypertension (baseline about 146/83) were treated to 110–130 or 130–150. Cardiovascular events fell 26% and cardiovascular death 28%, about 1% absolute per year, but all-cause mortality didn't

change.

- **Both of Peter's parents are hypertensive.**
  He measures often so that if his genes eventually overpower his habits, he starts medication immediately rather than missing a year or two.

- **Sodium restriction cuts both ways.**
  Going from the typical 3.5–4.5 g a day down to 1.5 g can lower systolic by 5–6 mmHg in hypertensives, but one Institute of Medicine analysis linked it to higher all-cause mortality. Nephrologist Rick Johnson suggests drinking water before or with a salty meal; sensitivity to salt is higher in older people, African Americans, and people with metabolic syndrome or kidney disease.

OTHER RELEVANT

- **Run a proper home protocol before acting on any number.**
  Use a correctly sized cuff on bare skin, back and feet supported, legs uncrossed, an empty bladder, the arm at heart level, and 5 silent minutes first. Take readings two or three times a day for about two weeks and decide on the averages.

- **Max out lifestyle first: weight, zone 2, lifting, sleep, potassium from food.**
  Combined lifestyle changes can match a drug's 12–15 mmHg. Get potassium from foods like potatoes and bananas rather than supplements. If you're already on medication, taper with your doctor as you lose weight to avoid fainting.

- **Drug choice: Peter's practice favors ARBs, with thiazides and calcium blockers as add-ons.**
  The four first-line classes (thiazides, calcium channel blockers, ACE inhibitors, ARBs) each lower pressure by about 12–15 systolic and 9–11 diastolic; beta blockers aren't first-line. His team's review found ARBs equal or slightly better than ACE inhibitors, which are cheaper but can cause a cough. Avoid calcium blockers in heart failure, be cautious with thiazides if you have gout or diabetes, and avoid ACE inhibitors and ARBs in pregnancy, angioedema or renal artery stenosis. In African Americans, thiazides and calcium channel blockers may work better. Titrate up from about half the maximum dose.

- **Check cystatin C, not just creatinine.**
  Peter treats a 'normal' GFR of 60 at age 50 as too low and often a clue to hidden hypertension.

406 Migraine, cluster headache, and tension headache: symptoms, causes, prevention, and treatment

Guest: Brian Grosberg
Date: 2026-08-31 · Duration: 2:09:10
URL: https://www.youtube.com/watch?v=uiNEP8A34SE

KEYPOINTS

- **Headache has over 300 types and causes; the first split is primary versus secondary.**
  Grosberg, a headache neurologist, says the differential is one of the longest in medicine. Primary headaches (migraine, tension-type, cluster) are disorders in themselves; secondary headaches stem from something else, which is why red flags matter.
- **Migraine has specific diagnostic criteria, and it isn't always one-sided.**
  At least five lifetime attacks lasting 4–72 hours untreated, plus two of: one-sided, throbbing, moderate-to-severe, worse with activity—along with nausea or light and sound sensitivity. Up to 40% have pain on both sides. Tension-type headache lacks nausea and can last 30 minutes to a week.
- **Migraine is common, disproportionately female, and badly under-served.**
  About 45 million Americans, roughly 18% of women, with a female ratio of about 3:1. Only around 50 fellowship-trained headache neurologists graduate per year. Episodic migraine is under 15 headache days a month; chronic is 15+ and affects 1–2% of the population.
- **Hormones matter: the speed of estrogen decline is a key trigger.**
  Studies since the 1970s link migraine to the late-luteal estrogen drop; newer work shows it's the faster rate of decline that's distinctive in women with migraine. Pure menstrual migraine occurs in under 10% of women. Perimenopause often worsens it; about two-thirds improve after menopause, but 10–20% continue or worsen. Migraine without aura improves in about 47% of women in the first trimester and 80–87% in the second and third.
- **A migraine has phases, and aura is only in a minority.**
  Premonitory symptoms can precede the attack; aura evolves gradually over 5–60 minutes; then the headache and a postdrome. Some attacks build over hours, others wake people at 3 a.m. Light sensitivity is present in about two-thirds to 70%.
- **Cluster headache is among the most severe pains known and is often misdiagnosed.**
  Attacks peak in 5–15 minutes, last 15 minutes to 3 hours, and are stabbing or boring around one eye. About 97% have same-side eyelid droop, tearing, redness or nasal congestion—often mistaken for sinusitis or allergies—and about 90% are restless. One patient likened it to giving birth to 100 babies without an epidural. The male:female ratio is now about 3–4:1.
- **Migraine is a neurovascular disorder, not just a blood-vessel problem.**
  The 1940s vascular theory was too simple. Pain signals from the dura and its blood vessels travel along the first branch of the trigeminal nerve to the trigeminal nucleus caudalis in the brainstem—where C2–C3 neck nerves also converge, explaining neck pain in migraine. Neuropeptides such as CGRP and an inflammatory response are involved; serotonin was noted to fall in blood during attacks decades ago.
- **Many more people qualify for prevention than receive it.**
  About 40% of people with migraine are medically eligible for preventive therapy, but only 16–17% receive it. Low-dose amitriptyline or nortriptyline are used at doses well below those for depression, which Grosberg explains to reduce stigma.
- **CGRP drugs changed treatment, with roughly 60% responding.**
  Monthly CGRP monoclonal antibodies (and oral gepants) work in up to about 60% of patients, with response defined as at least a 50% drop in headache days; Grosberg also counts patients whose severity or acute-drug response improves. U.S. prices are often 3–10x what other countries pay.
- **Triptans transformed acute care; injections are fastest for cluster.**
  Ergotamines came first; triptans arrived in the mid-1990s, targeting 5-HT1B/1D receptors. For cluster, injectable sumatriptan has a median time to relief around 9 minutes. Botox for chronic migraine uses the PREEMPT protocol of injections in the forehead, sides and back of head, neck and shoulders; verapamil is used for cluster, sometimes at very high doses.
- **Tension-type headache is the most common primary headache, and neck pain is a shared feature.**
  Like migraine, it is split into episodic (under 15 days a month) and chronic (15+ days). Because neck nerves converge on the same brainstem nucleus as the trigeminal system, neck and shoulder pain can be referred pain rather than the cause. Peter asks whether responding to 1,000 mg of acetaminophen implies tension-type; Grosberg cautions that response to a simple analgesic doesn't by itself settle the diagnosis.

EXAMPLES

- **The patient who connected them**
  A woman in her late 50s or early 60s with menopausal migraine, whom Peter referred about 10 years ago, was among the first on a CGRP drug through a clinical trial—'a resounding success'.
- **Over 1,000 mg of verapamil**
  Grosberg recently saw a cluster patient who at one point needed more than 1,000 mg of verapamil a day, illustrating how aggressive cluster prevention can be.
- **The 15-page intake**
  His chronic patients complete about a 15-page questionnaire plus a headache diary, because patterns differ from person to person.
- **Weekend caffeine**
  Diaries reveal patterns like coffee at 6 a.m. on weekdays but 9 a.m. on Saturday—a classic weekend-headache trigger.
- **Obesity and inflammation**

Grosberg notes obesity is an identified risk factor for migraine progression, possibly via shared pro-inflammatory mechanisms, so addressing risk factors is part of preventing episodic migraine from becoming chronic.

OTHER RELEVANT

• Keep a headache diary for a month.

Grosberg calls it the most important thing patients can do: 10–20 minutes a day logging attacks, sleep, meals, caffeine, cycle and medications lets a primary-care doctor act in a 10-minute visit.

• Regularity is preventive.

Because the migraine brain is hypersensitive to change, consistent meals, hydration, exercise and sleep—plus morning light exposure—pay dividends.

• Know the red flags.

New headaches after age 50, a change in pattern, systemic symptoms, or new headaches in pregnancy warrant evaluation for secondary causes, though most headaches are benign.

• Don't assume 'sinus headache'.

One-sided eye pain with tearing, droop and restlessness that peaks within minutes may be cluster headache and deserves a neurologist.

• Cannabis and gray areas need a clinician's input.

Some patients use THC for headache, but Grosberg says evidence and drug-interaction data are limited, making it hard to advise—another reason to tell your doctor everything you take.

404 Mental health beyond neurotransmitters: hormones in psychiatry, psychedelic therapies, & more

Guest: Linus Abrams
Date: 2026-08-17 · Duration: 2:19:21
URL: https://www.youtube.com/watch?v=fs89fhQCfj4

KEYPOINTS

- **Good psychiatry starts with understanding the person, not just picking a molecule.**
  Abrams, a psychiatrist with nearly 35 years in practice, deliberately trained at a Harvard program that taught both psychotherapy and psychopharmacology so he wouldn't split a patient's care. He still does a lot of psychotherapy and approaches every consultation similarly, whatever the diagnosis, because each patient is more complex than any provider's model of them.
- **Antidepressant classes are more of a continuum than tidy categories.**
  He jokes that if a drug scores 10/10 on serotonin and 3–4/10 on norepinephrine, at some point we just call it an SNRI. Effects involve receptor up- and down-regulation over time rather than simply 'adding' a neurotransmitter. Older MAOIs required tyramine-restricted diets that made patients anxious; escitalopram (Lexapro) is typically used at 10 or 20 mg.
- **Modern life likely creates far more anxiety, and plausibly more depression, than ancestral life.**
  Asked to imagine 10,000 years ago, Abrams thinks we'd see much less anxiety. Then it was impossible to live in isolation; people were outdoors by default; sleep wasn't necessarily 8 hours but fit natural rhythms. Loss of community, nature and movement are risk factors he weighs alongside biology.
- **Distress tolerance shrinks when foundational biology is off.**
  Peter offers a 'window' analogy: sleep loss, pain or hormonal disruption narrow the window of what you can tolerate, so irritability rises. He recalls being irritable two weeks into an injury until someone pointed out untreated pain makes anyone irritable. Abrams focuses on nutrition, exercise, sleep and especially endocrinology.
- **Abrams thinks of hormones as four axes: sex hormones, thyroid, cortisol and more.**
  Sex-hormone and thyroid problems are usually deficiencies that we know how to fix; the cortisol axis is hardest because most people have too much, driven by chronic hyperarousal, and there's no pill that is an antidote.
- **Estradiol and progesterone shape brain chemistry, and rapid drops drive mood disorders.**
  Estradiol supports neuroplasticity via BDNF, NMDA and glutamate. In PMDD, allopregnanolone, a progesterone derivative, falls late in the luteal phase. After delivery, estradiol may fall from around 30,000 to about 30 pg/mL and progesterone from several hundred to under 1 within 24–48 hours, contributing to postpartum depression. Severe postpartum psychosis is under 1%.
- **Women's testosterone matters, and units obscure it.**
  Testosterone is reported in ng/dL and estradiol in pg/mL—a 1,000-fold difference. Normalized, a woman's testosterone is about 10 times her estradiol, though about a tenth of a man's.
- **For men, exogenous testosterone generally beats clomiphene.**
  Abrams sees limited rationales for clomiphene/enclomiphene and considers hCG superior to clomiphene because it acts peripherally. Both discuss that estrogen is not 'bad' for men—it's important for male brain and body function.
- **A 'normal' thyroid panel can hide a deficiency that presents as depression.**
  TSH of 2.5–5 is often dismissed, but Abrams pays most attention to free T4: if it's suboptimal in a depressed patient, he refers to endocrinology or prescribes himself. He prefers combined T4 and T3, avoids compounded time-release T3, and doses immediate-release T3 twice daily—morning and 6–8 hours later—sometimes starting as low as 2.5 mcg twice daily, and sometimes uses T3 alone for treatment-resistant depression.
- **Ketamine can rapidly defuse suicidality.**
  He describes patients on the edge of hospitalization whose suicidal risk dissipates dramatically after a ketamine infusion, usually given at partially dissociative doses. He worries about recreational use and has friends who refer patients for ketamine addiction.

EXAMPLES

- **Menopause unmasking bipolar disorder**
  A woman described herself as 'just a high-energy person'; asked about her 20s and 30s, she admitted they were chaotic, with a depressive episode following a long hypomanic stretch. The menopause transition revealed underlying bipolar disorder, changing treatment—lamotrigine can help bipolar depression.
- **Very high-dose T3**
  Abrams recalls (conflating a few patients) a case of recalcitrant depression that finally responded to T3 at doses Peter considers very high, after atypical antipsychotics and other options.
- **The psilocybin-Alzheimer's report**
  A Japanese woman with supposedly decade-long severe Alzheimer's reportedly improved after 5 g of psilocybin, lasting until a second 3 g dose. Abrams is cautious: no metrics or imaging, and severe Alzheimer's plus 10-year survival 'don't go together' in his experience; he suspects a different underlying cause.
- **Peter's psychedelic experiences**
  Peter says he is resistant to dose-variable drugs; standard 5 g psilocybin does nothing, so he has used more than 10 g. One experience returned him to being 12 and feeling how much harder his parents' lives were than his—transforming that relationship.
- **Duration after one episode**
  For someone well for decades who has a single depressive episode, Abrams cites evidence to continue medication 8–12

months, then taper slowly, not necessarily indefinitely.

OTHER RELEVANT

- **Ask for free T4 and free T3, not just TSH, if depression resists treatment.**
  Abrams finds many depressed patients with low-normal levels respond to thyroid supplementation—under medical supervision. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Track mood across the cycle and life transitions.**
  PMDD, postpartum and perimenopause share a theme of rapid hormone withdrawal; recognizing it can redirect treatment.
- **Treat psychedelics as drugs with real risks.**
  Abrams expects a lasting role in psychiatry, perhaps via safer molecules, set-and-setting or combination therapy, but warns people don't hear enough bad stories, and serotonin-2A blockers can dramatically alter dose needs.
- **Lower doses of tricyclics aren't 'antidepressant treatment'.**
  Distinguishing mechanism and dose helps reduce stigma and supports informed, shared decisions. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Address chronic hyperarousal directly.**
  Because Abrams sees elevated cortisol as the hardest axis to fix with medication, the levers are behavioral and environmental: sleep regularity, time outdoors, social connection and reducing chronic stressors. These are the same ancestral defaults he argues modern life has stripped away.

403 Peptides: separating scientific promise from marketing hype

Date: 2026-08-10 · Duration: 0:50:17
URL: https://www.youtube.com/watch?v=Km_01CLEkYU

KEYPOINTS

• 'Peptides' is a category, not a verdict—each must be judged individually.
Peter stresses that some of the most important drugs ever made are peptides, including insulin and GLP-1 agonists. His aim is neither to promote nor dismiss them but to give a framework, because the same label covers rigorously proven medicines and essentially untested gray-market products.

• A five-question framework for anything you put in your body.
1) Is there a viable mechanism of action? 2) Is there credible human evidence of benefit? 3) Are dose, pharmacokinetics and safety characterized, with a plan for monitoring and intervening? 4) Does the likely benefit justify the risk for this person, compared with doing nothing? 5) Is there a better-characterized alternative, and what do you gain by choosing the less characterized one?

• Mechanism matters because it makes a claim falsifiable and reveals failure modes.
Unknown mechanisms exist but are the exception: among FDA-approved drugs, the share with genuinely unclear mechanisms is small. Even among compounds that clear preclinical testing, roughly 30–50% fail in phase 1 to advance, often because they don't behave in humans as predicted.

• A three-tier evidence system.
Tier 1: no validated mechanism and little human data. Tier 2: plausible, even demonstrated biology, perhaps working in animals, but little evidence of improved human outcomes. Tier 3: approved drugs with evidence for a specific dose, route, population, indication and endpoint—though that evidence doesn't automatically transfer to other uses or gray-market versions.

• BPC-157 is Peter's poster child for skepticism.
Described as a fragment of a 'body protection compound' from gastric juice, its parent protein sequence has never been published—the discoverer reportedly said, 'If you have your own child, you want it to be yours forever.' It doesn't clearly match any known human protein. Proposed mechanisms (VEGF/angiogenesis, nitric oxide, neurotransmitters) aren't established in humans, and 'peptide without a receptor' is not the same as having a mechanism.

• BPC-157's evidence base is thin and conflicted.
More than 80% of published work comes from one academic group with IP and commercial ties. After roughly three decades of claims, there are no published peer-reviewed human randomized trials showing faster healing; human pharmacokinetics and bioavailability are unknown, so dosing protocols are guesses; phase 1 safety trials haven't been run. If you believe the angiogenesis mechanism, Peter says, you should worry more about cancer, not less—though that's not proof it causes cancer.

• Expanding claims signal weakness, not a broad mechanism.
Legitimate drugs win one indication in rigorous trials and earn more over time. BPC-157's list of uses keeps growing while human trials—which are entirely feasible—aren't happening. A claim that explains away every failure by dose, timing, supplier or stacking isn't scientific.

• Biological activity isn't clinical benefit: CJC-1295.
CJC-1295 genuinely raises growth hormone and IGF-1, but almost every drug changes biology. The question is whether it improves outcomes at a known dose with acceptable risk—and stimulating the GH axis may itself be an argument against it. Peter says that case hasn't been made.

• Testimonials can't establish effectiveness, and placebo effects are large.
Stories are sincere but confounded: one friend credited peptides while also exercising, changing diet and taking tirzepatide. Pain trials have big placebo responses because pain is shaped by attention, expectation, sleep and mood. In STEP 1, semaglutide beat placebo substantially, but placebo participants also lost weight—showing why controls separate the drug from the drama.

• Doctors, compounding pharmacies and lab tests reduce some risks but validate nothing.
A physician can help with screening, technique and monitoring, and third-party testing can check contents, but none proves efficacy, a valid dose, or equivalence to the studied product. Two vials with the same amino-acid sequence aren't necessarily equivalent; trials validate a product, not a sequence in the abstract—relevant to gray-market GLP-1s.

• Approved molecules sold on the gray market are a different product.
Tier 3 evidence covers a specific manufactured drug at a studied dose, route and population. A gray-market version of an approved peptide may share a sequence but not purity, concentration, sterility or stability, so the trial evidence doesn't automatically extend to it. Peter asks people to be explicit about what they gain—cost, access, convenience—and what risk they are accepting in exchange.

EXAMPLES

• SS-31
A popular peptide with a legitimate rare-disease context; a risk acceptable when the alternative is early death can be unacceptable for a healthy person seeking energy or longevity.

• CJC-1295 versus tesamorelin
Same biology, developed around the same time. CJC-1295, named after ConjuChem, reached phase 2 and was abandoned; tesamorelin, closer to the native molecule, succeeded because its data were better.

• 'Big Pharma can't patent natural peptides'
Peter rebuts this: BPC-157 itself has patents on salts and production methods, and the whole GLP-1 industry is built on synthetic variations of a natural peptide.

• The pipeline
Roughly 100 peptide drugs are approved, about 150 are in clinical trials and 600–700 in preclinical development—while 90–

95% of drugs entering trials never reach market.

OTHER RELEVANT

- **Run any peptide through the five questions before using it.**
  If you can't answer mechanism, human evidence, dose and monitoring, the risk-benefit math rarely works for enhancement goals.
- **Prefer approved versions when a real indication exists.**
  FDA approval isn't infallible, but it provides evidence, dose clarity, safety characterization, manufacturing control and post-market surveillance.
- **Choose boring, proven alternatives for injury and recovery.**
  You don't need a perfect named alternative to reject BPC-157; standard approaches have clearer dosing, risks and evidence.
- **Demand that claims narrow over time.**
  Show efficacy in humans, define who benefits, characterize dose and risk, then decide—evidence should precede use, not 'catch up later'.
- **Be wary of the story more than the molecule.**
  Peter's point is that BPC-157 is chosen because its narrative is compelling, not because of superior human outcomes. Noticing when you're being sold a story—testimonials, stacks, ever-growing indications—is the most useful filter.

402 NMR blood analysis: how mortality risk and more can be assessed from a single blood sample

Guest: Jim Otvos
Date: 2026-08-03 · Duration: 2:27:11
URL: https://www.youtube.com/watch?v=IMbghqZ1iXI

KEYPOINTS

• NMR lipoprotein testing was born from debunking a flawed 1986 cancer test.
A New England Journal paper claimed the width of a plasma NMR signal could diagnose any cancer. Otvos ran six leftover plasma samples; half looked 'cancerous,' but three came from women who had just given birth. The signal turned out to be a superposition of VLDL, LDL and HDL lipid signals. 'Cancer' samples simply had higher triglycerides and lower HDL, which narrowed the peak. He turned that composite signal into a way to count lipoprotein particles.

• Most reported LDL cholesterol is still estimated, not measured.
Labs measure total and HDL cholesterol, then estimate VLDL cholesterol as triglycerides ÷ 5 (Friedewald) and subtract. Unless a report says 'direct,' LDL-C was probably calculated this way. Otvos helped develop a more accurate NIH equation used by LabCorp, but many labs still divide by five. Triglyceride assays measure glycerol, so rare free-glycerol states can falsely suggest high triglycerides.

• NMR counts particles because particle size shifts the signal frequency.
Identical lipid methyl groups resonate at slightly lower frequency in larger particles. A 30-second spectrum is deconvoluted into contributions from each VLDL, LDL and HDL size subclass. Because NMR can't tell cholesterol from triglyceride inside, results are particle concentrations in nmol/L, not mg/dL.

• Small dense LDL's extra risk is explained by particle number, not particle size.
At a given LDL-C, small LDL looks about threefold riskier. But smaller particles carry less cholesterol each, so the same LDL-C means more particles. Stratify by LDL-P instead, and size adds nothing. This matters because drugs that enlarge particles—niacin, fibrates, CETP inhibitors—failed outcome trials despite 'better' size profiles.

• 'Large, fluffy' LDL is not benign.
Asked about patients with LDL-P above 2,000 nmol/L who feel reassured by pattern A, Otvos calls it a specious idea. Familial hypercholesterolaemia patients have very high counts of large LDL particles; untreated homozygotes can die at 30–35.

• When LDL-C and LDL-P disagree, risk follows particle number.
In Framingham (2007) and MESA (2011), Otvos ranked LDL-C and LDL-P as percentiles and called people within 12 percentile points 'concordant,' splitting the cohort roughly into thirds. Event curves were identical when the measures agreed. When LDL-P exceeded LDL-C, events rose faster; when cholesterol was high but particles low, events were lower. Discordance rises with each metabolic-syndrome criterion and is almost guaranteed with all five.

• LDL-P/apoB is a management tool more than a risk-prediction tool.
Adding LDL-P to standard risk equations barely improves prediction, Otvos argues, because HDL-C in those models already captures the same signal indirectly. Where particles win is treatment: on statins, LDL-C often falls further than particle count. As LDL falls, triglyceride replaces cholesterol ester in the particle core, which can reveal residual risk and a case for adding drugs like PCSK9 inhibitors.

• LP-IR detects insulin resistance years before glucose rises.
Insulin resistance is to diabetes what LDL is to atherosclerosis: the cause, integrated over time. Yet medicine waits for glucose, by which point roughly half of beta-cell function may be gone. LP-IR combines six lipoprotein size/subclass measures into a 0–100 score. In unpublished Diabetes Prevention Program data, it beat fasting insulin. Its fall with lifestyle change, and less with metformin, predicted lower diabetes incidence. The Diabetes Risk Index adds branched-chain amino acids.

• GlycA is a stable, cheap marker of systemic inflammation.
The signal was first quantified just to subtract it from a fatty-acid peak. It comes from glycan decorations on acute-phase proteins, so it reflects both their levels and their glycosylation. Unlike hs-CRP, which can jump a thousandfold with infection and needs repeated measures, GlycA might double. It tracks IL-6 and falls with treatment of rheumatoid arthritis or psoriasis, but misses local inflammation.

• MVX predicts dying, more than getting a disease—'metabolic frailty.'
The Metabolic Vulnerability Index combines GlycA and small HDL-P (the inflammation subscore, IVX) with citrate and the three BCAAs (the malnutrition subscore, MMX). Low BCAAs signal wasting, the opposite of the diabetes signal. Its predictive power holds across sex, obesity, diabetes, heart failure and kidney disease. Otvos argues composite fatal plus non-fatal endpoints make it look disease-specific, when it really reflects susceptibility to dying of whatever comes.

• The technology is at risk because diagnostics economics don't reward free information.
One 150 µL plasma run yields a lipid panel, apoB via machine learning, glucose, LP-IR, GlycA and MVX at near-$1 marginal cost on $400–500k analyzers with no consumables. LabCorp bought LipoScience about a decade ago for lab revenue, not the in-vitro-diagnostics vision. It pulled the Vantera analyzers from places like Mayo and Cleveland Clinic, and the 15-year-old units are aging.

EXAMPLES

• Duke CATHGEN cohort
About 7,000 cath-lab patients, mean age ~60; 17% died within five years and about 60% of deaths were non-cardiac. Small HDL-P and GlycA predicted mortality, and a separate Salt Lake City cath cohort replicated MVX before the 2023 paper.

• MESA healthy 60-year-olds
After excluding anyone with disease, MVX still showed a stepwise mortality gradient. Hazard ratios were weaker than in cath patients, but the top versus bottom quartile meant roughly two- to threefold risk.

- **MVX in 30-year-olds (paper being submitted)**
  In 3,000+ healthy people aged 25–30 with roughly 35 years of follow-up, the MVX distribution matched 60-year-olds. Top-quartile average was ~51 versus ~27 in the bottom, scores were stable over time and barely associated with age, and it predicted premature death. Attia can't think of a comparable biomarker outside extremes like untreated FH.
- **Older-adult cohort: 186 variables**
  In a Minnesota study of older adults, small HDL particles were the strongest of 186 variables at predicting two-year mortality. Physical frailty correlated only ~0.2 with MVX; each added information.
- **CETP inhibitor obicetrapib (BROADWAY/BROOKLYN)**
  LDL-P fell more than apoB in the trials because an old algorithm couldn't separate huge HDL from small LDL and excluded small LDL. Reanalysis brought LDL-P in line with apoB. Otvos speculates CETP inhibitors' 10–20% cut in small HDL-P could blunt the expected benefit.
- **Reimbursement absurdities**
  A 14-test metabolic panel bills about $60 in components but Medicare pays about $12. ApoB pays roughly $20 versus about $13 for a lipid panel, and the NMR LipoProfile about $30.

OTHER RELEVANT

- **Manage to particles, not just cholesterol**
  If you're on treatment, check apoB or LDL-P; low LDL-C can hide residual particles, especially with insulin resistance or high triglycerides.
- **Don't chase particle size**
  Making LDL or HDL 'bigger' hasn't improved outcomes in trials; target total particle burden.
- **Act on insulin resistance before glucose rises**
  Glucose is a late signal. LP-IR, fasting insulin or an oral glucose tolerance test can flag the cause earlier. Otvos notes his wife has stayed prediabetic at ~105 mg/dL for 25 years, so prediabetes doesn't always progress.
- **Interpret hs-CRP and GlycA in context**
  Very high CRP usually means something acute; persistent low-grade elevation is more concerning. GlycA is steadier, but recent infection can still raise it.
- **Treat MVX as a promising but unproven lever**
  It's available at LabCorp and could help with surgical-risk screening, trial enrichment or predicting treatment response. Otvos stresses it raises more questions than answers: whether it's causal or modifiable remains to be tested in intervention trials.

399 - The evolution of Alzheimer's disease and dementia care | Gayatri Devi, M.D.

Guest: Gayatri Devi
Date: 2026-07-13 · Duration: 1:58:42
URL: https://www.youtube.com/watch?v=x7NhqMOwdOM

KEYPOINTS

• Dementia is a spectrum, and most Alzheimer's brains have mixed pathology.
Devi, a memory-disorders neurologist practicing on Manhattan's Upper East Side for 26 years, says autopsy studies find 98–99% of Alzheimer's patients have some other concomitant brain pathology. About 40% of Alzheimer's patients eventually show Lewy body pathology and 30–40% of Lewy body patients have Alzheimer's pathology. Vascular disease is so intertwined that a 2002 Circulation paper asked, 'Is Alzheimer's stroke?'—every Alzheimer's risk factor is also a stroke risk factor.

• Prevention may need to start in the 30s and 40s.
Because the cascade begins decades before symptoms, she argues for building anti-inflammatory habits early to keep it from being triggered. Neuroinflammation and viral infections are emerging factors; she sees stronger data for shingles vaccination, relevant since virtually everyone over 50 has had varicella.

• Standard screening tests miss high-functioning patients.
Her patients often score 28–30 on the MMSE or MoCA 10–15 years into their condition because they compensate so well. She uses detailed neuropsychological testing: someone at the 99th percentile overall but the 10th in language or visuospatial skills has likely declined substantially.

• Forgetting names is usually normal; word-finding trouble is more concerning.
Peter describes taking a minute to recall the name of someone he's met 30 times. Devi notes we now meet far more people than 100 years ago—some speculate we're built to remember about 150 names. Difficulty finding ordinary words is a more meaningful signal.

• Women's higher risk is tied partly to longevity and menopause.
Life expectancy has risen from about 50 to the late 70s or early 80s; 150 years ago most women died before menopause, when estrogen production stops. Perimenopausal cognitive changes can start in the 40s unnoticed. She calls women denied HRT after the 2002 WHI a 'lost generation' now in their 70s. She prefers transdermal estrogen (gel or patch) for lower stroke and clot risk.

• Amyloid alone doesn't mean Alzheimer's; biomarkers need context.
About 25% of community-dwelling people in their 70s, 30%+ in their 80s and about 44% at 90 have amyloid without symptoms. Blood tests are mostly standardized against amyloid scans, and she thinks they should be standardized against both amyloid and tau. About 30% of participants in Alzheimer's drug trials didn't actually have Alzheimer's pathologically.

• APOE4 raises risk but isn't deterministic.
Devi estimates lifetime risk around 6% for a man and 10–12% for a woman with 3/3; one E4 raises it about 60% versus wild type, and 4/4 much more. PSEN1, PSEN2 and APP mutations are close to deterministic, with PSEN1 essentially 100% associated with early-onset disease.

• Slow titration of anti-amyloid antibodies may cut brain swelling and bleeding.
Aducanumab had a greater than 40% rate of ARIA, so Devi developed a very slow titration protocol. In published data on 4/4 patients she reports about 4% ARIA. The FDA has since approved a slower titration for donanemab (350, 700, 1,050, 1,400 mg), letting her hold patients at 350 mg for four or five infusions; lecanemab starts at 10 mg/kg and insurers won't reimburse slower starts, though some 4/4 patients have had severe ARIA on 3 mg/kg.

• ARIA in E4 carriers reflects blood-vessel amyloid.
E4 homozygotes have more cerebral amyloid angiopathy; removing amyloid from vessel walls creates 'little tears in the fabric of the blood vessels'. She monitors rigorously with MRI and treats refractory ARIA-E with steroids, as for inflammatory amyloid angiopathy.

• She favors multimodal treatment.
Off-label MRI-guided TMS since 2008 to maintain network connectivity, management of vascular risk, shunts for normal-pressure hydrocephalus, and for patients on blood thinners for atrial fibrillation, a Watchman device so they can become eligible for antibodies.

• The benefit of anti-amyloid drugs is modest on average, so patient selection matters.
Devi acknowledges the change on scales like the CDR sum of boxes is small, and early donanemab data showed little difference in some measures. Her approach targets high-risk people in their 50s or 60s—perhaps 5–10 years from symptoms—treated 'very low, very slow, very safe', asking whether the disease course bends. She'd still choose aducanumab despite its discontinuation and reports two exceptional responders, one stable for 17 years.

EXAMPLES

• A 51-year-old on lecanemab for prevention
A young 4/4 patient developed bilateral ARIA-E at 3 mg/kg, still present after six doses (about 3 months), illustrating the risk of treating early E4 homozygotes.

• ARIA before a trip to Europe
A man in his early 60s on slow-titrated aducanumab reached 8 mg/kg and at about month 18–19 developed significant ARIA-E, found a few weeks after onset. They dropped to 6 mg/kg, then went back up.

• Misdiagnosed Parkinson's
A woman with a negative DAT scan had been placed on carbidopa-levodopa 25/100, three tablets three times daily, at an academic center for presumed Parkinson's; Devi suspected Lewy body disease instead.

- **Brain fog at 21**
  A college student seen for migraines had six months of brain fog and no periods; her estradiol was 22 pg/mL—menopausal range.
- **Costs**
  Antibodies cost about $26,000 a year, with infusion fees from roughly $400 at an infusion center to as much as $10,000 in some institutions; aducanumab launched around $56,000 a year.

OTHER RELEVANT

- **Ask for detailed testing if you're high-functioning and worried.**
  A 'normal' MoCA can be falsely reassuring; percentile profiles across domains catch compensation.
- **Interpret positive biomarkers carefully.**
  Amyloid positivity is common with age; decisions should weigh tau, symptoms, genetics and overall risk.
- **E4/E4 carriers: ask about titration and monitoring.**
  If considering antibodies, ask about slow titration and MRI surveillance; the risk-benefit may not favor late, high-dose treatment.
- **Address vascular risk and hormones in midlife.**
  Blood pressure, metabolic health and, for appropriate women, transdermal HRT are levers she emphasizes.
- **Stratified trials are the goal.**
  Devi hopes within five years the field will identify and stratify risk better and tailor treatment, rather than applying one protocol to everyone—her open-label results need randomized testing.

Building strength and muscle mass: optimize training & nutrition for longevity (AMA #71 rebroadcast)

Date: 2026-07-06 · Duration: 1:57:50
URL: https://www.youtube.com/watch?v=CqNqfb37gig

KEYPOINTS

- **Low strength and muscle mass carry mortality risks comparable to or larger than classic risk factors.**
  Peter compares hazard ratios: going from the bottom quartile to the middle quartile of muscle mass is associated with about a 2.3 hazard ratio (130% higher all-cause mortality); comparing above-average to elite strength is about a two-fold difference. For context, he cites type 2 diabetes at roughly a 40% increase, uncontrolled hypertension about 60%, and smoking around 2.8 in one study (1.4 in others). Low versus elite VO2 max is about a five-fold difference.
- **Grip strength is a cheap, powerful predictor.**
  In the PURE study of about 140,000 people across 17 countries, every 5 kg lower grip strength was associated with a 16% higher mortality. Other data put it at roughly 30% higher mortality per 10 kg. In a cohort aged 70–79 followed seven years, the separation was steep—partly why older populations are studied.
- **Genetic evidence hints strength is partly causal, not just a marker.**
  Randomized trials of 'being strong' are nearly impossible, so a study of 300–350,000 Finnish biobank participants used a polygenic score for grip strength. Each standard deviation was linked to about 7% lower vascular dementia, 6% obesity, 5% type 2 diabetes, 4% MACE and 3% all-cause mortality.
- **Strength, muscle and VO2 max integrate years of consistent work.**
  Like VO2 max, you can't cram for them; Peter tells patients moving VO2 max from 30 to 50 may take about three years. That's why these metrics say so much about long-term behavior.
- **Muscle improves healthspan through metabolism, resilience and fall protection.**
  Muscle is the major glucose sink—storing roughly 300–500 g—which supports lower blood sugar and lowers risk of diabetes, heart disease, dementia and cancer. Falls cause about 300,000 U.S. hospitalizations a year with 10–30% one-year mortality over 60; fall deaths rise from 1.1 per 100,000 at ages 25–35 to nearly 200 per 100,000 at 85+.
- **Strength peaks in the 30s–early 40s and then declines about 1–2% a year, accelerating after 70.**
  Population averages hide individual variation, but the lesson is to build the highest 'glider' possible when young—especially for kids—and then slow the descent.
- **After 50, rule number one is don't get injured.**
  Peter hasn't deliberately done a one-rep max in 15 years and says he never will again. Injuries that take someone in their 60s or 70s out of training for months are among his biggest worries.
- **Progressive overload drives gains, at different rates by experience.**
  Beginners can raise total load (weight, reps, rest, volume) by 5–10% per week in their first months; advanced lifters may manage about 1%. Beyond 12–15 reps, the stimulus shifts toward muscular endurance.
- **Fast-twitch fibers and power decline first, so train power.**
  Type II fibers responsible for explosiveness start atrophying in the 30s and 40s. A review of 13 studies found power training superior to traditional strength training for power. Peter ends a power set once he falls below 92% of peak power.
- **Train with 1–2 reps in reserve for most work.**
  Reps-in-reserve keeps intensity high while limiting injury risk; beginners start at 3–4 RIR and work toward 1–2 unless they have specific power or maximal-strength goals.
- **Protein targets are far above the RDA.**
  The RDA is 0.8 g/kg/day; for building or keeping muscle, Peter suggests 1.6–2.4 g/kg (roughly 1 g per pound), possibly more over 60. He now eats 40–50 g of protein about four times a day through meals, avoids small 10 g servings, and notes animal proteins easily meet leucine/essential amino-acid needs while plant-heavy diets need more attention.
- **Concentric and eccentric work play different roles.**
  The episode distinguishes the lifting (concentric) and lowering (eccentric) phases: eccentric loading is a strong stimulus for strength and hypertrophy and helps tendons and injury resilience, but it also produces more soreness, so it is dosed carefully. Combining compound lifts for efficiency with isolation work for weak links is how Peter balances a program with limited time.

EXAMPLES

- **The second-grader**
  Peter opens with a seven-year-old lecturing him about his diet soda containing a sweetener 500 times sweeter than sugar.
- **Teenage training**
  Peter credits training absurdly hard from about 13 to 19 for his high starting point; his cycling VO2 max once reached the 70s or low 80s.
- **LIFTMOR**
  He recalls Belinda Beck's trial in which women in their 60s who'd never lifted progressed to heavy deadlifts, improving strength, bone density and quality of life.
- **Fitness benchmarks**
  Targets include a farmer's carry of 100% of body weight (men) or 75% (women) split between hands, box step-ups holding 25% of body weight per hand for five reps per side, and about 20 well-controlled push-ups for men; he wants patients at or above the 75th percentile for ALMI/FFMI.
- **Extreme dieting**
  Peter recalls eating 200 g of protein on a roughly 800-calorie day; studies suggest with 30–40% calorie restriction, enough

protein plus resistance training can preserve some muscle.

OTHER RELEVANT

- **A time-efficient template**
  Three 1-hour full-body sessions weekly plus about 3 hours of cardio: 10–20 sets per body part per week, 3–4 sets per exercise, 6–15 reps, 90–120 seconds rest.
- **Make half your leg work single-leg.**
  Peter says about 50% of his leg-day work is unilateral, for balance and lower spinal loading.
- **Recovery is part of training.**
  Hydration (muscle is ~70% water), creatine, sleep and deloads matter; failing to recover blocks growth. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **De-risk as you age.**
  Choose movements and loads where adding weight carries little risk; machines can help beginners reduce form errors.
- **Returning lifters should rebuild before reloading.**
  Someone who lived in the weight room in high school and returns at 40 should start well below old numbers, prioritize scapular control and form, and accept that the goal is now the 'marginal decade', not a personal record.

397 - Endometriosis and adenomyosis: diagnosis, fertility, reproductive aging, & emerging treatments

Guest: Dr. Renato Tomioka
Date: 2026-06-22 · Duration: 2:00:26
URL: https://www.youtube.com/watch?v=IxHRYDM64dQ

KEYPOINTS

• Endometriosis affects about 10% of reproductive-age women (around 200 million) and is found in 30–50% of infertile women.

It's endometrium-like tissue (glands and stroma) growing outside the uterus: on the tubes, ovaries, bowel, bladder, appendix, even the diaphragm. Brazilian reproductive surgeon Dr. Renato Tomioka puts the chance of infertility with endometriosis at about 40%. Heritability is around 50%, and a mother or sister with it raises a woman's risk about sevenfold.

• Modern reproductive patterns mean about four times more retrograde menstruation than 200 years ago.

About 90% of women have some menstrual flow back through the tubes into the pelvis, but only those whose immune system (macrophages) can't clear it seem to develop disease. A woman two centuries ago, with first period at 16, first pregnancy at 20, five to seven children and two years of breastfeeding each, had around 100 cycles; today's woman has about 400. Tomioka sees hormonal suppression partly as a way to mimic that ancestral pattern. Microplastics, pollution, diet and poor sleep are suspected but unproven contributors to rising rates.

• Lesions make their own estrogen, resist progesterone and carry cancer-type mutations, but don't spread like cancer.

They overexpress aromatase, so suppressing the ovaries isn't always enough, and their progesterone receptors are downregulated, much like insulin resistance. Up to 37% of deep lesions and adenomyosis carry KRAS or PIK3CA mutations. Tomioka's analogy: a 1,000-horsepower F1 engine in a golf cart, because surrounding fibrosis and adhesions stop it from metastasizing.

• Adenomyosis, endometrial tissue inside the uterine muscle, is a separate disease affecting perhaps 20–30% of women.

It shares estrogen dominance, progesterone resistance and the same mutations, but single-cell studies show different molecular pathways. Up to 70% of women with endometriosis may also have some adenomyosis. The model is 'tissue injury and repair': the junctional zone between endometrium and muscle is breached, with miscarriage, C-section, curettage and hysteroscopy as risk factors. Once seen mainly in women in their 40s, it now shows up in younger women who have never been pregnant. It mostly causes heavy bleeding and anemia; only hysterectomy cures it.

• The '6 Ds' of endometriosis.

Dysmenorrhea (period pain that painkillers don't fix, sometimes needing IV drugs in the ER), deep dyspareunia (pain with intercourse), dyschezia (pain with bowel movements), dysuria (cyclic pain with urination), difficulty conceiving, and dysfunctional chronic pelvic pain lasting over six months. About 10% of women with endometriosis have no symptoms, or their only sign is infertility.

• Pain has three layers, and the third outlasts the disease.

Nociceptive pain from the lesion responds to surgery and hormones. Neuropathic pain from nerves invaded by lesions may need gabapentin or SNRIs and nerve-sparing surgery. Nociplastic pain (central sensitization) can persist even after a perfect surgery. Tomioka's analogy: surgery removes the burglar and hormones lock the door, but after years of ringing the rewired alarm goes off in the wind. Diagnostic delay drives that rewiring.

• Diagnosis takes 5–12 years (about 6 in the US, 7 in Brazil), and a normal routine ultrasound doesn't rule it out.

The reasons are normalization of women's pain, no blood biomarker, and a tradition of diagnostic laparoscopy. A specialist 'detailed protocol' transvaginal ultrasound with bowel prep (enema an hour before, low-residue diet, vaginal gel) can show bowel-wall layers and uses the 'sliding sign'; it takes about an hour, so few US centers offer it. MRI (non-contrast T1/T2) is also highly sensitive (around 95–98%) and better for the diaphragm and pelvic side walls but weaker for bowel lesions. Tomioka uses both before surgery.

• Hormonal therapy is first-line for pain, because surgery alone tends to recur.

For a 20-year-old not trying to conceive, start with a low-dose combined or progestin-only pill, or a hormonal IUD (Mirena or Kyleena) if she has no endometrioma and no myofascial pain, and reassess in 3–6 months. Without medication after surgery, recurrence runs about 10% a year, largely disease too small to see. One study found a Mirena after surgery cut recurrence by about 88% versus placebo. Treat it as a lifelong chronic disease, not a one-off procedure.

• Endometriosis infertility is mainly mechanical, and age outweighs everything.

Adhesions damage tube function. Older donor-egg studies found similar implantation and live-birth rates with or without endometriosis, though affected women yield fewer eggs and need more IVF cycles. Aneuploidy, mostly from egg meiosis errors, runs about 20–25% at 25, 30–35% at 30–34, about 40% at 35, 60% at 38, 70% at 40 and 80–85% after that. Very young women also have slightly more monosomies, so the curve is J-shaped with a sweet spot around 25.

• Adenomyosis lowers IVF success by about 30%, but pre-transfer suppression helps.

Failures often come at 6–8 weeks, as junctional-zone contractions expel the embryo; involvement of the junctional zone triples miscarriage risk. Two to four months of a GnRH agonist (Lupron or goserelin) before a frozen transfer, then low estrogen and high progesterone, raises implantation and live birth rates. The oral antagonists elagolix and relugolix look similar in one study but cost about $1,000 a month.

EXAMPLES

• Removing endometriomas can cut AMH by 40–50%.

These pseudo-cysts cling to the ovarian cortex where the primordial follicles sit, so stripping them takes healthy eggs too, yet the cysts also burn out follicles through iron-driven oxidative (Fenton) damage. Tomioka's answer: freeze eggs or embryos first,

then operate if the cyst is over 5–6 cm or causing pain, bowel obstruction, ureter involvement or appendix lesions.

- **A silent ureteral lesion cost one patient a kidney.**
  The endometriosis blocked her ureter and caused hydronephrosis, and a urologist removed the kidney. It's one of the 'operate even without symptoms' red flags.
- **Only about 10% of women who freeze eggs ever come back to use them.**
  In Brazil one cycle costs about $5,000 (roughly a third each for drugs, clinic and lab) plus about $150 a year storage. About 15 eggs at 25 give over 80% odds of at least one baby. Tomioka thinks 32–35 is more cost-effective; Attia argues that at 25 the downside is capped. Tomioka's typical social-freezing patient is 37–38.
- **The 40-year-old's funnel.**
  An AMH of about 1 ng/mL may yield about 8 eggs: about 75% mature, 30–60% reach blastocyst, and most of those are aneuploid, leaving perhaps one or two usable embryos. Attia calls it multiplying small numbers.
- **Mitochondrial replacement isn't 'egg rejuvenation'.**
  Two NEJM papers from a Newcastle group covered 22 patients with mitochondrial disease. Swapping the cytoplasm doesn't fix chromosome errors in the nucleus, which Tomioka calls 'a battery swap, not a new engine'. He sees eggs made from stem cells as about 10 years away.

OTHER RELEVANT

- **Push for a diagnosis if you have the 6 Ds.**
  Ask for MRI and, ideally, the bowel-prep specialist ultrasound. New 2025/26 ACOG guidance allows diagnosing and treating on symptoms alone, which may prevent progression and central sensitization in teenagers (50–75% of teens with pelvic pain have endometriosis).
- **Avoid the classic surgical mistakes.**
  Don't operate expecting to fix central sensitization; do about 8 weeks of pelvic-floor physical therapy before surgery and resume it 2–4 weeks after. Freeze eggs before removing endometriomas. Remove a damaged, fluid-filled tube (hydrosalpinx), which halves IVF success.
- **Don't delay at 40-plus by chasing natural conception after surgery.**
  Age is the dominant factor, and doctors underplay it. Check AMH early if you want children later.
- **A treatment that isn't hormonal may be coming.**
  HMI-115, a monoclonal antibody against the prolactin receptor, is in phase 3 trials for endometriosis pain.

396 – Breast cancer screening: understanding risk, deciding when to start, and more

Date: 2026-06-15 · Duration: 0:50:44
URL: https://www.youtube.com/watch?v=_9mBlZXA1Lk

KEYPOINTS

• Screening works, but under-screening is the fixable reason women still die

About 1 in 8 US women develop invasive breast cancer and roughly 42,000 die each year. Stage 1 disease has over 96% ten-year survival versus about 30% five-year survival at stage 4, and regular screeners are up to 40% less likely to die of it. Peter estimates only ~7–10% of cases are biologically aggressive enough to evade even perfect screening; the bigger, solvable problem is that roughly a third of women over 40 haven't had a mammogram in two years and ~20% of 50–74-year-olds aren't up to date.

• The MRI gap is a pure execution failure

At least 9% of women meet guideline criteria for screening MRI, yet actual utilization is about 0.4%. Peter stresses MRI isn't controversial for these women — the high-risk group is identifiable and the tool exists; the system simply fails to connect the two, partly because insurance follows USPSTF guidance that doesn't address high-risk women.

• Guidelines disagree because they answer a population question

The composite from the American Cancer Society, NCCN and American College of Radiology: formal risk assessment by about 25, annual mammography from 40 for average risk, earlier MRI for high risk, and screening as long as you'd accept treatment. The outlier is the USPSTF — biennial mammography for ages 40–74 — which balances cost and false positives across millions. Peter's framework for individuals: know baseline risk, decide your false-positive tolerance, then pick modality and frequency.

• Risk is usually many small inputs, not one red flag

Beyond sex (1 in 8 women versus about 1 in 750 men) and age (median diagnosis ~62), factors include BRCA1/2 (only ~1 in 400 people, more in Ashkenazi Jewish ancestry), family history (which also captures low-penetrance variants and can show up as prostate or pancreatic cancer), ancestry (Black women diagnosed younger with more aggressive subtypes), prior high-dose chest radiation such as adolescent Hodgkin's treatment, density, reproductive factors and modifiable ones like alcohol, obesity and inactivity. Calculators such as Tyrer-Cuzick combine these; lifetime risk above 20% is generally 'high risk'.

• Breast density is both a risk factor and a blind spot

Dense tissue modestly raises risk and makes mammograms harder to read because tumors and dense tissue both appear white. About half of screening-age women are dense (BI-RADS C or D), and the FDA now requires centers to notify women. The catch-22 is you usually learn your density only once screening starts, but it is roughly 60–70% heritable, so a mother's or grandmother's density is worth asking about.

• False positives are real but mostly cost anxiety

About 10% of US screening mammograms trigger a callback, and only ~5% of callbacks end in cancer — roughly 95 of every 100 recalled women don't have it. More than half of women screened annually for 10 years get at least one false positive. The higher your baseline risk, the easier it is to justify that burden; for average-risk women it's a preference call.

• There is a clear hierarchy of imaging tools

Mammography — ideally 3D tomosynthesis (DBT), which detects more cancer with fewer recalls, especially in dense breasts — is the foundation and is best at calcifications like DCIS (25–60% of which may become invasive). MRI with gadolinium is the most sensitive tool and supplements rather than replaces mammography. Contrast-enhanced mammography is the backup when MRI isn't feasible. Ultrasound adds the least consistent value and is the most operator-dependent.

• Abbreviated MRI is the most underused tool

Peter says the abbreviated protocol keeps nearly all of full MRI's sensitivity in 10–15 minutes instead of 30–60, making it cheaper and more scalable. In women with extremely dense breasts, adding MRI after a negative mammogram halved interval cancers from 5 to 2.5 per 1,000.

• Screen annually if you're optimizing for your own survival

No RCT compares annual versus biennial screening on mortality; it rests on CISNET modeling. The 2009 analysis (film mammography) found biennial kept ~81% of the benefit with half the false positives — an efficiency argument. The 2024 CISNET analysis with digital and DBT showed annual screening from 40–79 cut mortality 42% versus 30% biennial. Per exam, false positives were actually lowest with annual screening, likely because radiologists have a recent comparison image.

• Starting age depends on risk more than the calendar

Only ~5% of diagnoses occur under 40 and cumulative risk to 40 is under 1%; registry incidence rises smoothly with no spike at 40, so low early incidence looks real. But younger women get more aggressive disease — about 20% triple-negative under 40 versus 6–12% after — and triple-negative tumors can double in under four months.

• Inflammatory breast cancer and symptoms bypass the screening logic

Inflammatory breast cancer (1–5% of cases) often has no lump — instead swelling, redness, warmth or skin thickening — and may not show on a mammogram, so a normal screen doesn't rule it out. Any new symptom, in women or men, warrants prompt diagnostic evaluation rather than waiting for the next screen.

EXAMPLES

• 2024 CISNET numbers: 230 vs 165 life-years

Versus no screening, annual mammography for women 40–79 gained 230 life-years per 1,000 women versus 165 for biennial. Peter's point: other cancer and radiology groups read the same CISNET data as favoring annual screening; the biennial case is about population efficiency.

• Interval cancers: 11% vs 38%

Observational data among women 40–84 who developed breast cancer: annual screeners had 11% interval cancers versus

38% for biennial, and 76% versus 56% were diagnosed at stage 1.

- **6-million-mammogram study under age 40**
  Among women 35–39 with at least one risk factor (personal history, first-degree family history or dense breasts), detection was 2.1 per 1,000 versus 0.59 for average-risk peers — about 3.5-fold — and higher than the 0.71 per 1,000 in average-risk women 40–44. Peter's takeaway: risk factors can shift a woman's screening profile forward by a decade.
- **Ultrasound depends on what it's added to**
  Physician-performed handheld ultrasound added to 2D mammography found 4.2 extra cancers per 1,000; technician-performed ultrasound added to DBT found only about 1.1 per 1,000.
- **BRCA1 risk is front-loaded**
  A BRCA1 carrier in her late 20s has roughly 100 times a non-carrier's risk, about 44 times in her 30s and about three times in her 60s — which is why MRI, not mammography alone, suits young high-risk women.

OTHER RELEVANT

- **Do a formal risk assessment in your mid-20s**
  Use a validated calculator (Peter mentions Tyrer-Cuzick) early enough to change the plan; you don't want to learn at 42 that you should have started MRI years before.
- **Find out your density — consider a baseline mammogram in your 30s**
  Peter admits there's no direct evidence, but a single 30s mammogram mainly for risk stratification can reveal density that would change your strategy.
- **Match modality to risk and go to an experienced center**
  Average risk: annual mammography, preferably DBT, from 40. Elevated risk or dense breasts: add MRI (abbreviated is often enough), or contrast-enhanced mammography if MRI isn't possible. High-volume dedicated breast centers interpret more consistently, especially for MRI and ultrasound.
- **Alternating tests every six months is reasonable, not mandatory**
  Many high-risk women do mammography and MRI six months apart; evidence for alternating versus stacking is thin and inconclusive. Consistency matters more than scheduling.
- **Don't let a recent normal screen delay a symptom check**
  New lumps, skin changes, nipple discharge or persistent pain — in women or men — need in-person evaluation now.

395 – Brain lipidology: understanding APOE, cholesterol homeostasis, Alzheimer’s disease, & more

Guest: Dr. Tom Dayspring
Date: 2026-06-09 · Duration: 1:44:10
URL: https://www.youtube.com/watch?v=KWNgAyurXFY

KEYPOINTS

• The brain runs its own cholesterol system, almost completely separate from the blood.
Lipidologist Tom Dayspring's central point: apoB particles (LDL, VLDL) are far too big to cross the blood-brain barrier, so how much cholesterol is in plasma has 'zero to do with' brain cholesterol. A 2-year-old with LDL around 30 mg/dL is building brain tissue faster than at any other point in life, which shows that low circulating cholesterol doesn't starve the brain. That undercuts the common fear that drug-lowered LDL harms cognition.

• LDL's main job is bringing cholesterol back to the liver, not delivering it to cells.
Every cell can make all the cholesterol it needs. HDLs (about 90% of all lipoprotein particles) pick up excess cholesterol, then hand much of it to long-lived LDLs (3–5 day lifespan), which the liver clears through LDL receptors. This is indirect reverse cholesterol transport. When LDL falls, cells are simply in balance and less cholesterol needs returning.

• Plasma holds only a sliver of the body's cholesterol; the brain holds the most.
Of roughly 140 g of cholesterol in the body, the brain holds about 20–25 g versus 3–5 g in the liver, which is a transfer station rather than a vault. Brain cholesterol has a half-life of about five years, versus days in the periphery. Red blood cell membranes carry more blood cholesterol than lipoproteins do. Halving plasma cholesterol from 200 to 100 cuts total body cholesterol by only a couple of percent.

• Atherosclerosis comes from apoB particle number, mainly through poor clearance.
Above a threshold concentration, apoB particles diffuse into even healthy artery walls, get trapped, oxidize and are engulfed by macrophages that become foam cells. Every trial and Mendelian randomization study shows that lowering apoB lowers events. Insulin resistance, inflammation, blood pressure, smoking and autoimmune disease make entry easier. The rare 90-year-old smoker with high LDL and no plaque is genetically lucky, and Dayspring warns nobody can know in advance whether they're one of them.

• After about age 10, neurons stop making cholesterol and outsource it to astrocytes.
Building one cholesterol molecule takes 37 enzymatic steps and over 30 ATP, and neurons need their energy for firing. Oligodendrocytes make about 70% of brain cholesterol, mostly for myelin; astrocytes package cholesterol onto apoE into HDL-sized 'brain HDLs' that travel through the brain's tissue matrix. Neurons take them up mainly through LRP1 (which recognizes only apoE), plus LDL receptors and SR-B1. Dayspring suggests calling the LDL receptor the 'apoB/apoE receptor'.

• Plasma desmosterol tracks brain cholesterol synthesis; 24S-hydroxycholesterol signals neurons getting rid of excess.
The periphery mostly uses the lathosterol pathway, while astrocytes use the desmosterol (Bloch) pathway, so blood desmosterol correlates closely with levels in spinal fluid and brain. Neurons convert surplus cholesterol into water-soluble 24S-hydroxycholesterol, which crosses the barrier and goes to the liver for excretion. Rising plasma levels suggest a neuron under stress; only research labs measure it.

• APOE4 makes dysfunctional brain HDLs, disturbing neuron membranes and tilting APP processing toward toxic amyloid-;#C"à
Peter's numbers: about 55% of people are E3/E3, 20–25% E3/E4, 1–2% E4/E4, and E2/E2 is under 0.5%. One E4 copy roughly doubles Alzheimer's risk (some series say triples); two copies are now usually put at 8–12x, down from older estimates of 20–25x. E4 particles bind neuron receptors poorly, so cholesterol lodges in membranes but doesn't reach the cell interior. Membrane cholesterol excess favors beta/gamma-secretase cleavage of APP into A;#C" ðver the alpha-secretase route; brains with Alzheimer's at autopsy are cholesterol-overloaded.

• Statins are the only lipid drugs that reach the brain, and randomized trials show neutral or beneficial cognitive effects.
Lipophilic statins enter faster, but at steady state hydrophilic ones like rosuvastatin get in too, so Dayspring doesn't pick a statin by solubility. Peter's earlier review of meta-analyses found neutrality or improvement for MCI and dementia, though dementia was always a secondary outcome. The hypothesis: modestly slowing brain synthesis may help, while oversuppression may explain the occasional statin 'brain fog' that clears when the drug stops.

• HDL's real value is its protein cargo and immune function, not its cholesterol count.
More than 200 proteins have been found on HDL particles, each particle carrying one or two. The tiniest, protein-laden apoA-I species can cross the blood-brain barrier and join apoE brain HDLs, possibly delivering anti-inflammatory and antioxidant proteins. No commercial test measures whether HDL is functional or dysfunctional.

EXAMPLES

• A study from about a decade ago: low desmosterol tracked with cognitive impairment.
Using mass spectrometry, researchers found plasma desmosterol closely matched spinal-fluid levels, and people with low desmosterol had more cognitive impairment and Alzheimer's. Dayspring proposes watching desmosterol in statin-treated patients, especially E4 carriers. If it's oversuppressed, lower the dose or switch to other apoB-lowering drugs.

• BROADWAY trial: obicetrapib moved Alzheimer's biomarkers.
NewAmsterdam Pharma's CETP inhibitor was tested to lower apoB and cardiovascular events, but biomarkers including phosphorylated tau and the amyloid 42/40 ratio moved favorably. People with genetic CETP loss of function have less Alzheimer's. The proposed mechanism: the liver overproduces apoA-I, which may enter the brain and 'rescue' E4 brain HDLs. It isn't FDA-approved; cognitive trials are expected, led by John Kastelein and Michael Davidson.

• Ezetimibe's metabolite may reach the brain.

Ezetimibe works in the gut and can't cross the barrier, but its glucuronide metabolite enters in small amounts and, in animals, reduces protein glycosylation and brain inflammation. Neurologists Richard Isaacson and Kellyann Niotis report anecdotal cognitive benefit. Dayspring suggests using banked serum from ezetimibe trials to check p-tau.

• PREDIMED as a model for trial design.

Peter expected a dietary primary-prevention trial to fail, yet Mediterranean versus low-fat was stopped early. Choosing people 'about to drive off the cliff' gives answers within a few years, which is how he thinks the obicetrapib and E4 cognition trials should be built.

OTHER RELEVANT

• Don't avoid low LDL out of fear for your brain.

Cholesterol in the brain is made locally. In Peter's practice they often combine a low-dose statin with ezetimibe, and use ezetimibe from day one in people who absorb a lot of dietary cholesterol, after testing synthesis and absorption markers.

• If you carry E4, consider tracking plasma desmosterol on a statin.

This is a plausible strategy but not trial-proven. A low value suggests possible oversuppression of brain synthesis. Statin brain fog that clears on stopping is a signal to adjust.

• Omega-3s: aim for an omega-3 index of about 8–9%; going higher is guesswork.

The brain takes up DHA and EPA mainly as lysophospholipids through a specific transporter at the barrier, so the supplement form matters less than checking the label is accurate. Brain evidence is observational (Bill Harris links the index to brain volume). Dayspring sees little downside.

380 The seed oil debate: are they uniquely harmful relative to other dietary fats?

Guest: Layne Norton
Date: 2026-01-19 · Duration: 2:25:58
URL: https://www.youtube.com/watch?v=iB49uq-t1UM

KEYPOINTS

• This was meant to be a pre-registered 'courtroom' debate; when the opposing expert withdrew, Attia steelmanned the anti-seed-oil case himself.

Over about a year, both sides were to pre-submit every paper so nothing could be asserted that couldn't be checked live. Attia stated his lean upfront: he doesn't see much here. Norton noted his own possible bias ran the other way—he trained in a low-carb-leaning lab and was funded by the National Dairy Council, Cattlemen's Beef Association and Egg Board.

• Attia framed four arguments that seed oils are uniquely harmful.

(1) Some old RCTs that swapped saturated fat for polyunsaturated fat lowered cholesterol but not mortality. (2) Linoleic acid makes LDL more oxidisable and fuels arachidonic-acid inflammation. (3) Industrial refining—heat, hexane—adds harm. (4) Evolutionary mismatch: linoleic-acid availability rose from under 3% of food to roughly 10%, and tissue levels more than doubled.

• The 'harmful' RCTs are confounded by trans fat from margarine.

In the Minnesota Coronary Experiment (1966–73, ~9,000 institutionalised patients), the polyunsaturated arm used corn oil and margarine. Margarine then contained about 25–40% trans fat, which is clearly atherogenic and now effectively banned. Each 30 mg/dL fall in total cholesterol came with roughly 22% higher mortality. Results waited about 13 years for publication. Patients could also check themselves out of wards, and average exposure was only 1–2 years.

• Saturated and trans fats pack straight, making stiffer particles; cis double bonds kink and loosen them.

Trans bonds keep chains straight like saturated fat but still carry an oxidisable double bond—'the worst of both worlds.' Membrane fluidity matters downstream for LDL-receptor recognition and for how readily particles aggregate in the artery wall.

• When trans-fat-confounded trials are removed, swapping PUFA for saturated fat reduces risk.

Lumping all trials together gives a null effect. Ramsden's reanalysis removing omega-3-confounded trials shows a trend to harm—but still includes trans fat. A 2017 analysis excluding trans-fat trials found roughly 29–31% lower risk. Norton insists on 'logical symmetry': if you remove one side's confounders, remove the other's.

• Mendelian randomisation shows lifelong LDL exposure is causal and dose-dependent.

About a dozen variants affecting LDL clearance, production or absorption all give the same effect. Each 1 mmol/L (~39 mg/dL) lower LDL brings about 50–55% lower cardiovascular risk, with R above 0.9. That consistency makes pleiotropy unlikely. CETP variants underdeliver because cholesterol falls more than apoB. The same genetics showed LDL has no causal link to cancer.

• Statins give ~22% per mmol/L, not 50%, because of timing, not hidden harm.

Statins usually start around 40 or later, after decades of exposure; genetic variants act from birth. Norton uses compounding-investment and 'truck rolling downhill' analogies. He runs LDL around 150 despite a high-fibre, low-saturated-fat diet, and started a statin at 40.

• Linoleic acid doesn't measurably raise arachidonic acid or population heart disease.

Cohorts of roughly a million people, and tissue biomarker studies that avoid recall error, link higher linoleic acid to lower cardiovascular disease. Conversion to arachidonic acid seems saturated, so eating more doesn't feed forward. Healthy-user bias would blunt a harm signal, not flip it to protection.

• Oxidation mostly happens inside the artery wall, so fewer particles getting in beats slightly more oxidisable particles.

Under 1% of plasma LDL is oxidised; particles clear in hours and plasma is rich in antioxidants. Once apoB-particles under ~70 nm cross the endothelium and bind proteoglycans, an estimated 30–80% may oxidise over weeks. PUFA-rich LDL is fewer in number, less prone to apoB modification, and less prone to aggregation than saturated-fat-rich LDL. Saturated-fat LDL is acted on by sphingomyelinase, making ceramides that drive clumping. Antioxidant trials failing fits this picture.

• Refining residues are far below harmful doses, and refining actually lowers oxidation products.

Hexane boils at about 69 °C and is steam-stripped under vacuum. Residues run around 0.05–0.5 ppm, often undetectable. Norton calculates about 11,340 kg of oil at once for even mild hexane effects, and hexane doesn't bioaccumulate. Refining cuts peroxides 5–10-fold and lowers aldehydes. It adds about 0.5% trans fat and some polymerised triglycerides.

• The ancestral argument cuts both ways.

Modern beef isn't ancestral either, and cardiovascular disease rose largely because people now live long enough to get it. The Hadza, our best ancestral proxy, have LDL around 50–70 mg/dL, with only one individual found above 100. 'Natural' isn't a reliable guide to longevity.

EXAMPLES

• Sydney Diet Heart Study

About 500 men after a heart attack moved from 16% saturated fat and 6% PUFA to 10% and 15%, using safflower oil and safflower margarine. There were 37 deaths versus 28 (CI about 1.03–2.8), the only significant harm signal, again with heavy trans fat.

• Rose Corn Oil trial

About 80 patients, with cardiac deaths of 1 (control), 3 (olive oil) and 6 (corn oil); hazard ratio 4.64, CI 0.58–37. Olive oil 'tripling' deaths shows the noise.

• Finnish Mental Hospital Study

A crossover of two hospitals, about 1,200 people, six years on each diet: 9% saturated and 14% PUFA versus 18% and about 4%. No trans or omega-3 confounding; about 41% fewer cardiovascular events. Weakness: randomised by hospital, not individual.

- **LA Veterans study and STARS**
  About 850 veterans for nearly nine years showed 18% lower risk (CI 0.56–1.21). STARS tracked plaque progression rather than events.
- **Frying-oil caveat**
  Thin layers of oil, or oil reused all day, generate oxidised and trans products within 20–30 minutes. A 5 cm depth oxidises far more slowly than 1 cm.

OTHER RELEVANT

- **If you avoid seed oils, still cut saturated fat**
  Use olive or avocado oil and leaner proteins, eat plenty of fibre, and measure apoB.
- **Don't treat lard-fried fries as health food**
  Both options are poor; marketing 'tallow' or 'no seed oils' mainly persuades people to eat more. Neither guest could say which is worse for occasional fries without trial data.
- **Mind the substitution effect**
  Cutting seed oils often helps because you cut chips, cookies and junk sauces—not because of the oil. Canola in a home salad dressing is fine.
- **Major in the majors**
  Norton notes Americans average about 3,500 kcal a day and under 20 minutes of activity. Obesity, fitness and strength carry far larger mortality effects than oil choice. Attia's verdict: we're 'majoring in the minor.'
- **Read the study, not the hot take**
  Weigh converging lines of evidence—mechanisms, cohorts, clean RCTs and Mendelian randomisation—over any single surprising trial.

378 Women’s health & performance: how training, nutrition, & hormones interact across life stages

Guest: Abbie Smith-Ryan
Date: 2026-01-05 · Duration: 2:24:21
URL: https://www.youtube.com/watch?v=CDsH60jt34o

KEYPOINTS

• Osteoporosis starts in childhood, so early play and lifting matter

Peter recalls a prior guest's line that osteoporosis is a childhood disease: women hit their genetic bone-density ceiling around 19 and spend the rest of life defending it. Abbie Smith-Ryan argues for broad, varied play and multiple sports rather than early specialization, plus resistance training as injury prevention — she loved Romanian deadlifts at 11 or 12 — using bands, light weights, plyometrics and med balls.

• Intense training that delays puberty costs bone, and asymmetric sports leave marks

Gymnasts, runners, swimmers and cyclists can have delayed periods, often from unintentional underfueling, and that delayed estrogen harms bone. In 15 years of DEXA scanning at UNC, Abbie says nearly every high jumper and gymnast shows a distinct spinal curve, often unknown to them — not fixable at 18–20, but something to stabilize with musculoskeletal work.

• Young female athletes need to be taught food as fuel

Rather than food rules, Abbie emphasizes adequate energy, with calorie-dense swaps (whole milk instead of skim, full-fat yogurt, nuts, seeds) for girls who can't eat much before early practice. Exercise blunts hunger, and GI distress — sometimes linked to the menstrual cycle — is common, so intake must be planned. She pushes back on the trend of protein-centric, low-carb messaging for young female athletes.

• You can train in any cycle phase; women just feel different

Her lab's data says performance largely holds across the cycle, but women feel worse in the late luteal phase: fatigue, bloating, poorer recovery and soreness. The early follicular phase brings more carbohydrate oxidation and feeling good; late follicular around ovulation is when women typically feel their best. Peak performance seems preserved; recovery is what to manage.

• Late luteal phase: prepare for the progesterone crash

Thermoregulation, water retention, inflammation and protein breakdown rise, and resting energy expenditure increases by roughly a couple hundred calories a day — just as women often eat less and the scale rises from water. Strategies Abbie mentions for symptomatic women: 2–3 g omega-3s, zinc and magnesium for sleep, more fruit and vegetables, caffeine (possibly more helpful in this phase) and creatine.

• Creatine moved fluid into cells in the luteal phase

Her lab compared phases and found creatine shifted extracellular fluid into the cell, helping with bloating and indirectly performance. Studies load at 20 g/day (four 5 g doses) for 5 days then 5 g/day; she notes midlife and brain-health data go up to 10 g. Peter says after talking with Rhonda Patrick his practice moved maintenance from 5 to 10 g. Abbie cautions creatine is helpful but not magic or the first lever for midlife women.

• Protein of about 1.6 g/kg removes most cycle concerns

A paper in review on muscle protein synthesis across the cycle suggests adequate protein (~1.6 g/kg) and amino acids around training make phase differences minor. Peter targets 2 g/kg so that misses still clear 1.6, admitting a week in Asia left him nearer 1.2. Vegetarians or older women should pay extra attention in the luteal phase.

• Perimenopause is the critical window

Abbie's work following up on the SWAN cohort finds the biggest changes in metabolism, muscle size and quality, bone and metabolic flexibility occur during perimenopause rather than after. Peter suggests tracking day-5 FSH (day 1 = period start): low when fertile, around 10 signals the transition, 25–50+ in menopause. Abbie's lab also uses daily at-home urine hormone tests to see day-to-day swings.

• Muscle quality, not just size, declines — 'ribeye versus filet'

In a two-year longitudinal study, women who followed guidance maintained muscle size but still lost quality (measured by ultrasound and pQCT, consistent with MRI), echoing Australian work by Séverine Lamon. Peter notes whether fat is intra- or intercellular matters for insulin resistance. HIIT improved metabolic flexibility regardless of hormones, and protein around exercise didn't blunt the post-exercise insulin response.

• Body composition, not weight, should be the goal

Abbie measures composition (DEXA, multi-frequency BIA or a home scale), aiming for body fat around the 25th NHANES percentile or lower, away from the 50th. For Peter's hypothetical 5'6", 150 lb, 30%-fat 40-year-old wanting 130 lb, she'd suggest ~140 lb, a modest deficit, more fiber, ~30 g protein spaced through the day, and complex carbs. She warns chronic time-restricted eating in midlife can lower metabolism and hurt protein synthesis.

• GLP-1 drugs demand resistance training and high protein

On tirzepatide or semaglutide, she'd prioritize lifting and 130–150 g protein (based on goal weight), plus amino acids around workouts. Peter prefers the lowest dose for the longest time (2.5–5 mg tirzepatide over a year); Abbie is studying checking lean mass before titrating up. She flags low energy availability on these drugs can mimic perimenopausal symptoms and may explain bone loss.

• Power declines first and matters most for falls

Citing Andy Galpin, Peter calls type 2 fiber hypertrophy central to aging: power goes first, then strength, then size. The stumbled curb is his example of why power matters. Abbie notes women may lose type 2 characteristics faster, and midlife joint pain complicates plyometrics — which Peter believes hormone therapy would often relieve.

EXAMPLES

• Nine stress fractures below ~15% body fat

As a 5'6" D2 distance runner (~115–120 lb), Abbie had nine stress fractures, all left leg/foot, each time she dropped below about 15% fat, while amenorrheic. Her bone density was actually high; she attributes it to fueling gaps and long fasting windows between twice-daily sessions.

- **Three-hour weekly plan for a busy midlife woman**

  Two 30-minute full-body lifts (6–8 reps at 60–80% 1RM, 30 s between exercises, 2 min between rounds), plus HIIT and easy cardio. For a GLP-1 recomposition case, she settled on three strength days, one HIIT and two low-intensity days, all 30 minutes.

- **10 × 1 minute on, 1 minute off**

  Her go-to HIIT, used from fit people to cancer patients: up to 10 one-minute efforts at roughly 90–110% of VO2max-level intensity — practically, a pace you couldn't hold for 1:20 — starting with six. Peter prefers RPE or ergometer power over heart rate for short intervals.

- **Pregnancy and postpartum self-tracking**

  She gained about 8% body fat per pregnancy without losing muscle, was back to baseline about six months postpartum while breastfeeding, and is unchanged eight years after her second child. She lifted (squats, lat work) until delivery, walked within days and lifted lightly within weeks.

- **Only ~19% of women resistance train**

  She cites a Bill Kraemer paper: about one in five women lift, typically once a week.

OTHER RELEVANT

- **Match time to intensity**

  Peter's reading: with lots of time, volume dominates; with ~2–3 hours a week, intensity must carry the load, so short sessions can't be phoned in. Many people who think they're doing zone 2 are really in zone 1.

- **Track your cycle and give yourself grace**

  Knowing your bleeding pattern and phase helps separate hormonal dips from problems needing a change in nutrition, medication or recovery.

- **Starting at 70 is not too late**

  For a never-exercised 70-year-old, hire a referred trainer, use machines and bands, glute activation, a push-pull for each muscle group, calves, three lifting days plus daily movement, and add submaximal carries (a minute on, a minute off).

- **Don't accept 'no' on hormone therapy**

  Peter calls the hormone-therapy retreat medicine's biggest error of the past 25 years and, citing Rachel Rubin, says being 60 and 10 years past menopause isn't automatically disqualifying; seek a competent prescriber.

#377 Special episode: Understanding true happiness and the tools to cultivate a meaningful life

Guest: Arthur Brooks
Date: 2025-12-22 · Duration: 1:38:44
URL: https://www.youtube.com/watch?v=2mbG7n5_yps

KEYPOINTS

• Happiness isn't a feeling; feelings are evidence of it.
Arthur Brooks, the social scientist who teaches Harvard's happiness course, distinguishes happiness from happy feelings. Emotions arise from a limbic system shaped over tens of millions of years of evolution. The average person spends about 40% of their time with predominantly positive feelings and about 16–17% with predominantly negative ones—and happiness and unhappiness can coexist.

• Negative emotions dominate attention by design.
Negative affect grabs attention because ignoring a threat could cost your life. The limbic system reacts first; about three seconds later the prefrontal cortex catches up ('I shouldn't have flipped him off'). Political contempt exploits the insula so opponents feel disgusting, and grief is the brain demanding a separation that can't be undone go away.

• Most adults rate themselves 7–9 out of 10, and a 5 is below the middle.
On an anonymous 1–10 scale (anonymity matters—people lie in front of spouses and friends), most adults from their early 20s to early 50s land between 7 and 9. A 5 is roughly the 40th percentile. Happiness generally declines from 28 to 38 to 48 for many people, contrary to what they expect.

• Happiness has three 'macronutrients': enjoyment, satisfaction and meaning.
The happiest people—the 8s and 9s—have all three in balance and abundance, like a good diet of protein, carbs and fat. You can't run on just one.

• Enjoyment is pleasure plus people plus memory; pleasure alone is dangerous.
Brooks notes beer ads never show a man alone pounding a 12-pack—they show friends laughing, selling enjoyment rather than pleasure. Pure pleasure supercharged becomes fentanyl (which he links to about 100,000 deaths a year) or slot machines at 4 a.m. Peter adds that Mendelian randomization suggests alcohol is harmful at any dose, though the Mediterranean, communal pattern shows some association with benefits.

• Satisfaction requires struggle and wears off quickly by design.
Students who earn an A through struggle get satisfaction; copying last year's exam gives none. A raise feels great until it shows up three weeks later and homeostasis resets. The hedonic treadmill echoes Buddhism's first noble truth—life is unsatisfying—and the second, that attachment causes the dissatisfaction.

• Meaning is the 'protein'—you can't substitute for it.
Brooks frames meaning as coherence, purpose and significance. He uses a two-question 'exam': why are you alive, and for what would you be willing to die? Flunking it starts the adventure of finding answers.

• Fame and success addiction hijack happiness.
Workaholism and the pursuit of worldly success often trade away relationships. Peter pushes back that society benefits from people who make enormous sacrifices; Brooks agrees highly successful people often succeed in spite of messy mental hygiene, not because of it.

• Metacognition lets you observe emotions rather than be run by them.
Brooks' practices include the 'reverse bucket list' (deciding what to stop wanting), rationing news to 15–30 minutes a day in one sitting, and not answering emails on days of very good or bad news so neurochemistry doesn't drive decisions. 'I need fewer opinions because I need more friends.'

• Transcendence 'makes you small'.
Whether secular or religious, transcendent experiences shrink the ego; Brooks quotes Steve Martin's 'get small.' He says science is one reason he's religious, while Peter, more agnostic, spends his time coming to grips with mortality.

• Understanding happiness works like understanding health: no single biomarker, many inputs.
Peter draws the parallel explicitly—he tracks VO2 max, strength and body composition for longevity, and Brooks' philosophy of happiness is 'all one thing' with it. Brooks admits there's no clean biomarker for happiness the way there is for fitness, so he breaks the problem into dimensions (the macronutrients and their 'micronutrients' like family, friendship, faith and work) and tracks them. He compares the complexity to Formula 1: you wouldn't replace races with computer simulations just because racing is risky and messy.

• Don't chase emotional highs.
Brooks says the 'pro level' of self-management is not seeking highs, because highs don't add much to well-being. He uses the example of bipolar disorder, where patients often struggle to stay on medication because they miss the mania. The romantic notion that great artists need emotional chaos rests on spectacular cases; most succeed despite it.

EXAMPLES

• The 42° ice bath
Brooks says the cold plunge still hurts every day, but because he chooses it and sees value in it, it doesn't come with 'I hate this'—his model for voluntary discomfort.

• The class that fills in nine seconds
His Harvard elective is competitive; students spend their elective points to get in.

• Peter's smoking
Peter's wife smokes twice a year with her sister; Peter can't, because he got 'the monkey on his back immediately' and stripped the pleasure out of tobacco to quit.

- **Love your enemies**
  Brooks cites Martin Luther King's sermon on Matthew 5:44: love is a decision, not a sentimental feeling—what happens between spouses too.
- **60% happier**
  Brooks says his well-being has risen about 60% in four years, testing every practice before writing about it, 8–9 weeks ahead in his Atlantic column.

OTHER RELEVANT

- **Audit your three macronutrients.**
  Ask whether you're short on enjoyment (shared experiences), satisfaction (earned achievement) or meaning—and stop trying to fix one with another.
- **Choose enjoyment over isolated pleasure.**
  Pair indulgences with people and memories; solitary pleasure-seeking is where addiction lives.
- **Practice a reverse bucket list and ration news.**
  Reducing wants and inputs lowers dissatisfaction more than accumulating achievements. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Accept suffering as part of a full life.**
  'If it feels terrible, make it go away' is a poor motto; some suffering builds meaning.
- **Balance the 'I self' and the 'me self'.**
  Brooks describes the observing self and the self-conscious, socially compared self; you need both—social comparison and even envy evolved for survival—but metacognition keeps the comparing self from running your life.

375 - The ketogenic diet, ketosis, and hyperbaric oxygen: weight loss, cognition, cancer, and more

Guest: Dominic D'Agostino
Date: 2025-12-08 · Duration: 2:25:27
URL: https://www.youtube.com/watch?v=jW0cVEgW9YY

KEYPOINTS

• Dom D'Agostino came to ketosis through Navy oxygen-toxicity research

Navy SEALs use closed-circuit rebreathers with near-100% oxygen to avoid bubble trails, but below about 50 feet oxygen toxicity becomes possible and at ~100 feet a diver may seize within minutes. Oxygen acts as a stimulant: it drives glutamate release, inhibits the enzyme converting glutamate to GABA and bursts reactive oxygen species. Because ketogenic diets control seizures when drugs fail, D'Agostino pivoted to ketones; Duke trials now push volunteers in chambers to an EEG seizure and compare latency under dietary, supplemental or combined ketosis.

• Nutritional ketosis is defined by blood BHB above 0.5 mM

Fasting suppresses insulin, mobilizing fatty acids that the liver turns into beta-hydroxybutyrate and acetoacetate, which fuel the brain. The original epilepsy diet was ~90% fat; modern versions are 60–70% fat with more protein, because restricting protein stunted kids' growth. D'Agostino calls it the most researched diet with an objective biomarker, with 'pleiotropic' effects on metabolism, neuropharmacology and epigenetics.

• Ketogenic therapy works where seizure drugs fail

In drug-resistant pediatric epilepsy about two-thirds respond; of those roughly a third get 95–100% control, and 10–15% are 'super responders' who stay seizure-free after one or two years on the diet. Adults respond less (~30–40%), partly adherence. In brain slices, sodium BHB silenced evoked seizure activity and made neurons more resilient to toxins.

• For weight loss: high protein, fiber-carbs, and count calories

D'Agostino's mistakes list starts with not tracking. He recommends 20–30% protein (he eats up to ~220 g at 220 lb), up to 50–100 g carbs if about a third is fiber (broccoli, cauliflower, avocado, cucumber, asparagus — not carrots, tomatoes or most peppers), and a 10–20% calorie deficit. Tracking apps showed him eating ~4,000 kcal when he believed 3,200; 'calories don't matter on keto' is false.

• Watch lipids and certain genotypes

A strict keto diet sent his LDL and apoB soaring; he has an NPC1L1 variant, so a small dose of ezetimibe controls it. He's seen LDL and triglycerides rise and HDL fall in some people, especially APOE4 homozygotes, and urges tracking ApoB, LDL, triglycerides, HDL, A1c and insulin. Early on, cutting protein from ~250 g to 70–80 g cost him strength.

• Esters, salts and 1,3-butanediol are not the same thing

1,3-butanediol, a NASA-era food preservative, is metabolized by alcohol dehydrogenase like ethanol; ~150–200 mL/day for therapeutic ketosis doubled his liver enzymes over two weeks and can make people 'drunk stupid'. Esters bind BHB or acetoacetate to butanediol for a fast double peak. Salts ionically bind BHB to sodium, potassium, calcium and magnesium; he argues hypertension risk is tied to sodium chloride, not sodium BHB.

• Rapid ketone spikes trigger insulin and crashes

Rising above about 1.5–2 mM quickly prompts a counter-regulatory insulin release; two hours after a big ester dose people can be both hypoglycemic and low in ketones. Salts don't produce that effect in his experience. He says higher isn't better: above 2–3 mM from supplements approaches 'energy toxicity' and acidosis, and animals above 6–7 mM on some esters died. 1 mM BHB supplies roughly 10% more brain energy.

• D- and L-BHB behave differently

Meters and continuous ketone monitors measure only D-BHB. D is burned quickly for fuel; L is metabolized three to four times slower, accumulates in the brain and retains signaling effects such as NLRP3 inflammasome suppression. Pure D-BHB monoester didn't help seizures in his models; a 1:1 BHB-acetoacetate mix (redox balance) did.

• Cancer: a metabolic adjunct, still lacking trials

A 49-author framework led by Thomas Seyfried proposes a glucose-ketone index of 1–4 plus drugs targeting glucose and glutamine for glioblastoma. Pressed by Peter, D'Agostino concedes it won't cure GBM, the goal is extending survival, and there are no RCTs; funding now favors adjuncts to CAR-T and checkpoint inhibitors. Peter suggests pancreatic cancer may be a better first model.

• Alzheimer's: a fuel-rescue rationale with patient selection

Brain glucose use declines with age while ketone uptake is preserved (Stephen Cunnane's dual PET work). Acute ketone elevation improves cognition in impaired people, but long-term randomized amyloid outcomes are pending; D'Agostino would select patients with marked glucose hypometabolism.

EXAMPLES

• Keto Start salts on a road trip

One packet (6–10 g BHB, ~1 g electrolytes, 50/50 D/L) kept his measured D-BHB at 1–2 mM for four to six hours with sharp focus; true total may be roughly double. His wife advises the brand; he says he has no financial stake.

• Carbs in Greece, six pounds lighter

Tripling or quadrupling carbs on a Greek trip while swimming and walking daily, he came home six pounds lighter — evidence, he says, of metabolic flexibility.

• The Newport case and AC-1202

Samuel Henderson's 2008 caprylic-triglyceride product improved MMSE scores; Mary Newport gave her husband coconut and MCT oil, documented in a long case report co-authored by Veech.

• Hyperbaric oxygen protocol for acute concussion

Within 48–72 hours: about 2 atmospheres, 60–90 minutes, 3–5 days a week, up to 40 sessions. Peter calls that 'a job' and remains on the fence; soft chambers reach only ~1.3 ATA.

- **USF's $30 million sham-controlled trial**

  A DoD study in veterans with PTSD and brain injury uses a sham that pulses pressure at start and end, with assessors checking blinding, because a prior DoD study used hyperbaric air as control and both arms improved.

OTHER RELEVANT

- **Track food, ketones and lipids**

  Use an app occasionally, measure blood (or breath acetone with something like Keto Air), and check ApoB, triglycerides and insulin.

- **Transition over four to six weeks and bridge with ketone electrolytes**

  Keto causes sodium and water loss and a brain energy gap; ketone salts can ease the 'keto flu' and practitioners report better adherence with a gradual start.

- **Aim for 1–2 mM, not more**

  Pair a salt with MCT for sustained levels; avoid big ester or butanediol doses, especially in elderly people or those with liver disease.

- **Use fasting situationally**

  He now does five-day 'sardine fasts' and fasts for focus days or flare-ups rather than as a daily default.

374 - The evolutionary biology of testosterone: male development & sex-based behavioral differences

Guest: Carole Hooven
Date: 2025-12-01 · Duration: 2:25:41
URL: https://www.youtube.com/watch?v=rQ-LTW3c5vc

KEYPOINTS

• Sex is defined by gamete type; chromosomes determine it in mammals but don't define it across nature.
Hooven, a Harvard-trained evolutionary biologist who studied chimpanzees in Uganda, notes that birds use a different chromosome system and some reptiles use temperature. Across sexually reproducing species, sex means being organised around making sperm or eggs. That reproductive role coordinates body, hormones and average behaviour.

• XX and XY embryos are nearly identical until about weeks 5–6, when SRY switches the shared gonad toward testes.
The undifferentiated gonad can become either organ—evolution's way of not building two systems. Without SRY it becomes ovaries, though that is an active genetic process, not a passive 'default.' Testes then make testosterone, which keeps the Wolffian (male) ducts, and anti-Müllerian hormone, which removes the Müllerian (female) ducts.

• DHT gives a strong local androgen signal without flooding the fetus.
5; ×&VGV7F 6R 6öæ6VçG ated in genital tissue turns testosterone into DHT, roughly 2–5× more potent. DHT drives penis, scrotum and prostate development. In 5; ×&VGV7F 6R FVf–6–Væ7•, XY individuals may look female at birth but masculinise at puberty with normal testosterone, without facial hair or male-pattern baldness. Hooven says DHT isn't needed for male-typical muscle, which matters in sports-eligibility disputes.

• About 20% of genes on the 'silenced' second X escape inactivation, and that matters.
That partial double dose helps explain Turner syndrome (a single X): short stature, other features and usually sterility. The 70–100 Y-chromosome genes may also act in the brain before testosterone does.

• Prenatal testosterone shapes the brain; childhood testosterone barely differs.
Male fetal testosterone begins around week 8 and peaks at weeks 15–20, perhaps 400–600 ng/dL—approaching pubertal levels. 'Mini-puberty' follows, peaking around three months and fading by about six, and is linked to boys' later activity levels. Five-year-old boys and girls have almost no testosterone. So Attia's sons' rough-and-tumble play reflects how their brains were organised, not current levels.

• Above a male threshold there's little dose-response; in females small differences matter.
Men carry roughly 10–20× women's testosterone. Variation within the normal male range predicts little about sex drive or aggression, and Hooven warns you can't judge anyone by their current level. Different brain regions may have separate critical periods for sexual versus aggressive behaviour.

• Eggs are costly and sperm cheap, which drives different reproductive strategies.
A hunter-gatherer woman's lifetime output might be 8–10 children, each requiring pregnancy and nursing under energy scarcity. Men can gain from competing for status and more partners, and can 'live fast, die young' successfully; women benefit from caution and longevity. Hooven offers only a speculative idea for why eggs are made upfront and winnowed—perhaps selection.

• Rough play is adaptive and teaches boys hierarchy, limits and how to back down.
Dominance hierarchies reduce overall fighting. Male chimps play rougher, and subordinate chimps may cup a dominant's testicles to signal trust. Boys' insult-based intimacy follows a similar logic. Hooven worries phones are replacing physical play. Girls tend toward indirect reputational aggression and, she argues, lack equivalent quick conflict-resolution rituals.

• Testosterone is the ultimate cause of the male skew in violence; culture sets the rate.
About 95% of murders and roughly 98% of sexual assaults are committed by men everywhere. But Canada's lower murder rate than the US isn't a testosterone difference. Laws, religion and norms change rates while the sex gap persists. A biological tendency is not destiny.

• Involved fatherhood lowers testosterone, and that's adaptive.
Pair-bonding and hands-on care of young dependent children suppress testosterone in humans and birds. Raising it in birds makes males neglect offspring. Hooven suggests exogenous testosterone may override these social signals, with behavioural effects users don't consider.

• Estrogen does not masculinise the human brain; androgen-receptor function does.
In rodents, testosterone converted to estrogen inside the brain masculinises behaviour, but human alpha-fetoprotein doesn't sequester estrogen the same way. Aromatase-deficient men are behaviourally typical. In complete androgen insensitivity syndrome, XY people with testes and high testosterone but non-functional receptors develop as typical women, often learning the diagnosis when periods don't start.

EXAMPLES

• Graded testosterone ± aromatase inhibitor study (NEJM)
Attia recalls men chemically castrated, then given five testosterone doses with or without an aromatase inhibitor. Higher testosterone with estrogen preserved gave the best body composition, mood and libido. He argues men on physiologic TRT (about 100–150 mg/week) generally shouldn't suppress estradiol.

• Hunter-gatherer testosterone
Hunter-gatherer men peak at least a third lower than Western men, show no ~1%/year decline, and remain fertile—making Hooven sceptical that falling testosterone itself explains Western fertility trends.

• Attia's residency testosterone
At 28–30 his level was about 220 ng/dL from sleep deprivation. It normalised within a few years of leaving residency, without TRT.

- **Hooven's own hormones**
  After her ovaries were removed at 57, still producing some hormones, she noticed hair loss and plummeting libido. She now uses estrogen, progesterone and testosterone, and began lifting weights at Attia's urging.
- **The 'flick in the nuts' ratio**
  Attia's quip: across ~110 billion humans who've ever lived, boys have flicked friends' testicles countless times, versus essentially zero female equivalents. It illustrates insult-based male intimacy.

OTHER RELEVANT

- **Let kids' rough play run while it's fun**
  If they're laughing, let them work it out; intervene when someone is actually getting hurt.
- **Fix sleep, nutrition, exercise and weight before TRT—especially when young**
  Attia rarely sees a case for exogenous testosterone at 25. If treating a young man, he'd prefer hCG to preserve testicular function and fertility; TRT can permanently impair fertility and is hard to stop.
- **One man's 400 ng/dL isn't another's**
  Androgen-receptor density and CAG-repeat length vary. Change one variable at a time; if a trial to ~900 doesn't help, receptors may already be saturated. Attia wishes a clinical receptor assay existed.
- **Treat sex differences as averages with wide overlap**
  Hooven stresses huge variation—a boy who likes dolls is normal—while arguing that denying average differences distorts policy and education.

373 – Thyroid function & hypothyroidism: how new approaches are transforming care

Guest: Dr. Antonio Bianco
Date: 2025-11-17 · Duration: 2:34:14
URL: https://www.youtube.com/watch?v=jT33TbUVCGI

KEYPOINTS

• The thyroid mostly secretes inactive T4; tissues activate it into T3 as needed, and the whole system evolved to conserve iodine.

Dr. Antonio Bianco, a thyroid physician-scientist who researches how T3 shapes chromatin and gene expression, explains that receptors bind T3 strongly and T4 barely. T4 has a half-life of about 8 days and T3 about 12 hours, so activation is brief and tightly controlled. Removing an iodine from T4's outer ring makes T3; removing one from the inner ring makes reverse T3, which is inactive and can't be converted back. Iodine is recycled each step.

• Three deiodinase enzymes decide how much T3 each tissue gets.

D2 has about 1,000 times more affinity for T4 than D1 and makes roughly 80% of the T3 produced outside the thyroid. D1, in the liver and kidney, makes about 20%, clears reverse T3, and rises with insulin and carbohydrate intake. D3 only inactivates, turning T3 into T2 and T4 into reverse T3. Blood levels barely move (about 10–15%), while tissue T3 can swing tenfold within hours. Most T3 in the brain is made locally by D2.

• Fasting deliberately slows the thyroid: low insulin and leptin tell the hypothalamus to ease off.

Peter's numbers from 7–10 day quarterly fasts: TSH rose from 2 to 7, free T3 fell from 0.3 to 0.2, and reverse T3 rose from 10 to 35. Bianco explains that TSH stays 'inappropriately normal' because the hypothalamus wants to save energy, and that T4 is shunted toward reverse T3 while low D1 activity slows its clearance. Weight loss plateaus partly for this reason. The free T3/reverse T3 ratio is a decent stand-in for deiodinase activity, which can't be measured from blood.

• TSH itself causes no symptoms, and the hypothalamic control center sits outside the blood-brain barrier.

The chain runs TRH !' TSH !' T4. Symptoms come from too much or too little thyroid hormone, never from TSH itself. The mediobasal hypothalamus and pituitary are rich in D2 and read both blood T3 and locally converted T4. Diagnosis depends on TSH plus free T4. Free hormone matters because about 99.5% is bound to proteins like TBG; total T4 can read 14–15 in pregnancy while free T4 is normal.

• T3 and reverse T3 immunoassays are unreliable, especially at low levels, and mass spectrometry is needed.

The free T4 immunoassay is good, but T3 assays track mass spec only at high values and diverge below about 90–100 ng/dL. When Bianco's lab ran one sample through four reverse T3 assays, the results were 'completely crazy'. He knows of no mainstream lab offering mass spec T3, and stick to the same lab for consistency.

• Hypothyroidism affects about 20 million Americans (4–5% of adults), mostly women at about 10 to 1, and is usually autoimmune.

About 60% have TPO antibodies (Hashimoto's). Diagnosis typically needs a TSH above 10 with low free T4; a positive TPO with TSH around 4 and normal free T4 is the 'honeymoon' phase, monitored and repeated in about 3 months. Selenium, vitamin D or antioxidants may lower TPO and prolong the honeymoon, but that isn't standard care. TPO positivity alone in pregnancy raises the risk of miscarriage and prematurity.

• Graves' disease and hot nodules cause most hyperthyroidism, and the field is moving away from radioactive iodine.

In Graves' an antibody mimics TSH: palpitations, tremor, weight loss, warm sweaty hands, TSH near zero. The options are antithyroid drugs for 1–3 years (30–40% remission), surgery by a high-volume surgeon (100–150 thyroidectomies a year), or radioactive iodine, now linked to more cancers. Hot nodules don't remit, so Bianco leans toward surgery.

• Levothyroxine fixes TSH but may leave tissues like the liver hypothyroid.

T4 alone works for most patients, but in treated rats with normal TSH the liver stayed hypothyroid. Statins are the most common drug co-prescribed with levothyroxine, a hint that LDL clearance isn't fully restored. Bianco now treats hypothyroidism as a cardiometabolic risk factor requiring closer follow-up.

• For patients still symptomatic on T4, add T3, after ruling out look-alike conditions.

Symptoms aren't specific: in blinded studies they can't separate hypothyroid from euthyroid people. Menopause is the biggest confounder (he orders FSH with TSH), along with anemia, iron deficiency and obesity. A low morning temperature doesn't mean low thyroid. Secondary (central) hypothyroidism is under 1% of cases and requires a low free T4. A healthy thyroid makes about 80% T4 and 20% T3; desiccated pig thyroid has been standardized since 1985, carries about a 4:1 ratio, and is as safe as T4 alone.

EXAMPLES

• Two teachers who 'lost their jobs to hypothyroidism' changed Bianco's research.

Both had normal TSH and free T4 on levothyroxine but disabling brain fog; one said her brain stopped working the day she left the hospital after thyroid surgery. He had been sending such patients to psychotherapy. Seeing two in two weeks made him refocus his lab, which he now describes as a mea culpa.

• 1.1 million treated hypothyroid patients versus 1.1 million controls over 20 years.

His group's retrospective study found about 2.5 times higher mortality in treated patients, mostly cardiometabolic. In about 90,000 matched patients on combination therapy (half desiccated, half synthetic), mortality was 30% lower than on T4 alone. Hospitalizations in the year before diagnosis were similar between groups. Peter notes that more health-conscious patients and doctors could still confound it.

• A 1965 Brigham study by Dr. Selenkow found an optimal T4:T3 ratio of about 3.5:1.

That happens to match pig thyroid. About 1.5 million Americans take desiccated extract and about 400,000 take synthetic combinations. In blinded studies, patients prefer combination therapy.

• Peter's patient with a TSH of 74.7.

A healthy man in his 50s reached only about 13 on treatment and felt hyperthyroid at higher doses. Bianco suspects assay interference from antibodies against mouse proteins (testable) or aggregated TSH, and advises dosing to free T4 instead.

OTHER RELEVANT

• Don't treat a mildly high TSH in older adults.

After 50 the upper limit of normal rises about 1 point per decade (about 8 at 80), so a 70-year-old with TSH 6 is probably fine. At 40, a TSH of 8–9 is abnormal; look at family history, ultrasound pattern and TPO, and treatment often makes sense.

• Skip compounded 'slow-release' T3 and branded-only dogma.

No published study shows compounded T3 actually releases slowly, and dosing 5 µg accurately is hard. Brand and generic levothyroxine are equivalent (potency held to ±5%), and 40–50% of patients are switched without knowing within two years. Check FDA recall lists.

• Don't megadose iodine.

Adults need about 150 µg a day (250 in pregnancy). Japan's 500–600 µg diets come with more autoimmune thyroid disease, and excess iodine can unmask a silent nodule as hyperthyroidism.

• Watch for true slow-release T3.

A polymer form is through phase 1 with the FDA, and a T3-sulfate approach in Italy relies on steady liver conversion. Bianco also wants mass spec T3 assays made routine.

371 – Women’s sexual health: desire, arousal, and orgasms, navigating perimenopause, and more

Guest: Dr. Sally Greenwald
Date: 2025-11-03 · Duration: 2:00:42
URL: https://www.youtube.com/watch?v=_SZUHFA8KyM

KEYPOINTS

• Sexual health is part of physical health, and mismatched desire, not how often a couple has sex, predicts divorce.
OB-GYN Dr. Sally Greenwald notes the area is understudied and the data are mostly heterosexual. Orgasm shifts the body into parasympathetic mode and releases dopamine and oxytocin, and sleep metrics improve; women slept best after an orgasm with a partner, better than alone or after intimacy without orgasm. Sex burns about 6–7 METs (60–70 kcal per encounter). Among couples aged 30–60, about 20% have sex twice a week or more, about 10% not at all in the past year, and about 70% somewhere in between.

• There's a large orgasm gap: about 95% of men versus about 30% of women regularly orgasm in partnered sex.
In one-night stands the figures are about 90% for men and 12% for women. Alone, women reach orgasm in under 4 minutes on average; with a partner it takes 21–25 minutes. When foreplay lasts more than 21 minutes, over 90% of women orgasm. Arousal lengthens and widens the vagina (about 3.5 by 9 inches at rest) and changes its angle, which matters because about 30% of women have pain with intercourse.

• Most women have responsive desire rather than spontaneous desire.
Only about 15% of women feel desire in anticipation of sex; most feel it once arousal has started. That's why 'chore play', lubricant, vibrators, erotic audio or reading, and mindfulness (Lori Brotto's work) work better than waiting to be visually turned on. Emily Nagoski compares it to going to a party you weren't in the mood for and ending up enjoying it. Consent stays paramount, and stopping is always allowed.

• The clitoris is a large, wishbone-shaped, often asymmetric organ with more than 8,000 nerve endings, and most women need external stimulation.
Fewer than 10% of women orgasm from penetration alone; a clitoris-to-vaginal-opening distance under about 1 inch makes it more likely. About 10% orgasm from the internal branch on the front wall (the 'G-spot', about a third of the way in, found with a 'come hither' motion); Dr. Lauren Streicher calls the other 90% normal. One side is often more sensitive. Only 41% of Gen Z men could identify the clitoris on a diagram.

• Vibrators are evidence-based as nerves age, not a reflection on the partner.
Type A fibers, which sense vibration and deep pressure, are myelinated and age better than type C fibers, which sense light touch and heat. A couple whose usual routine stops working after decades may need an external wand or air-pulse device. Using a vibrator alone doesn't impair partnered orgasm if the technique is brought into partnered sex; 'orgasms beget orgasms' and 'sex begets sex'.

• Testosterone is the best-studied treatment for hypoactive sexual desire disorder in postmenopausal women.
The diagnosis requires more than six months of low desire that bothers the woman herself, not just her partner. Greenwald prefers a compounded daily cream on the inner thigh (or about 0.5 cc of Testim via oral syringe), aims for total testosterone above about 20 (range 20–80 ng/dL), and titrates by symptoms. Estrogen raises SHBG, which binds testosterone; more androgenic progestins blunt that rise. Estrogen therapy tends to help desire indirectly, through better sleep and fewer hot flashes.

• In perimenopause the first question is whether she wants to keep ovulating.
Some women love the energy and libido around ovulation (the late follicular phase is also a performance peak, so athletes time events to days 9–15), but 70–80% of her patients prefer not to cycle because of worsening PMS or PMDD, irregular cycles and heavy bleeding. Menopause hormone therapy doses don't suppress ovulation, while many contraceptives do. A meta-analysis of 32 trials (more than 14,000 women) found ovulation-suppressing contraception raised desire in 20%, left it unchanged in 65% and lowered it in 15%.

• Lubricant is like sunscreen for the vagina: use it every time, ideally silicone and iso-osmolar.
It reduces micro-abrasions and the pain cycles that lead to vaginismus. Vaginal osmolality is about 300; Astroglide runs about 8,000 and KY about 4,000–6,000, which pull water out of tissue. She names Uber Lube (about 600) and Good Clean Love Almost Naked (280–300). She suggests applying it about 30 minutes before sex, using an applicator to place it higher up. Nightly moisturizers (Revaree hyaluronic acid, Replens) are the 'moisturizer', and local vaginal estrogen is the 'serum'. About 30–40% of her patients on systemic hormone therapy also need local estrogen.

EXAMPLES

• Her perimenopause contraception menu.
For women who can't take estrogen: Slynd (drospirenone, a spironolactone derivative) suppresses ovulation in about 98% of women versus 50–70% for older progestin-only pills. Slynd plus an estradiol patch gives contraception with 'real' estrogen, at the cost of more breakthrough bleeding. Nextstellis pairs drospirenone with estetrol (E4), which causes less bloating and spotting, but bone data are pending. Natazia (estradiol valerate) is the only pill FDA-approved for heavy menstrual bleeding. Bioidentical-estrogen pills run about $100 a month and are rarely covered. Among synthetic pills she likes Lo Loestrin, Loestrin and Yaz/Yasmin.

• 'F* it February'.**
Couples schedule sex 2–3 times a week for the shortest month. The initiator stops fearing rejection, and the less interested partner is practicing responsive desire. She says desire stays elevated for months afterward.

• Debut survey of 1,200 high schoolers.
70% of boys described their first sex in terms of pleasure and 70% of girls in terms of pain, which is her case for teaching foreplay and lubricant early.

• The FDA-approved desire drugs are modest.

Addyi, a nightly pill taking about 6 weeks to work, added about one satisfying encounter a month over placebo; no alcohol, and it can cause nausea. Vyleesi, an injection related to PT-141 (the 'Barbie drug'), causes nausea in about 40%, can be used at most twice a week, and has been available since 2019. Sildenafil (25–50 mg) helps only specific groups: diabetics, MS, spinal cord injury and SSRI users. Where legal, 1–2 mg THC showed stronger effects in studies than either drug.

- **Sensate focus for trauma or a long break.**

Dr. Leah Millheiser's four steps: touch without breasts or genitals, then genitals without orgasm, then orgasm without penetration, then intercourse. Each stage can last a week or longer.

OTHER RELEVANT

- **Advice for partners.**

Use lube without taking it personally. Learn her anatomy, including which side is more sensitive. Invest in foreplay outside the bedroom. Near orgasm, don't change anything (about two-thirds of women want exactly the same stimulation to continue). Edging can intensify orgasm. Resources: Ian Kerner's She Comes First, Vanessa Marin's Sex Talks, OMGYes.

- **See a pelvic floor physical therapist as routine maintenance.**

A stronger pelvic floor improves orgasm, and therapy also relaxes muscles that carry pain and stress. Local vaginal estrogen is considered safe for nearly all cancer survivors.

- **Postpartum: resume sex around 6 weeks after any birth.**

High prolactin is a natural libido brake that helps space pregnancies about 18 months apart. Breastfeeding brings a menopause-like low-estrogen state in the vagina, for which she prescribes estrogen cream. Sex is safe through a healthy pregnancy unless there's a low-lying placenta or a short or weak cervix.

- **Teach kids accurate, pleasure-inclusive anatomy and consent.**

Without it, teens learn from porn. Unprotected oral sex often carries more STI risk (for example, herpes) than penetrative sex with a condom.

369 Rethinking protein needs for muscle and longevity, and the benefits of creatine & sauna use

Guest: Rhonda Patrick
Date: 2025-10-20 · Duration: 2:01:15
URL: https://www.youtube.com/watch?v=VhbpSc6pKRQ

KEYPOINTS

• The 0.8 g/kg protein RDA is a minimum based on flawed methods; the true floor is closer to 1.2 g/kg.
The RDA came from nitrogen-balance studies that suffer from incomplete urine collection, nitrogen lost by other routes, and varying nitrogen-to-protein ratios across foods. Stable-isotope studies using 13C-phenylalanine oxidation put the requirement 30–50% higher, around 1.2 g/kg. Surveys suggest adults average about 0.9 g/kg (men) and 0.8 (women)—at the flawed RDA, not the corrected floor.

• There's no amino-acid reserve except muscle.
Fat can be stored almost without limit and glycogen buffers carbohydrate, but skeletal muscle is the only amino-acid 'tank.' Falling short means breaking down muscle immediately—what Attia calls an unforced error.

• Anabolic resistance is driven more by inactivity than by age.
Given the same protein dose, adults 65+ get about half the muscle protein synthesis of young adults, so they need roughly double the protein for the same response. But older people who resistance-train respond like young people. Luc van Loon's one-leg-cast study showed the immobilised leg became anabolically resistant while the trained leg didn't. Only about 32% of adults, and 22% of older adults, resistance-train.

• Sarcopenia arrives in steps, not as a smooth slope.
Population curves average out what individuals experience: a surgery, fall or flu causes weeks of immobility and muscle loss that older people never fully regain. Repeated hits push people past a 'disability threshold.' Attia says frailty, alongside cognition, largely determines the quality of your last decade, so build muscle 'headroom' at 40–60.

• Above 1.2 g/kg, more protein still adds lean mass, with diminishing returns.
Stu Phillips' meta-analysis of about 49 resistance-training trials found adding protein up to roughly 1.6 g/kg gave about 27% more lean-mass gain and 10% more strength than training alone. Benefits taper toward ~2.2 g/kg—Phillips' 'wringing a washcloth' analogy. Intakes around 3 g/kg add little, but neither guest knows of human data showing harm in healthy people.

• Attia's rule: aim for 2 g/kg so your bad days still land at 1.6.
Real life means missed meals and pasta nights. Because the downside of falling short is larger than the upside of overshooting, aiming at 1.6 means bad days fall to 1.2 and aren't made up. He notes David Allison's public call for harm data has met 'crickets.' The worst result he's seen is that high-protein IV nutrition in ICU patients showed no benefit—not harm.

• Use target body weight, not current weight, if you carry a lot of excess fat.
A 300 lb person whose healthy weight is around 220 should calculate from 220. Higher needs apply in calorie deficits and body recomposition ("e2.2 g/kg), heavy training, pregnancy and adolescence.

• The mTOR fear misreads where leucine goes in active people.
Only calorie restriction and rapamycin extend life in yeast, worms, flies and mice, both by lowering mTOR, and leucine strongly activates mTOR. But exercise increases leucine transporters so amino acids go into muscle, where you want mTOR on. Lab mice are sedentary, warm, fed freely, and never face catabolic illness. Attia likens mTOR to inflammation or cortisol: on when needed, quiet otherwise.

• Creatine: 5 g/day saturates muscle; 10 g/day may be needed to raise brain levels.
The body makes about 1–2 g a day and meat supplies more; vegetarians benefit most from supplementing. About 5 g a day saturates muscle in 3–4 weeks without loading. It works by recycling ATP so you can do more reps—it doesn't build muscle for a couch potato. Patrick cites a German dose-response study where brain creatine rose only at about 10 g, because muscles take up the first 5 g. Studies using 5 g may wrongly show no brain effect.

• Creatine's cognitive benefits show up mainly under stress.
Gains appear with sleep deprivation, exams, aging or neurodegeneration—the brain uses about 20% of calories at under 2% of body weight. Small studies show sleep-deprived subjects given about 20–25 g kept, or even beat, baseline processing speed. A pilot gave 20 g in Alzheimer's patients with improved cognition. Patrick says the literature is still small and you can't hang your hat on it.

EXAMPLES

• Attia's recomposition year
Eating one meal a day for calorie restriction, he still drank whey shakes outside the window. That kept him in a calorie deficit but an amino-acid surplus.

• Tirzepatide in Attia's practice
About 15–20% of patients use it, with DEXA scans before and after. He favours slow, steady low doses—most benefit by 5–7.5 mg—and avoiding yo-yo cycling. Two lean patients with unexplained beta-cell dysfunction saw near-normal glucose-tolerance tests within about three months on 2.5 mg without weight loss.

• Creatine gummies
Third-party testing found essentially no creatine in about 95% of gummy products. Patrick looks for NSF certification; Creapure is fine but not essential.

• Sauna and dementia (Finnish data)
Laukkanen's cohort linked 4–7 sessions a week at about 175–179 °F for 20+ minutes to roughly 66% lower dementia risk than once weekly. A separate Finnish study found higher risk among people going above ~200 °F, around 212 °F.

• Hyperthermia for depression

Charles Raison's single session raising core temperature about 2 °C produced an antidepressant effect lasting six months versus a sham. Ashley Mason's 4–8 sessions in a head-out infrared bed (~85 minutes) are extending that work.

OTHER RELEVANT

• Practical protein targets

Never go below 1.2 g/kg. Aim for about 1.6–2.2 g/kg if training, older, dieting or on a GLP-1, where easy-to-digest shakes help.

• Practical creatine use

Take creatine monohydrate powder, 5 g doses in water, about 10 g a day; Patrick uses 15–20 g when jet-lagged. Kids: about 0.1 g/kg. Ask your doctor for cystatin C, since creatine raises creatinine and can falsely suggest kidney trouble.

• Sauna dose

About 175–180 °F for 20 minutes several times a week raises heat-shock proteins about 50%. A hot bath at about 104 °F, shoulders down, for 20 minutes is comparable. Infrared at about 140 °F likely needs roughly double the time. Attia dropped from ~190–200 °F after hearing the >200 °F dementia signal, and a sauna hat helps.

• Exercise remains the master lever

Protein and creatine support training, not replace it. Olympic athletes, often eating "e2 g/kg, live about five years longer than average.

368 The protein debate: optimal intake, limitations of the RDA, & whether high-protein is harmful

Guest: Dr. David Allison
Date: 2025-10-13 · Duration: 2:01:10
URL: https://www.youtube.com/watch?v=k2qZT8OQRjc

KEYPOINTS

• Protein is the latest macronutrient to be demonized, in a predictable cycle of food villains.
Obesity researcher and methodologist David Allison (now at Baylor's Children's Nutrition Research Center) says food carries culture, identity, religion and economics, so people keep hunting for 'angels and demons' among fat, carbs, seed oils, phytoestrogens and now protein. Enthusiasm for protein is driving sales, which provokes people who dislike others 'taking the easy way out'. Both he and Peter disclose ties to David Protein; Allison also lists beef and pork industry funding.

• The 0.8 g/kg RDA was a nitrogen-balance survival threshold, not an optimum.
It came from nitrogen balance studies in lean, sedentary young men weighing about 65–70 kg. Nobody claimed it was ideal or an upper limit. A 1928 Polish study kept two young adults in nitrogen balance for 6 months on almost nothing but potatoes, without diabetes or weight gain, but that says nothing about older adults, pregnancy, injury recovery or training. Allison's conclusion: almost nobody should aim for just the RDA.

• Allison's target for thriving: about 2 g/kg/day, spread across meals.
He sees three zones: too little; a 'known superior' zone up to roughly double the RDA, with no evidence of harm in any group except rare cases like PKU or a specific protein allergy, even in kidney disease; and above about 2 g/kg, more uncertainty and diminishing returns but no demonstrated downturn. Peter's clinic advises 1.6–2 g/kg (about 1 g per pound), and settles for about 1.2 for lifelong vegetarians who struggle to get more. Don Layman would add roughly 30 g per meal.

• 'Trustworthy' depends on data, methods and logic, not on who funded the work.
Allison separates being trusted (others' judgment) from being trustworthy (process). Critics without good arguments turn to ad hominem attacks and innuendo. He argues scientists should aim to build trust in the scientific process, even at the cost of losing particular arguments.

• Nutrition trials are chronically underpowered because food isn't patentable.
Drug trials enroll tens of thousands because patents and FDA requirements justify billions in spending; nutrition RCTs are tiny by comparison. Allison guesses total US spending on research into the effects of food, across all commodity groups and companies, is under $1 billion a year. That's why most nutrition scientists piece together industry and government funding. He'd shift money from expensive observational epidemiology, which yields little new information, to randomized trials.

• Studies showing a plateau in muscle protein synthesis are misread when applied to trained people.
Untrained people max out muscle protein synthesis at lower intakes, just as a sedentary person gains hugely from three 30-minute workouts a week that would do almost nothing for Peter. Allison's analogy: using such data to cap protein is like telling a student 10 minutes of algebra a day is enough to master it. The ICU parenteral-nutrition trials showed no mortality benefit from more protein, but no harm either, and don't generalize to people shopping for dinner.

• No compelling human evidence shows higher protein causes harm, so the burden of proof should shift.
Observational studies point both ways and protein intake is heavily confounded by social class. Allison also distrusts mouse data: benefits of protein and calorie restriction show up mostly at 22 °C, which is chronic cold stress for a mouse, rather than at thermoneutral 27–30 °C. His black-swan argument: after searching thousands of ponds with drones and binoculars without finding a black swan, it's reasonable to stop worrying about them for practical purposes.

• 'Ultra-processed' is a social construct that's too broad to describe what a food does in the body.
The NOVA classification lumps meal-replacement shakes, Big Gulps and IV nutrition together. Allison quotes food scientist Joe Schwarcz: a substance's effect 'depends on its molecular structure, not its ancestry'. Nearly everything is processed (pasteurized milk, cheese, wine), and 'natural' foxglove and hemlock are poisons. Avoiding ultra-processed food might work as a rough rule of thumb, like shopping the perimeter of the store, but it says nothing about cause. He prefers David Kessler's 'ultra-formulated'.

EXAMPLES

• A Frito-Lay–funded snack trial.
Allison's group compared chips and snacks fried in corn oil, low-fat versions, and traditional saturated/trans-fat versions. With calories controlled, the corn-oil versions came out best on cardiovascular biomarkers, saturated/trans fat was worst, and low-fat was worse for triglycerides. Critics such as Marion Nestle attacked the funding rather than the design.

• Kelly Brownell's 1990s speech to food executives.
At a meeting convened by Michael Mudd of Kraft, Brownell said social change needs a villain, 'and guess who it is? You.' Allison sees that as the start of food-industry villainization, with 'ultra-processed' as its latest form.

• 'A heart attack on a plate'.
Michael Jacobson of the Center for Science in the Public Interest held up fettuccine Alfredo on national TV in the early 1990s. Allison's point: scientists who later say 'science evolves' should have expressed uncertainty in the first place.

• The Hall–Ludwig crossover debate.
Crossover designs, which give each participant both diets in sequence, save money and suit metabolic-ward throughput (Kevin Hall's case), but carryover effects can never be absolutely ruled out (David Ludwig's critique). Allison sides with accepting them as limited but valid evidence, as with epidemiology.

• Policy has mostly failed against obesity.
School programs, farmers markets, menu calorie labels, nudges and parent training show no large effects across meta-analyses. Smoking policy succeeded partly because you can quit smoking entirely but can't quit eating. Allison's long-shot research bets are general education, financial security and parenting, citing Moving to Opportunity and the Abecedarian study.

OTHER RELEVANT

- **Aim for about 1.6–2 g/kg/day, spread across meals.**
  The RDA is a passing grade, not an A. Above about 2 g/kg there are diminishing returns and opportunity costs: money, attention, and crowding out foods like fruit or the carbohydrate that fuels training.
- **Judge a study by its population.**
  Before applying a finding to yourself, ask whether you're bigger, older, more trained or chasing a different goal than the people studied.
- **Judge foods by composition and calories, not processing labels.**
  High-protein bars and shakes aren't harmful because they're processed. Any rule of thumb only helps while you actually stick to it, and marketers will route around it. Allison's own favorite protein: chicken gizzards.
- **Low-dose GLP-1 drugs may become a population-wide default.**
  Allison raises a polypill-like idea of broad, subsidized access to GLP-1 drugs, given how limited non-drug public health measures have proven.

367 - Tylenol, pregnancy, and autism: What recent studies show and how to interpret the data

Date: 2025-10-06 · Duration: 1:30:57
URL: https://www.youtube.com/watch?v=GWVM_5knTXg

KEYPOINTS

• Peter's four-step framework for any 'X causes Y' headline.

First, confirm there really is a statistical association. Second, and hardest, estimate how likely it is to be causal, using sensitivity analyses and falsification tests, because 'there are no proofs in biology'. Third, if it's probably causal, judge the effect size, since a real but tiny effect may not change behavior. Fourth, be ready to update as new data arrive. Peter adds that complex conditions like autism almost never have a single cause, and that humans are 'not wired to think scientifically'.

• Autism prevalence rose about fivefold, which makes it easy to find spurious culprits.

CDC figures went from 6.7 per 1,000 children in 2000 to 32.2 per 1,000 recently. Searching countless variables runs into the multiple comparisons problem. Peter's example: with a 7-out-of-10 coin-flip 'psychic test' (about a 5% chance by luck), test 100 people and about five will 'pass'. The Spurious Correlations website finds a 98.5% correlation between margarine consumption and Maine's divorce rate.

• The August review in Environmental Health overstated the evidence.

The review, led by Andrea Baccarelli, was not a meta-analysis. It said six autism studies 'consistently' showed a positive link with dose-response in four of five, but two showed no significant association and only three directly tested dose. When Peter's team pooled the risk ratios themselves, the overall association was about a 5% relative increase, and the pooled result essentially matched the Swedish study, which had more than 10 times as many participants as all the others combined.

• The study with the strongest signal (Ji, 2020) has major limitations.

It sorted about 1,000 Boston Birth Cohort children into thirds by acetaminophen in umbilical cord blood. But acetaminophen clears within roughly 24 hours, so the measure mainly shows use just before delivery, like estimating a year's doughnuts from your birthday. About 70% of samples had no detectable metabolites. Only around 3,000 of nearly 9,000 pairs stayed in follow-up, and autism prevalence in the analyzed group was about 11%, versus about 3% in the general population. Peter sees that selective retention as the single biggest problem.

• In the two largest cohorts, comparing siblings eliminated the association.

Sweden (Ahlqvist et al., 2024; about 2.5 million children, median 13.5 years of follow-up) found a hazard ratio of 1.05 (1.02–1.08), an absolute increase of 0.09% at 10 years. Among siblings who differed in exposure, the effect disappeared. The authors called it 'non-causal'. A recent Japanese cohort of about 220,000 children, roughly 40% of them exposed (closer to US use than Sweden's about 7.5%), found a non-significant 6% (0.98–1.15) that also vanished with sibling control. Peter says the review's claim that the Swedish siblings were selected as doubly discordant would create collider bias, and the senior author says that's not how it was done.

• Most of the Bradford Hill criteria come out weak or against causation.

Strength is weak: 1.05 against the 1.5 threshold for pharmacoepidemiology, and 10x for smoking and lung cancer. It's weaker than red meat and diabetes (1.10) or exercise and prostate cancer (1.05), both likely confounded. Consistency is moderate. Specificity is weak. Temporality holds, though Baccarelli and William Parker disagree on the critical window. The dose gradient is inconsistent. The prostaglandin mechanism is 'hand-wavy'. Analogy argues against it: aspirin, another prostaglandin inhibitor, showed about a 13% lower autism risk in the Swedish sibling analysis.

• Genetics and changes in diagnosis explain most of the rise.

Heritability of autism is about 80–90%, versus about 80% for height and 60% for body weight, estimated from identical vs fraternal twin comparisons. Expanded criteria (DSM-III-R in 1987, the PDD family, then the single ASD umbrella in DSM-5 in 2013) are estimated to account for 40–60% of the increase, and greater awareness for 20–30%. Older parents account for 5–15%: average paternal age rose from 27.6 to 31.1 and fathers over 40 went from 4.1% to 8.9%. Maternal obesity, preterm birth and PM2.5 air pollution cover much of the rest.

• Fever and infection are themselves risks, and they may explain part of the link.

Maternal infection is associated with a 25–40% higher autism risk and maternal fever with up to 200%. Fever, especially in the first trimester, is associated with 25–200% higher risk of cleft palate and neural tube defects. Since acetaminophen is the safest fever reducer in pregnancy (NSAIDs are category D in the third trimester because they can close the ductus arteriosus too early), its use may simply be marking infection.

EXAMPLES

• The old FDA pregnancy categories.

A, about 2–5% of drugs (thyroid hormone, prenatal vitamins); B, 15–25% (acetaminophen, metformin, some antibiotics, Benadryl); C, 60–75% (gabapentin, amlodipine, trazodone, GLP-1s, some SSRIs); D, 5–8% (valproate, phenytoin, lithium, third-trimester NSAIDs); X, 1–3% (statins, methotrexate). The 2015 labeling rule replaced them but has been slow to catch on.

• Ice cream and drowning.

Senior author Brian Lee's illustration of confounding in a JAMA interview: heat drives both. Genetics could play the same role here, for example if a mother's own predisposition affects pain sensing and Tylenol use.

• Collider bias, illustrated.

If acetaminophen were necessary but not sufficient for autism, keeping only sibling pairs that differed in both exposure and outcome would discard every exposed child without autism, and you'd falsely conclude a 100% risk.

• Weighing a drug during pregnancy.

A woman with high ApoB can pause lipid-lowering drugs for nine months, while withholding thyroid hormone from a hypothyroid woman would endanger mother and baby. The question for GLP-1s is whether they prevent gestational diabetes; metformin has more safety data.

OTHER RELEVANT

- **Minor aches: consider skipping it.**
  Peter's general rule is to stop non-essential drugs in pregnancy, but pain bad enough to keep a woman in bed for days is itself a risk to the pregnancy, and judicious use with a physician is reasonable.
- **Fever: the balance favors treating it.**
  Peter says the evidence clearly tips toward using acetaminophen to bring down a fever during pregnancy.
- **Ask for the absolute risk and the sibling analysis.**
  A 5% relative increase can mean less than a tenth of a percentage point in absolute terms, and if it disappears within families, confounding is the likely explanation.
- **Talk decisions through with your obstetrician.**
  Peter isn't telling anyone to start or stop a specific medication. He's describing how to weigh one.

366 Transforming education with AI and an individualized, mastery-based education model

Guest: Joe Liemandt
Date: 2025-09-29 · Duration: 2:03:23
URL: https://www.youtube.com/watch?v=2g2n_CkAolg

KEYPOINTS

• US K-12 spending is huge and results keep slipping

Peter notes the US spends about $1 trillion on K-12, roughly a seventh of global education spending, with poor returns — paralleling healthcare. Joe Liemandt cites the national NWEA MAP norms: the average eighth grader in 2025 knew less than in 2020, who knew less than in 2015, so it isn't just COVID. Only the 99th percentile improved. AP exams were re-normed easier because college students now know less.

• Straight-A transcripts hide years of gaps

Placement tests at Alpha show incoming A students range from one year ahead to three years behind, and B students from three to seven years behind — a seventh grader missing many fourth-grade questions. Joe tells parents paying $40,000 for private school that the grades were misleading, but stresses the gaps are quick to fix.

• Fact fluency frees working memory

Drawing on cognitive load theory, Joe says memorized facts don't occupy working-memory slots, so skipping multiplication tables in favor of calculators handicaps higher math. 'Careless errors' often signal overloaded working memory from a missing foundation rather than a lack of grit.

• Knowledge is hierarchical, so time-based promotion compounds holes

Physics is calculus with word problems, chemistry is algebra with word problems, algebra is advanced fraction manipulation, and fraction scores predict algebra scores. Passing kids on with 70–80% mastery creates holes that surface in algebra or chemistry. His sports analogy: a point guard losing the ball 20% of the time works on dribbling, not dunking.

• With mastery and AI tutors, a grade level takes 20–30 hours

Instead of ~180 days of class plus homework, Alpha students finish a grade level of a subject to mastery in about 20–30 hours (around 22 each for sixth- and seventh-grade math). Bloom's 'two sigma' finding — individual tutoring to mastery lifts average students to roughly today's top 10% — underpins Joe's claim that, excluding the bottom 5%, 95% of eighth graders could reach top-10% performance in math.

• Motivation is 90% of the problem; 'time back' is the motivator

Edtech handles placing kids at the right difficulty; it fails at engagement. Pitching '2x learning' fell flat with parents — fewer than 10% prioritize academics — but '2-hour learning' that frees the afternoon for workshops, sports or projects motivates every kid. Lecture classrooms retain maybe 5%. Their AI watches screens and coaches against scrolling and guessing; a 'waste meter' tracks unproductive time.

• Keep students in the zone of proximal development

Questions should be answered correctly about 80–85% of the time — 99% is too easy, 50–60% causes disengagement — with lessons completed first-time-right 90–95% of the time. A Stanford lecture conveys one to five facts or concepts per hour; their engines reach 20–40, aiming for 100 with generative AI.

• Mastery turns ability into a decision

Joe argues good grades in a time-based system track IQ plus conscientiousness; mastery removes the IQ ceiling for K–8 concepts, and extrinsic motivators compensate for low conscientiousness. Once kids see their remaining gap in hours ('you're 60 hours behind'), reaching the top becomes a choice of effort. He says the 'I'm not a math girl' story has no basis in learning science.

• Paying kids is kindling, not the fire

Alpha uses extrinsic rewards — time back above all, but also money, such as $1,000 for middle schoolers who reach the top 1%. Critics worry it undermines intrinsic motivation; Joe says those studies cover already-motivated kids, while his students gain belief in their capability. Peter's framing: kindling you don't need forever.

• AI is education's light microscope

Peter compares the light microscope enabling germ theory to AI enabling 40 years of learning science to finally work at scale: precise teaching plus closed-loop measurement of what each child knows. Joe expects this year's math curriculum to teach more in 20% less time based on last year's data. He's adamant that schools, adults and classmates remain; the teacher's role changes.

EXAMPLES

• 740 to 790 by relearning times tables

A student stuck at a 740 math SAT reviewed 'game film', found she knew the material but made careless errors, went back to third-grade multiplication and division to fluency, and scored 790.

• $100 for 100 on any grade's state test

Joe offered seventh-grade boys $100 for a perfect Texas STAAR score at any grade level. They aced third and fourth, hit 75–85 at fifth, let the AI generate lessons for the gaps, and climbed to grade level for about $400 each. Fewer than 10% of incoming parents think their kid can score 100; after a year, about 90% of kids say they can.

• His daughter and the $1,000 Amazon cart

His younger daughter, sure she wasn't 'top 1% like her sister', filled a $1,000 Amazon cart and ground through lessons to reach it — then told her skeptical mother it had changed how she saw herself. She later weighed about 20 extra hours to chase a perfect 800 SAT math.

• Second graders run a 5K

Guide Faith, teaching Atomic Habits, signed second graders up for a 5K: walk it first, then add a quarter lap of running at a time, until all ran it by December.

- **Peter's daughter**

  She arrived in seventh grade convinced she couldn't do math; after filling third- and fourth-grade gaps she was acing math by eighth grade and still is in public high school.

OTHER RELEVANT

- **When a student struggles, look backward**

  Struggles in algebra or chemistry often trace to fractions or times tables; filling prerequisites is faster than grinding current material.

- **Review 'game film' on tests**

  Classify each miss as careless or not-known; repeated careless errors suggest a fluency gap.

- **Pair high standards with high support**

  Citing David Yeager's 10 to 25, Joe argues kids thrive on struggle and failure with a caring adult; guides hold the standards so parents can focus on love and support.

- **Know the caveats**

  Alpha is selective and expensive ($40k–75k, with scholarships); real-time AI costs about $10,000 per child per year now, though Joe predicts an on-device tablet under $1,000 within three to five years. He insists dropping the software into a six-hour classroom won't work without rebuilding the school day.

365 Training for longevity: A roundtable on building strength, preventing injury, protein, & more

Guest: Gabrielle Lyon, Jeff Cavaliere & Mike Boyle
Date: 2025-09-22 · Duration: 2:31:26
URL: https://www.youtube.com/watch?v=ac0Nm71GpOY

KEYPOINTS

• Nothing beats exercise, yet very few people lift

Peter sees no evidence that any other pillar does more for lifespan, chronic-disease risk and quality of life. The panel's rough numbers: about 50% of Americans don't exercise, around 20% have a gym membership, half of them use it, and many of those only do cardio. Peter puts real resistance training at 5–15% of people. Only about 20% of Jeff Cavaliere's digital buyers finish a program, which is about twice the industry norm.

• The barriers are time, not knowing it matters, and making it seem harder than it is

Mike Boyle says jobs, kids and commutes get in the way, and people only notice decline when it's too late; the years from 50 to 65 go downhill fast. Gabrielle Lyon blames a culture of comfort and self-imposed limits: a woman who won't lift a 40 lb weight will still carry her 40 lb toddler. Cavaliere says you can build a great body on six lifts (row, squat, deadlift, bench, pull-up, curl).

• Beginners need to keep showing up, not to suffer

Boyle runs his gym like a hospitality business. New clients get a text that day and the next, and the goal is two sessions a week for a year. Nobody should wake up sore: 'we did a bad job.' Each session is 'a recipe, not a menu': rolling, mobility, warm-up, medicine-ball throws and jumps, about 36 minutes of lifting, then easy conditioning, all in an hour. Adult clients never use a barbell.

• Lean athletes still gain metabolically from more muscle

Lyon describes a 100-mile ultrarunner of about 60. Adding two lifting days a week and cutting her mileage raised her strength and improved her fasting insulin, glucose and triglycerides. Muscle is the main place the body disposes of glucose, so more muscle allows more flexibility in the diet. In her words, the markers of metabolic syndrome are markers of muscle health.

• Very low body fat comes from eating, not training

Cavaliere says getting from 12–15% to around 7% body fat 'has nothing to do with training.' He eats five times a day (35 meals a week) and aims for 90% compliance, so about three imperfect meals a week. The panel agrees most people assume exercise is what makes someone lean. You can't out-train a bad diet after your teens.

• Lyon's protein minimum is 100 g a day, set by body weight rather than sex

The RDA would give a 115 lb woman about 45 g, which Lyon says isn't enough. She adjusts for age, activity and metabolic health. She suggests 2–3 g of leucine as a basic need and about 8–9 g for best results. For overweight patients she doses for target weight (lean mass at 16% body fat) and keeps protein steady or higher while cutting calories. She favours animal protein for quality and nutrients like iron and zinc, and eats plants for fiber.

• Carb tolerance depends on activity

Lyon estimates a sedentary adult clears only about 40–50 g of carbohydrate in two hours before insulin rises sharply, so she often aims for about a 1:1 ratio of protein to carbs at meals. A very active person like Cavaliere can handle around 100 g. Blood work showing metabolic health determines how much leeway a patient gets.

• Single-leg work can replace heavy barbell squats and deadlifts for most adults

Boyle dropped back squats after linking them to back pain in about 20% of his athletes. He cites the bilateral deficit: each limb alone is relatively stronger than both together. Peter filmed every heavy set but still hurt his back about one workout in eight, so he quit. Cavaliere's go-to substitute is a wide-stance reverse lunge with a slight twist toward the front leg, which takes about 75% of the load.

• The 'iron graveyard' is for exercises with an equally good safer option

Cavaliere has dropped the upright row (its position is the PT test for shoulder impingement; a high pull with elbows below the wrists works the same muscles), the Cuban press, and the free-weight fly, which loads the shoulder capsule at full stretch. A floor fly keeps the stretch with a built-in safety stop.

• Kids should play many sports until about 12

Boyle says to 'follow the money': people selling year-round single-sport play profit from it. He kept his daughter, later a scholarship and pro hockey player, out of summer hockey until 13 and made her swim, dive, play soccer and do judo. The panel says playing more has meant more injuries, and NBA teams now run about 200 more stop-start miles a season. Boyle traces the myth that lifting stunts growth to a study of malnourished child laborers.

EXAMPLES

• Split squats matched front squats

On Boyle's hockey team, players' back-foot-elevated split-squat loads matched their front-squat maxes. One 190 lb player did 240 lb for 20 reps on one leg.

• Peter's 407 lb tire

A PT friend watching him flip it pointed out his heavily loaded lumbar flexion, which helped convince him heavy lifts weren't worth the risk.

• Lyon's narrow squat and hip dysplasia

She kept squatting too narrow despite undiagnosed hip dysplasia and wore down her hip. She now does only single-leg work and has a new hamstring tear on MRI.

• Women's pulling strength

Boyle's best female client does chin-ups with 45 lb added for seven reps.

• What each guest changed their mind about

Lyon: intramuscular fat may predict insulin resistance better than body-fat percentage. Boyle, after losing a foot of colon: fiber and water. Cavaliere: balance training with eyes closed. Peter adds that biotech money is moving to anti-sarcopenia drugs after GLP-1s.

OTHER RELEVANT

- **Start with two hours a week and keep it painless**
  Boyle treats any answer to 'does it hurt?' that isn't a plain no as a yes. Find a movement that doesn't hurt (standing cable presses work for most painful shoulders) and build from there.
- **Protect your Achilles**
  Foam roll and stretch the calves, do ankle mobility work, and do equal sets of seated and standing calf raises, including single-leg. Don't sprint or jump on sore calves: Tatum and Haliburton both had calf strains before their Achilles tears.
- **Train balance with your eyes shut**
  Stand on one leg and trace the alphabet with the other foot, eyes closed, then add head turns. Falls are the danger later in life.
- **Women around menopause don't need a different program**
  Good progressive training applies to everyone. Get fit before perimenopause, watch for tendon problems like frozen shoulder, coach knee position on landing, and get your heart rate really high once a week.
- **Teach kids movement before load**
  Start with body weight, go slowly, and stop when form breaks down, as it did with Peter's boys trying to one-up each other with kettlebells.

363 A new frontier in neurosurgery: brain-computer interfaces, new hope for brain diseases, & more

Guest: Dr. Edward Chang
Date: 2025-09-08 · Duration: 2:09:14
URL: https://www.youtube.com/watch?v=y7LXTyUhSVM

KEYPOINTS

• Neurosurgery has steadily moved toward less collateral damage, though the craniotomy still has its place.
UCSF neurosurgeon Edward Chang traces modern neurosurgery to Harvey Cushing, who diagnosed early pituitary tumors and helped bring in electrocautery, and to Wilder Penfield, who popularized awake surgery and the homunculus map. Aneurysm repair used to mean a 7–9 inch incision and a microscope. Today about 90% are treated with coils through a catheter in the groin. Clot retrieval has turned many severe strokes into 'brain attacks' handled like heart attacks, and some patients go home the next day. Laser probes and focused ultrasound can now treat deep targets such as the nuclei behind tremor.

• Glioblastoma is still lethal, but molecular profiling and immune strategies are shifting the approach.
GBM arises from glial support cells and grows so fast it outstrips its blood supply, leaving necrosis. It isn't considered heritable, and each tumor has a different combination of mutations. Genetic profiling is now routine at academic centers, opening the door to targeted chemotherapy. GBMs also hide from the immune system, so 'unmasking' them is a major goal. For now, the more of the tumor surgeons remove, the longer patients survive, but microscopic cells beyond what MRI shows grow back. Focused ultrasound that temporarily opens the blood–brain barrier for drug delivery is being studied at UCSF. Chang's 2040 hope is to turn an average survival of about 18 months into a chronic condition.

• Awake surgery works because the brain itself feels no pain.
The scalp is numbed with lidocaine and epinephrine. Bone and brain tissue have no pain receptors, but the dura and some blood vessels do, so they're numbed too. Patients aren't intubated. The head is fixed in a holder and light propofol sedation is used at the start. The awake window is usually only 1–2 hours of a 6–8 hour operation, for mapping language or movement with electrical stimulation. The trade-off is resecting more tumor or seizure tissue against the risk of paralysis or aphasia.

• The '10% of the brain' myth has a grain of truth: some regions are redundant and plastic.
Roughly 10–15% is critical for basics like moving, speaking and seeing. Chang has removed an entire frontal lobe on one side many times. With slow-growing lesions, the other hemisphere, which was already sharing the work, takes over through synaptic plasticity. Language sits in the left hemisphere for about 99% of right-handers, about 2 cm above the left ear, and that real estate can't be sacrificed.

• Severing the corpus callosum stops seizures from spreading rather than curing them.
For drop attacks, where seizures spread so fast that patients collapse and may need to wear helmets, surgeons usually cut the front two-thirds of this heavily myelinated left–right highway. Chang compares a seizure to a whole stadium doing the wave instead of holding separate conversations. Cutting it fully risks a disconnection syndrome, with one hemisphere unaware of what the other is feeling, which is why partial cuts are preferred. The delicate step is protecting the pericallosal arteries, since injuring them can paralyze the legs.

• Recording from the brain's surface is the sweet spot for brain–computer interfaces.
Taking scalp EEG as 1, electrodes on the cortical surface (ECoG) give roughly 1,000x the resolution, because skull and scalp blur the signal. Penetrating single-neuron electrodes add perhaps another 5x, but scar tissue forms around them and their recordings drift from neuron to neuron within hours or days, so decoders must be recalibrated. Because ECoG doesn't break the brain's surface membrane, it avoids much of that reaction and can blanket a whole region, which absorbs individual variation in exactly where functions sit.

• The decoder translates attempted speech, not inner thoughts.
The array sits over the speech-motor cortex controlling the lips, jaw, tongue and larynx, so the patient must actually try to speak. Reading or imagining a sentence isn't enough. AI breaks the signal into 10–20 ms windows and maps them to statistically derived speech units, using an open-source speech-recognition model from Meta. A language model then infers the likeliest words, much as autocorrect does, and a synthesizer can recreate the person's pre-injury voice.

• Hearing loss deprives the brain and may accelerate cognitive decline.
Many older adults with normal hearing tests struggle in noisy restaurants because the problem is signal processing in the brain. Unrecognized hearing loss leads to social isolation and less stimulation, and Chang says many studies link it to accelerated memory loss. Peter's practice treats the link as causal, while noting that a recent trial suggesting otherwise had methodological problems. Chang thinks vision loss has less of this effect.

EXAMPLES

• Ann's story.
A vertebral artery stroke that damaged her pons while she was playing volleyball, months after her second daughter was born, left her quadriplegic and unable to speak. She communicated by eye-tracking letters. About 18 years later, after waiting until her daughter graduated, she joined the BRAVO trial and received a credit-card-sized array of 253 electrodes spaced 3 mm apart.

• From NATO code words to 80 words a minute.
Training started with the 26 NATO code words, chosen because they're easy to tell apart: about 50% accuracy after roughly 90 minutes of data on day one, and 95–100% within about a week. The 2023 Nature paper reached about 80 words a minute (conversation runs 150–160). A 2025 study streamed speech with under a second of delay using the same hardware and a new algorithm. Her face and jaw muscles also grew stronger from the constant practice.

• Fetal dopamine-cell grafts for Parkinson's.
These were tried 20–30 years ago. Some patients benefited, but unregulated dopamine caused severe dyskinesias. New stem-cell approaches aim for tuned dopamine output, better delivery and less immunogenic cells. Immunosuppression is still used for now as a precaution.

- **Neck manipulation and vertebral dissection.**
  Chang says it's 'not a wives' tale': certain chiropractic neck movements, and high-velocity sports injuries, are statistically linked to tears in the vertebral artery wall, though the incidence is very low.

OTHER RELEVANT

- **Get hearing checked and treated.**
  Unrecognized hearing loss is common, and both Chang and Peter see it as a modifiable contributor to cognitive decline.
- **Be cautious with aggressive neck adjustments.**
  The risk is rare but catastrophic. Chang advises against forceful, high-velocity neck manipulation.
- **Expect brain–computer interfaces outside the lab by about 2030.**
  Chang's stretch goal is fully implanted wireless arrays with about 4x more channels (his group is roughly a year from a wireless version), serving ALS, spinal cord injury, stroke and MS patients. He expects scalp-only systems to stay limited by physics.
- **Expect progress on Parkinson's sooner than on Alzheimer's.**
  Chang is more optimistic about movement disorders because the cell loss is concentrated in one small area that surgery can reach. Alzheimer's involves many brain systems at once, so he expects early detection and early treatment to bring the first gains there.

360 How to change your habits: why they form and how to build or break them

Guest: Charles Duhigg
Date: 2025-08-11 · Duration: 2:27:34
URL: https://www.youtube.com/watch?v=yhLHfPZEKgU

KEYPOINTS

• Every habit is a loop of cue, routine and reward, and habits make up roughly 40–45% of daily behaviour.
Duhigg, author of The Power of Habit, cites Wendy Wood's research at USC for the 40–45% figure. The basal ganglia strengthens the links between cue, behaviour and reward until the behaviour runs automatically. He became interested after an Army major in Iraq told him 'the military is a giant habit change machine,' and after realising that despite professional success he couldn't make himself run or lose weight.

• Positive reinforcement is roughly 20 times more effective than punishment.
In Duhigg's example, you'd need about 20 cane strikes to match the motivation of one post-run smoothie. Negative rewards work best as tension imposed before the behaviour and relieved by doing it, like the interrogator's 'I'll let you out of the box if you talk.' He suggests the brain prices punishments accurately but overvalues rewards, especially unexpected ones—the slot-machine effect—so pair any punishment with a reward.

• Rewards must be immediate, then shift from extrinsic to intrinsic.
Newcomers to exercise don't anticipate the runner's high, so it can't motivate them yet. Start with a smoothie, a long shower or praise. Over time the felt reward—accomplishment, endorphins, relief—takes over. Many people sabotage new habits by accidentally punishing themselves, such as rushing a shower and running late after a morning run.

• Cues fall into five types; stack as many as possible for a new habit.
The five: time of day, place, emotional state, other people, and a preceding ritual. For a new running habit: alarm at 7, shoes and clothes by the bed, a friend waiting at the corner, and a reward decided in advance. Attia finds other people—accountability partners or trainers—among the most powerful cues.

• You don't break a bad habit; you change it.
Neural pathways for habits rarely thin, which is why a lapsed meditator restarts quickly and an ex-smoker still craves a cigarette after breakfast. Identify the cue and the reward, then insert a new routine that delivers a similar reward. Duhigg says physical nicotine dependence fades within about 100 hours; the habit loop is what persists.

• Willpower is like a muscle: trainable, but it fatigues within a day.
Errors cluster in surgeons' second or third operations or very long cases; affairs among lawyers and doctors cluster after 9–9:30 pm. Plan for depleted moments. Duhigg says willpower has low heritability and is learned through parenting, sport and practice.

• Relapse is data; treat yourself like a scientist.
Prochaska's work shows committed smokers quit about seven times before it sticks. Early attempts rely on willpower; later ones succeed with 'implementation intentions,' such as keeping candy ready for the mother-in-law visit that triggers a cigarette. Attia coaches patients never to judge a missed day—just don't let one become two—because self-blame floods the brain with negative reward.

• Mental habits matter as much as behavioural ones, and contemplative routines enable deep thinking.
The mind produces something like 47 thoughts a minute. Serial innovators build rituals—a weekly reflection or a walk before brainstorming—that trigger depth on demand. 'Making the right choice is so much more powerful than executing really well on the wrong choice.' Cal Newport's work explains why walks feel unproductive compared with clearing email, and why they aren't.

• Decision fatigue is real; design which decisions you make, and when.
Obama wore identical suits to save decisions for important ones. Decide in a 'cold' state—choose lunch after breakfast, not when starving. Attia admits he struggles to pick a restaurant late in the day; Duhigg says the fix is to plan for frailties, not deny them.

• Motivation is the prerequisite no coaching can supply, and it changes across life.
Duhigg argues information and reinforcement—whether from a book like Outlive or an AI coach—only help someone already motivated. Tony Robbins' gift is generating motivation, not sophisticated advice. Attia's reasons for training at 52 differ completely from those at 20, so keep experimenting with what motivates you.

EXAMPLES

• Soap in South Asia (Val Curtis's research)
Families saved soap for guests or prayer. Health messaging failed. What worked: a less perfumed scent that felt medicinal, and ads framing handwashing as being a good parent—an identity reward—built on disgust research.

• Marines and IED dust
Training used charges that made dust clouds without noise or fire, because dust is a more reliable cue than sound. The reward was squad-mates saying 'good job,' and camaraderie becomes why soldiers stay.

• Savings experiment (Wharton)
In cash economies in South America, a bank clerk praising savers each week raised savings by about 40% compared with the same box and information alone.

• Qantas Flight 32
After an engine blew apart and 12 of 14 key systems failed, Captain Richard de Crespigny reframed the A380 as a Cessna and landed all 469 people safely; simulators usually crash. Before every flight he quizzed co-pilots on emergencies and argued with their answers.

• Toothpaste mint and vitamin gummies
Mint's tingle made brushing feel like it was working; sugar coatings boosted vitamin use. Both manufacture immediate rewards.

- **Katie Milkman's 'temptation bundling'**
  She listened to Harry Potter audiobooks only on the bike. Attia does the same with favourite podcasts during zone 2.

OTHER RELEVANT

- **Start additive habits absurdly small**
  Attia's prescription for a cardio-hater: three 15-minute rides a week, tracking only time; showing up is the win. For subtractive habits, control your environment—an hour of grocery-store willpower buys 167 easy hours.
- **Make a game board for long-horizon goals**
  Duhigg and Attia both use spreadsheets to gamify saving. Duhigg updates his weekly, tracking 1–3-year earnings next to net worth so market dips don't kill motivation.
- **Parent for agency**
  Praise effort ('you worked hard') rather than traits (Carol Dweck). Narrate your own cues and rewards out loud, and admit failures as data points.
- **Find a reward you actually want**
  Kale smoothies rarely work as rewards; experiment. For a pill with no felt benefit, attach a meaning—'I'm staying around for my kids.' Social praise turns intrinsic fastest; AI encouragement may help some people.

359 How metabolic and immune system dysfunction drive the aging process, NAD, aging clocks, & more

Guest: Eric Verdin
Date: 2025-08-04 · Duration: 2:31:47
URL: https://www.youtube.com/watch?v=818-8vS5JpA

KEYPOINTS

• The immune system and brain may set the pace of whole-body aging

Verdin points to work from Tony Wyss-Coray's lab finding that aging markers for the brain and immune system best predict lifespan. Both are spread throughout the body. In mice, removing the DNA-repair gene ERCC1, or causing mitochondrial dysfunction, only in immune cells speeds up aging and senescence in every organ. Whether this holds in humans is 'the million-dollar question.' Peter adds the endothelium; Verdin sees barrier function (blood vessels, skin, blood–brain barrier) as a key target.

• The oxidative-stress theory isn't dead just because antioxidants failed

Electrons leak from the mitochondrial respiratory chain and form reactive oxygen species, and the leakage grows with age. Vitamin C and E trials failed, but Verdin says these molecules also do useful signaling: blunting them can blunt the benefits of exercise. Peter adds that the trials never had a good marker to show the antioxidants actually reduced free radicals. Martin Brand at the Buck found that blocking some production sites helped and blocking others didn't; that program was dropped.

• Fuel choice matters, and glucose is the 'dirtiest' fuel

Verdin ranks beta-hydroxybutyrate as the cleanest fuel, then fatty acids, with glucose worst. Mice fed pure fat that never saw a carbohydrate lived longer, though Peter notes most 'high-fat' mouse diets are really high-fat, high-sugar 'donuts.' Many ITP drugs that extend life (acarbose, canagliflozin, and metformin combined with rapamycin) act on glucose. Verdin's main suspect is the insulin and IGF-1 spikes from fast-absorbing carbohydrate, and he uses CGMs to flatten them. He found a ketogenic diet socially isolating and is developing a ketone ester.

• When it comes to glucose and blood pressure, lower is usually better

Peter cites data in non-diabetics showing all-cause mortality falls steadily as A1C goes down, with no lower limit found, so 5.0 beats 5.6 even though both count as 'normal.' Verdin's own doctor dismissed his creeping fasting glucose of 96. Both say blood pressure of 105/65 beats 115/70 if you have no symptoms. BMI is crude: Peter is 'overweight' by BMI at 11% body fat, and Verdin estimates that about 20% of overweight people are metabolically healthy, though he worries about the long term.

• Immune decline is the 'fifth horseman'

Peter says he should have added immune health to the four horsemen in Outlive. During COVID everyone could be infected, but people over 75 had about 84-fold excess mortality. Flu and RSV follow the same pattern. Verdin explains innate immunity (fast, non-specific, no memory) and adaptive immunity (T and B cells that expand and leave memory cells). In his recollection, vaccine response drops to about 30% after 70. The two of them couldn't square that with how protective COVID vaccines seemed in the very old, and left it for the show notes.

• The thymus shrinks early, and growth hormone is a double-edged sword

After about 50 the thymus is mostly fat, so few new naive T cells are made. Small growth hormone studies in HIV patients, and later the Fahy TRIIM trial (GH plus low-dose metformin and DHEA), suggested some thymus regrowth. Peter calls GH the only active ingredient. Verdin worries GH causes glucose intolerance, and notes that bigger dogs, driven by GH, live shorter lives, as do taller people. Peter says every patient he has seen on GH feels better, but testosterone is far better against sarcopenia.

• Rapamycin: dose and timing separate immune suppression from immune benefit

Joan Mannick's 2014 trial (as Peter recalls it, 300+ people over 65 in four groups) found that 5 mg weekly boosted vaccine response about as well as 20 mg, with fewer side effects. Verdin took 4–6 mg weekly and got a pimple on his nose the next day, so he was clearly briefly immunosuppressed. He stopped because he noticed no benefit. He questions ITP results because lab mice live shorter than their size predicts, have high growth (mTOR) drive, eat poor chow and live sterile, sedentary lives. He would advise a 40-year-old against rapamycin.

• NAD decline seems driven by CD38, and supplements may just pour water into a leaky sink

NAD is used by 600+ enzymes, plus sirtuins and PARPs. Eduardo Chini showed that mice without CD38 don't lose NAD with age and live about 15% longer, though Verdin suspects that isn't only because of NAD. Factors released by senescent cells (the SASP) increase CD38 in macrophages. CD38 also breaks down NMN, pushing excess nicotinamide into methylation, which drains the methyl-donor pool and raises homocysteine. Recycling is so fast that blocking it empties a cell of NAD in four to six hours.

• Epigenetic clocks aren't ready for clinical use

Clocks can swing about five years with time of day. Matt Kaeberlein's duplicate samples disagreed within and across clocks. Blood mixes 500+ cell types: Verdin's lab found naive T cells look 20–25 years younger than memory T cells, so infections that expand memory cells fake 'accelerated aging.' His 'IntrinClock' excludes those sites and doesn't move with COVID, HIV or the GH trial. He favors DunedinPACE for tracking response to interventions. Peter notes no clock yet predicts lifespan better than chronological age.

EXAMPLES

• Verdin on tirzepatide

As a self-experiment, not an endorsement: A1C fell from 5.4–5.5 to 5.0 and fasting insulin to 5, with six to seven pounds lost and no muscle loss while exercising. After two weeks he felt full for the first time in his life. Peter suggests an oral glucose tolerance test with insulin.

• 1 g of NMN doubled his homocysteine

It rose from about 7 to 15 and took three to six months to return to 7–8 after he stopped. Peter suggests trying TMG. Lab animals typically get about 10 times typical supplement doses.

- **Intravenous NAD**
  NAD hardly exists in plasma and is too big to enter cells. A study cited by Verdin shows the liver mostly converts infused NAD into nicotinamide, which is cheap at a pharmacy, versus about $700 an infusion. He has heard anecdotes of striking motor improvement in Parkinson's but calls them unstudied.
- **Organ-specific proteomic clocks**
  Wyss-Coray's UK Biobank work (40,000+ people) uses organ-specific blood proteins to flag a struggling organ. Verdin sits on the board of the startup. Peter worries about false positives, as with whole-body MRI and thyroid nodules.
- **IL-11 blockade**
  Blocking IL-11 in mice extended life. Verdin frames chronic innate immune activation in response to accumulated damage as 'Jekyll and Hyde': it helps repair, but it also depletes NAD and harms stem cells.

OTHER RELEVANT

- **Exercise first**
  Verdin calls exercise in all its forms the one proven anti-aging intervention. It also improves vaccine and infection responses. Optimize it before adding drugs.
- **If you take NAD precursors, keep doses modest and track homocysteine**
  Verdin's former approach was about 250 mg each of NR and NMN, possibly reasonable at 60+. Be cautious if you might have an early cancer: animal data hint precursors could speed tumor growth, and raising NAD may feed the SASP.
- **Be skeptical of tests sold alongside fixes**
  Both say to run from a company selling an unvalidated test and the supplement to 'correct' it. Only order tests whose results would change what you do.
- **Check your titers**
  Verdin, born in 1957, had his measles titer checked to see whether he needed revaccination. This is a simple routine way to assess specific immunity.

357 A new era of longevity science: models of aging, rapamycin trials, biological clocks, & more

Guest: Brian Kennedy
Date: 2025-07-21 · Duration: 2:12:32
URL: https://www.youtube.com/watch?v=7yNvz_0Q1eQ

KEYPOINTS

- **The 'hallmarks of aging' are readouts of one connected network, not 12 separate targets.**
  Kennedy, former CEO of the Buck Institute and now running about 35 PIs in Singapore, wrote the 'pillars of aging' companion review and drew lines connecting all the pillars. Interventions like rapamycin improve every hallmark at once. Healthy aging means a homeostatic network that stays responsive. Fixing hallmarks one by one won't work.
- **Inflammation keeps emerging as central—and baseline mTOR creeps up with age.**
  Almost every lifespan-extending intervention reduces chronic inflammation, and inflammation dominates the main components of his lab's aging clocks. Baseline mTOR rises in aging stem cells, losing the dynamic range to switch on for a wound or meal and off otherwise. Elevated mTOR feeds chronic inflammation, which feeds mTOR. Good interventions restore youthful range rather than push anything supra-physiologic.
- **Aging looks like linear damage plus an oscillating 'how well you're coping' component.**
  Breaking UK Biobank-type data into principal components, one aging component rises linearly—'damage' or accumulated stochastic change. Another oscillates around it with illness, behaviour and drugs. Nearly all current interventions, including everything in Attia's book, act on the oscillation. Kennedy says that could mean 5–10 extra healthy years—'a revolution'—but probably not 150-year lifespans.
- **The 'valley' resilience model explains exponential mortality from linear damage.**
  Following Peter Fedichev's work at Gero, health is a ball in a valley. When young the walls are steep, so you're pulled back after junk food or illness. Damage lowers the hills, so the chance of tipping into a failure state rises exponentially, consistent with Gompertz mortality. With about 50 possible failure states, treating one disease barely helps; you must keep all the hills high.
- **Bending the slope may need new kinds of interventions, such as lowering system 'noise' or reprogramming.**
  Kennedy wonders whether we should target noise—such as transcriptional noise—rather than how long worms live, since worms are already in a failure state. He expects fitness trade-offs, which timing might avoid. Long-lived yeast mutants mostly wouldn't survive in the wild. Partial reprogramming could replace damaged cells but is early. He's returning to basic discovery science for this.
- **Methylation clocks are overhyped as causal; many data types make equally good clocks.**
  Proteomic, microbiome and facial-structure clocks (Jackie Han's facial clock rivals methylation) also predict age; association isn't causation. In NHANES with about 200 months of follow-up, some first-generation methylation clocks predicted mortality worse than chronological age. GrimAge and PhenoAge beat it. Matt Kaeberlein's eight simultaneous commercial tests disagreed even with identical repeats.
- **A ~50-marker routine-lab clock beat every other NHANES predictor of death, and it's actionable.**
  About 30 of the markers come from a complete blood count; the rest are standard labs, inflammatory markers and a few self-reports, costing about $300 in Singapore. It outperformed ASCVD risk scores. Principal components flag fixable drivers, such as four in-range markers adding about four years of biological age, roughly 50% higher mortality risk. At 65 in NHANES, about 20% of people needed but lacked treatment, and well-controlled people on medication aged slower than those who needed none.
- **Rapamycin remains the gold-standard small-molecule geroprotector, but probably with modest human effect.**
  Weekly dosing that lets trough levels fall likely avoids immune suppression and may even protect against respiratory infection, as Mannick's trials suggested. Kennedy expects it to extend healthy years rather than change the damage slope. His Singapore trial gives about 5 mg weekly for six months to 150–200 healthy 40–60-year-olds, measuring clocks, cytokines, pulse-wave velocity, DEXA, strength and cognition. Attia doubts most of those endpoints will move.
- **Combining many supplements is more likely to cancel out than add up.**
  In mouse combination studies Kennedy sees interference more often than synergy—'mixing 20 colours of paint' gives grey. He adds one compound at a time and measures before and after. With $100 million a year instead of about $4 million, he'd run factorial combination trials and map each compound's binding target.
- **Cardiovascular and metabolic disease are the most preventable of the big four; cancer is the most inevitable.**
  Cancer requires accumulated mutations plus immune decline, so it may respond least to longevity interventions. Dementia is likely modifiable, but the data are thin. Kennedy criticises Alzheimer's research for spending 30 years on plaque and imagines an epitaph: 'cleared plaques, died of Alzheimer's at 94.'

EXAMPLES

- **Yeast deletion screen with Matt Kaeberlein**
  Of about 5,000 yeast genes, roughly 300 deletions extended lifespan, pointing to mTOR and protein translation. The paper had about 80 authors.
- **Time-release alpha-ketoglutarate (Rejuvant; Kennedy sits on the company's board)**
  In mice: 5–10% longer life and a large drop in frailty, with added benefit from vitamin A in males and vitamin D in both sexes. A placebo-controlled six-month human trial, about US$1–1.5 million, finished but isn't analysed. An earlier uncontrolled methylation study claimed a few years of 'reversal.'
- **Urolithin A and spermidine**
  Urolithin A cut frailty in male but not female mice; it's being repeated, and Kennedy's lab found unpublished binding targets. Spermidine reversed high-fat-diet metabolic dysfunction in old mice and extended lifespan in his hands.
- **Kennedy's n=1 sublingual NAD effect**

100 mg sublingual NAD with apigenin (a CD38 inhibitor) plus AKG: he could run at 150–155 bpm with less breathlessness and once ran 12 km instead of 5. He stresses it's anecdotal. He notices nothing from NR or NMN and doubts they raise NAD much.

• Rapamycin timing

Kennedy has poor runs within 24 hours of a dose and good training 3–4 days later. Attia plans to test shifting his own dosing day.

OTHER RELEVANT

• Expect healthspan, not immortality

Attia tells patients the realistic gain is 7–10 extra years of far better life. Kennedy's grandmother bowled a 238 at 93 and lived to 101—a 20-year phase shift, not escape from decline.

• Skip commercial epigenetic age tests

Their reliability is poor; standard labs managed aggressively are more informative and actionable.

• Vet longevity clinics for safety and honesty

Kennedy wouldn't pay ~$100,000 for follistatin gene therapy. He's tried IV MSCs and is cautious with growth hormone. He's seen infections from offshore treatments, and judges providers on transparency about data and safety.

• Don't forget proven basics

Kennedy finds HRT use remarkably low worldwide and thinks most women should be asked why not, rather than whether. Protect lean mass—his biggest worry with GLP-1 drugs—and do resistance training, as he started doing.

Navigating bone health: early life influences & strategies for improvement & injury prevention

Date: 2025-07-07 · Duration: 1:46:07
URL: https://www.youtube.com/watch?v=Zld5iuH5anQ

KEYPOINTS

• Falls become a leading cause of death after 75, and hip fractures are especially deadly

Peter's team plotted CDC data from 2019. Before about 60, overdoses dominate accidental deaths. After 65, falls do. Per 100,000 people, fall deaths at 75+ trail only heart disease, cancer and Alzheimer's. This 2022 AMA, rebroadcast in full, argues you can't wait until you're in that age group to act, just as you wouldn't wait for a heart attack to fix apoB.

• A hip fracture carries a higher one-year death risk than smoking

In one data set more than 40% of men over 90 die within a year of a hip fracture, and roughly a third of people over 80 do. A ~200-person study found 25% six-month mortality after 65. A Finnish series of ~400 patients found about 27% one-year mortality. A pooled cohort of ~122,000 people aged 60+ found a one-year hazard ratio of 2.78, above end-stage kidney disease (~2.76) and smoking (just under 2).

• Bone is living tissue that's constantly rebuilt

Osteoblasts build bone; osteoclasts break it down. Bone is 50–70% mineral (mostly calcium), 20–40% organic matrix, and the rest water and fat. The whole skeleton turns over in about 10 years, and bone holds nearly all the body's calcium. Low blood calcium raises parathyroid hormone, which pulls calcium from bone and activates vitamin D, which helps the gut absorb calcium. Bone marrow also houses the memory B and T cells behind lasting immunity.

• Osteopenia and osteoporosis are points on a continuum

Osteopenia is about a 10% drop in bone mineral density versus a young healthy adult; osteoporosis is about 25%. Diagnosis uses both hips and the lumbar spine (L1–L5), where the deadly fractures happen. A T-score compares you with a healthy young adult; a Z-score compares you with people your age. A Z-score of " 2 means lower density than 97.5% of peers.

• Ask for a DEXA scan that reports each hip and the spine separately

DEXA is quick and very low-radiation. Many centers report only whole-body BMD, so confirm they'll report left hip, right hip and lumbar spine. Peter estimates basic body-composition scans at about $100–150 and full analyses at up to ~$400. Guidelines screen women at 65 and men at 70 (earlier if high risk). The WHO suggests women by 40. Peter looks at BMD in patients in their 30s and finds a Z-score of " 1 at 35 as concerning as a bad glucose tolerance test.

• Peak bone mass is built from about 8 to 20

BMD roughly doubles between 8 and 20, peaks in the early 20s and stays flat until 40–50. Around menopause women lose about 3–7% a year for 7–10 years, slowing to 0.5–2% after 65. Men over 65 lose 1–2% a year from a higher starting point. Women lose mainly spongy (trabecular) bone. A woman who misses her genetic peak by 20 starts lower for life, though work before menopause can narrow the gap.

• Estrogen controls how bone responds to load

Bone cells sense the strain muscles put on them through tendons and add bone in response. Estrogen regulates that signal, so the sudden withdrawal at menopause is devastating without replacement. Men make estrogen from testosterone and lose it gradually as testosterone falls. Extra body fat may add load and estrogen.

• Peter thinks bone health should be part of the HRT decision

The consensus still says HRT isn't standard care for postmenopausal bone loss. Peter notes the Women's Health Initiative clearly showed fewer fractures. He calls its breast-cancer increase (about 0.1% absolute) virtually non-existent and says the cardiovascular concern came from oral estrogen. Topical estradiol avoids that, and he believes HRT lowers cardiovascular risk.

• Resistance training and high-force sports build the most bone

Resistance training beat running, swimming, cycling and even plain jumping for preserving BMD. Powerlifting beat regular strength training in postmenopausal women. Football and MMA had the highest BMD, but come with head and joint injuries. Peter suspects running underperforms because elite runners are very lean. Walking, gardening and golf (and his own racing and archery) don't load bones enough.

• How you lose weight affects bone

Weight loss by diet alone tends to reduce BMD. In a small study, people who lost weight with substantial exercise slightly gained BMD, although they lost a bit less weight. Changes in leptin, adiponectin and estrogen may explain some of the loss, and loading the bones may offset it.

EXAMPLES

• The child whose bones were 'rubber bands'

A friend doing mission work in Rwanda showed Peter a five-year-old whose legs bent painlessly because of rickets. Within about six months of better nutrition, he was normal.

• Starting smoking before 16

Never-smokers had the best bone density later in life, people who started before 16 the worst, and later starters were in between. A patient with a 20-pack-year history who had quit more than 15 years earlier still had very low BMD and needed an endocrinologist.

• Bisphosphonates in mice immobilized with Botox

Female mice given a bisphosphonate while one leg was paralyzed kept femoral BMD similar to controls. Peter has no idea if it applies to humans.

• Bed rest and paralysis

Unused bone can lose about 2% a month in microgravity or partial paralysis, and up to 7% a month with complete paralysis, again mostly spongy bone.

• Peter's shoulder surgery

Right after surgery he got his surgeon's OK to use cycling blood-flow-restriction cuffs to keep stressing his biceps. That was only possible because the biceps tendon itself wasn't repaired.

OTHER RELEVANT

• Know your risk factors

A parent with a hip fracture (genetics account for up to 50%), a fracture from standing height or less, BMI under about 18–19, the female athlete triad, smoking history, and long-term corticosteroids. Prednisone at 5 mg a day can measurably reduce BMD within 3–6 months, and inhaled steroids used for childhood asthma count too. PPIs and phenytoin carry weaker risks.

• Cover calcium, vitamin D and magnesium

Peter treats these as minimums: calcium 1,000–1,200 mg, D3 800–1,000 IU, magnesium 300–500 mg a day. He takes about 1 g of supplemental magnesium a day across several forms. Some forms loosen the bowels, so choose based on your gut.

• Load bones heavily and often

Lift, carry, and ruck: Peter rucks five days a week and seeks out hills, since walking downhill strains muscles more. Even isometric holds count when you're laid up.

• For kids: nutrition, activity and power

Make sure they eat enough, aren't too lean and don't smoke, and do sports with jumping and lifting rather than running alone.

• Leave drugs to specialists

Bisphosphonates (Fosamax, Boniva, Actonel) raise BMD about 4–6% at the hip and spine and cut fractures, and are usually stopped after about five years. Peter's practice refers patients needing them to endocrinologists.

355 – Skincare strategies, the science of facial aging, and cosmetic-intervention guidance

Guest: Dr. Tanuj Nakra & Dr. Suzan Obagi
Date: 2025-06-30 · Duration: 3:10:33
URL: https://www.youtube.com/watch?v=9iHxTvG1_3k

KEYPOINTS

• Facial aging means losing scaffolding: bone, fat pads and skin.

Oculofacial plastic surgeon Tanuj Nakra and dermatologic cosmetic surgeon Suzan Obagi describe about 11 plump fat compartments on each side of a young face, most of which shrink with age. CT studies following the same people over 15–20 years (Rohrich and Pessa) show the eye sockets widening and the cheekbones, maxilla and mandible receding. Retaining ligaments that tether skin to bone then show up as tear troughs and folds. Nakra frames it as four changes: skin, volume, gravity and bone.

• Women's faces age about 20 years faster than men's between 50 and 60–70, largely because of hormones.

Obagi says facial bone loss mirrors the post-menopausal drop in hip bone density. As the mandible recedes the neck loosens, which is why 50-year-old women often say 'I hate my neck'. She argues for discussing hormone replacement early in menopause. Weight cycling also thins the face: each pregnancy's gain and loss comes off the face and doesn't return there.

• Facial fat behaves differently from body fat, and chronic stress may speed up its loss.

Why facial fat shrinks while body fat grows isn't understood. Fat pads even differ in color within the eyelid, partly from beta-carotene. Nakra sees peak-stress decades (30s–40s) accelerating facial volume loss and changes in collagen and elastin, and Peter suggests cortisol may break down facial fat even as it builds body fat. Fat grafted from the abdomen keeps behaving like abdominal fat and swells if the patient gains weight.

• Daily sunscreen is the non-negotiable first step. Obagi insists on mineral formulas.

An Australian randomized trial found that four years of daily sunscreen meant fewer lines and wrinkles. UVA ('aging') and UVB ('burning') damage DNA, collagen and elastin, and visible and infrared light add pigment and possibly deeper changes. Obagi prefers zinc oxide or titanium dioxide, citing absorption of avobenzone and oxybenzone into the blood and possible hormone effects. She and Nakra say chemical filters degrade within about an hour in strong sun and that nothing above SPF 50 is meaningful. Those are their clinical views. Darker skin ages more slowly, mainly because melanin forms a 'parasol' over the cell nucleus.

• Retinoids are step two, and the strength should rise with age.

Collagen production peaks around 18. Retinol (over the counter, weakest) converts to retinaldehyde, which converts to retinoic acid (prescription: 0.025/0.05/0.1%, about $80–100 a tube that should last about 3 months). Obagi starts sensitive patients on retinaldehyde five nights a week and tretinoin two, and says skin adapts within 6–8 weeks. Nakra builds up from 2–3 nights a week or mixes in 1% hydrocortisone. Use a fingertip unit including under the eyes, never stop in summer (sensitivity to light fades), and keep it beside your toothbrush.

• Simple routine: gentle cleanser, antioxidant serum, then sunscreen or retinoid.

In the morning: a non-foaming glycerin-based cleanser (body soap strips the face), a vitamin C serum, then sunscreen. At night: cleanser, serum again (Obagi says the day's oxidative load depletes it), then retinoid, applying thinnest to thickest. Vitamin C supports collagen synthesis, acts as an antioxidant and evens pigment, and topical application reaches far higher skin levels than oral doses. It degrades easily, so stabilized formulas are worth paying for, unlike retinoids and sunscreen. Nakra's 'cheapest trick': nightly petroleum jelly visibly thickens and smooths skin within 30 days.

• Treat cystic acne early, because the scars last a lifetime.

Obagi calls cystic acne, which affects perhaps 20% of adolescents, a dermatologic emergency because of scarring and psychological harm. She avoids long antibiotic courses because of the gut microbiome and moves quickly to isotretinoin, about 5 months, which clears roughly 85% of people. It requires pregnancy prevention, no alcohol, and checking triglycerides and liver enzymes. She considers the depression scare poorly supported, since depression scores often improve. Photodynamic therapy with ALA and red light is an alternative.

• Obagi's 5 Rs of rejuvenation: relax, refill, resurface, redrape, renew.

Relax overactive muscles with neuromodulators, refill volume with fat or filler, resurface the skin (Obagi says better skin gets noticed before a lift does), redrape with energy devices or a facelift, and renew with ongoing maintenance, mostly through skincare at home. Resurfacing runs from non-ablative options (light peels, IPL/BBL, fractional lasers) to ablative ones (CO2, deep TCA or phenol peels). A full CO2 treatment means 7–10 days in dressings, about 3 weeks of redness, and is done every 5–10 years. Ablative lasers are riskier for darker skin types.

EXAMPLES

• Peter's face as a case study.

Hooded upper lids push his forehead muscle to work constantly (likely enough to qualify for an insurance-covered blepharoplasty), so freezing the forehead with Botox would make him look heavier. His tear-trough hollow could take fat or filler (about $800–1,000 a syringe). The suggested definitive fix is a transposition lower blepharoplasty that moves the eye-bag fat into the hollow, plus resurfacing. Under-eye dark circles have four causes: visible muscle, shadowing, hemosiderin and pigment. He had all four.

• Fillers don't simply vanish after a year.

Nakra regularly finds hyaluronic filler injected 8–10 years earlier still stretching ligaments during surgery. Overfilling of lips and cheeks is his biggest concern.

• Fat grafting, step by step.

Obagi harvests about 120 cc (mainly from the flanks, for the stromal tissue), centrifuges it, and adds PRP and 'nanofat' to improve how much survives. Grafted patients seem to age better.

- **Newborns prefer attractive faces.**
  In Judith Langlois's preferential-looking studies, weeks-old infants looked longer at attractive faces. Symmetry, averageness and sexual dimorphism appear across cultures.

OTHER RELEVANT

- **Choose injectors and surgeons carefully.**
  Look for board certification in the specific area, enough volume (for example at least 25 facelifts or rhinoplasties a year), honest personal complication rates and a comprehensive assessment. Filler injected into a vessel near the eyes, nose or temples can cause blindness or stroke, so seek experienced, physician-supervised care.
- **Skip 'preventive' Botox at 18 and tightening devices before about 40–45.**
  Obagi warns that ultrasound and radiofrequency tightening may cause fat atrophy in younger faces.
- **Don't judge your face by one bad photo or a filtered image.**
  Front-facing cameras distort faces, and almost everyone is asymmetric. Nakra says 95–99% of patients haven't noticed their own asymmetry.
- **Be cautious about big decisions during emotional upheaval.**
  Both doctors start with reversible, low-risk steps and sometimes refer to therapy before considering surgery.

354 – What the dying can teach us about living well: lessons on life and reflections on mortality

Guest: Dr. BJ Miller & Bridget Sumser
Date: 2025-06-23 · Duration: 2:34:59
URL: https://www.youtube.com/watch?v=EBVsRIRj31Q

KEYPOINTS

• Dying is something bodies are built to do, and most of the work happens long before the final moment.
Hospice and palliative physician BJ Miller (who nearly died at 19 after an electrical injury and spent about three months in a burn unit, losing both legs and an arm) and social worker Bridget Sumser push back on the movie deathbed epiphany. More than 80% of people now die of chronic illness, meeting the cause of their death well in advance. 'There's nothing wrong with you for dying. This is the way it's supposed to go.'

• Palliative care is the broad umbrella. Hospice is its final, narrower part.
Palliative care is team-based care focused on quality of life 'as defined by the patient' for anyone with serious illness, alongside full curative treatment and without a prognosis requirement. Hospice, the older model, enshrined in Medicare in 1982, requires giving up curative treatment and certification of six months or less to live if the disease runs its course. Miller calls palliative care 'just good healthcare', yet few patients get it. People confuse it with hospice, clinicians assume they already provide it, and there aren't enough trained staff.

• Americans enter hospice far too late, averaging about three weeks.
Sumser and Miller say patients, families and especially referring physicians wait too long, adding suffering and treatments that no longer help. Peter describes the trap: an older patient admitted for an emergency ends up intubated and on dialysis, can't be moved to hospice, and dies in the ICU. Miller says anyone stating 'I never want to die in a hospital' should be flagged for early referral, and that the six-month cutoff was an arbitrary political choice. The original thinkers wanted a year.

• Home hospice is a service, not a place, and families carry most of the work.
About 80% of hospice is delivered where people live. Hospice houses are rare because room and board count as social rather than medical costs. The famous six-bed house where Miller worked closed for lack of funding. The team is on call 24/7 and visits perhaps a few times a week, but most of the daily care falls to family. Private caregivers in the Bay Area cost about $20–55 an hour. The result is costly cycles of hospital, rehab and home that are worse for everyone.

• End-of-life delirium is common, and what people say during it shouldn't be taken literally.
It's often quiet (hypoactive) and easy to miss. Miller recalls a widow tormented for two years by her husband's harsh last words. He has become slower to sedate delirium automatically and prefers to ask patients in advance what they'd want. Sumser stresses minimizing triggers like lighting, noise and interruptions. Loss of appetite and thirst is the body's signal that the gut is shutting down, and forcing food or fluid can cause pain or fluid buildup.

• Pain can almost always be controlled, but suffering is a different thing.
Miller says no one in 2025 needs to die in physical distress if palliative sedation is included, and that dosing opioids for symptoms is not euthanasia. Suffering is when symptoms threaten your sense of self. Someone who sees pain as redemptive may hurt without suffering, while mild pain can be devastating to someone else. Turning down symptoms is only the starting point, so the 'meaty' work on fears, unfinished business and faith can begin. Sumser explores what opioids mean to each patient, including people in recovery.

• Advance directives are free, need no lawyer, and the proxy is the key choice.
Most people think they matter, but only about 20% have one. Everyone over 18 should. Sumser made hers in her late 20s, picturing her estranged parents and a casual partner trying to decide for her. Peter tells friends who name him as proxy that they must talk it through over dinner first. Because people adapt (healthcare workers say they wouldn't want to live with quadriplegia, while most people who have it are glad to be alive), revisit the directive over time and frame it around what makes life worth living, not just DNR/DNI. One proposed term is 'AND', allow natural death.

• We tend to die the way we lived, so practice now.
Sumser: people who lived connected and reflective tend to die that way. If you want forgiveness or connection at the end, build it now. Miller's biggest lesson is honesty with yourself. The common thread in regrets is not letting themselves feel, letting shame drive 'a wedge' between them and others. Most often patients need to forgive themselves. 'I love you, I forgive you, please forgive me, thank you' holds up across cultures. Accept fear and regret rather than chasing fearlessness.

EXAMPLES

• Meeting a 42-year-old with stage 3 breast cancer.
Sumser would start not with prognosis but with 'what has this meant to you?', the 4 a.m. fears and effects like changes in sexual function. Rapport may take several visits. Friends often minimize ('you'll be fine'), which is why an outside listener helps.

• A new Alzheimer's diagnosis.
The first question is what the person understands, and the family is part of the unit of care. Spouses often cry when asked 'how has this been for you?' because no one has asked them. About 60% of clients at Mettle Health, Miller and Sumser's service, are family members.

• The last 24–48 hours.
Kidneys shut down and the resulting metabolites cause dreaminess. Skin becomes mottled and bluish, breathing includes long pauses, and the 'death rattle' is probably harder on listeners than on the patient. Many people seem to die in the moment loved ones step out.

• Psychedelics at end of life.
Miller has seen psilocybin achieve in one session what years of talk therapy didn't, a felt sense of connection, while urging caution and more study.

OTHER RELEVANT

- **Complete an advance directive and name a proxy this year.**
  Download a free form, then have a real conversation with your proxy about what a good day looks like for you.
- **Ask for palliative care early in any serious illness.**
  It can run alongside curative treatment and covers emotional, family and practical needs, not just pain.
- **If you keep vigil, take care of yourself.**
  Sleep, eat and take walks. Your loved one may need you out of the room to let go.
- **Make mortality a daily practice.**
  Sumser reminds herself 'this is my life' in each moment. Miller suggests the Serenity Prayer, including practicing being comfortable with what you can't control.

352 Female fertility: reproductive health, treating infertility & PCOS, and the IVF process

Guest: Paula Amato
Date: 2025-06-09 · Duration: 2:37:00
URL: https://www.youtube.com/watch?v=UvgPh7wSH94

KEYPOINTS

- **Women have a finite egg supply, and the real constraint with age is egg quality.**
  Amato, a reproductive endocrinologist in Oregon, explains that egg numbers peak in the womb. There are about 2 million at birth and about 400,000 by first period, with most lost through atresia. Eggs stay arrested mid-meiosis until the days before ovulation. Errors in splitting the chromosome pairs at that stage, which become more likely as a woman ages, produce aneuploid eggs. Even with regular ovulation, many released eggs can't make a viable pregnancy.
- **About 90% of first-trimester miscarriages come from chromosomal errors.**
  Women shouldn't blame coffee or stress for an early loss—it's almost always a 'bad split.' One miscarriage isn't usually investigated. Two in a row warrants a workup at any age, even at 40, because a treatable cause such as a uterine abnormality could be missed.
- **Infertility means a year of trying under 35, or six months over 35—and both partners get tested.**
  Roughly a third of cases are female factor, a third male, and a third combined, so a semen analysis comes early. Lifetime infertility risk is about 1 in 6. Rising rates are partly explained by delayed childbearing, with possible roles for falling sperm counts and STIs. Irregular cycles or suspected PCOS justify seeing someone before the year is up.
- **Untreated gonorrhoea and chlamydia can silently scar the fallopian tubes.**
  Ascending infection—presenting as pelvic pain, fever and discharge, though not always noticed—damages tubes without affecting the eggs or uterus, so IVF still works. Scarred tubes also raise ectopic pregnancy risk, typically presenting at 6–8 weeks; a late rupture often means removing the tube. A dye X-ray of the uterus and tubes (HSG) checks they're open.
- **PCOS affects about 6–8% of women and links irregular cycles, high androgens and insulin resistance.**
  Not trying to conceive: birth control pills suppress LH-driven ovarian testosterone, raise SHBG and protect the uterine lining from overgrowth. Long gaps between periods can lead to hyperplasia and even cancer. Patients should be screened for diabetes, often with metformin. Many women are put on the pill without being told they have PCOS and its metabolic implications.
- **For PCOS and fertility, letrozole for five days is first-line and works for most women.**
  A head-to-head randomised trial found higher pregnancy rates than with clomiphene. If there's no period, a withdrawal bleed is induced with progesterone (5–10 mg medroxyprogesterone or 200 mg micronised for 7–10 days). Letrozole runs on cycle days 3–7, with an ultrasound around day 12. About 80% of PCOS patients conceive with ovulation induction plus IUI.
- **Stop GLP-1 drugs at least two months before trying to conceive.**
  They're very effective for weight loss in PCOS, but there are no pregnancy safety data. An 'Ozempic baby' registry hasn't shown birth defects so far, but numbers are small.
- **IUI success depends heavily on age.**
  With oral drugs, per-cycle rates are about 20–25% in the 20s, 10–15% over 35 and 1–5% over 40. Multiples risk is about 5–8% with oral drugs versus 25–35% with injectables. That's why injectables with IUI—the source of tabloid 'octuplet' stories—have largely been dropped in favour of IVF.
- **IVF is a funnel, and a normal embryo implants about 70–75% of the time.**
  A typical sequence: about 10 eggs retrieved, about 70% fertilise, about half reach blastocyst by day 5–6, and genetic testing (5–6 trophectoderm cells) removes more. Single-embryo transfer is the norm because twins raise risks of preeclampsia, haemorrhage, C-section and prematurity. Donor eggs give about 70–75% success, versus 10–20% per cycle for over-40s using their own untested embryos.
- **The lab matters as much as the doctor.**
  Amato says success depends more on embryologists than physicians. Training is mostly a 4–5-year apprenticeship, and there's a national shortage. Choose clinics using SART.org clinic-specific success data (about a two-year lag) and volume—at least 100 cycles a year. Ask how genetic testing is offered. Avoid clinics that push add-ons on everyone or where you rarely see the doctor. A cycle costs about $20,000; 24 states mandate some fertility coverage, about 15 including IVF.

EXAMPLES

- **How an IVF cycle runs**
  Birth control pills sync follicles, then 8–12 days of FSH injections (with some LH) are given, along with a GnRH antagonist to block early ovulation. An hCG trigger follows, and retrieval happens 36 hours later under sedation with a 16-gauge needle through the vaginal wall into each 1.5–2 cm follicle.
- **ICSI is often used even without male factor**
  Success rates match conventional IVF when sperm are normal, but ICSI avoids the rare catastrophe of zero fertilisation. It adds about $1,000.
- **Attia's friend and a blunt gynaecologist**
  After a son was born with Down syndrome, the doctor told the mother it was 'your fault'—technically a maternal nondisjunction, but a lesson in bad bedside manner.
- **Embryo testing limits**
  Aneuploidy screening is routine. Carrier screening allows targeted testing for conditions such as CF or sickle cell. Polygenic or APOE4 selection remains controversial scientifically and ethically.
- **Future technologies**
  Lab-on-a-chip automation, in vitro maturation and making eggs from skin cells (done in mice, perhaps 10–20 years away for

humans). Mitochondrial replacement trials are running outside the US, where they're not legal.

OTHER RELEVANT

- **Egg freezing is best done in the early-to-mid 30s**
  Freezing in the 20s mostly wastes eggs you won't use. About $10,000 per cycle plus about $1,000 a year for storage; aim for 10–20 mature eggs around 30, and far more near 40.
- **Your cycle is a health signal**
  Absent, very irregular, very painful or heavy periods deserve evaluation in the teens or 20s. Overtraining or under-eating (RED-S) can stop ovulation and harm bone through low estrogen.
- **Lifestyle basics over fertility supplements**
  Amato recommends a Mediterranean diet, sleep, coping with stress and exercise without excess. Correct real deficiencies (folate, iron, vitamin D). CoQ10 and DHEA have weak evidence; she's fine with CoQ10 if it reduces stress.
- **Don't use rapamycin to extend fertility**
  A Columbia trial is testing it with AMH as the outcome, but the animal data are mixed. AMH (around 2 normal, under 1 low) reflects egg number, not quality.

351 Male fertility: optimizing reproductive health, treating infertility, & navigating TRT

Guest: Paul Turek
Date: 2025-06-02 · Duration: 2:37:18
URL: https://www.youtube.com/watch?v=RCGX5J3VQj0

KEYPOINTS

• Conception is a brutal elimination race

Of about 100 million ejaculated sperm, roughly 5 million get through the cervix past acidic vaginal fluid (pH about 5), only 100–500 reach the fallopian tube, and one reaches the egg. Turek describes research (from a company he consults for) suggesting sperm advance in waves, like a phalanx: early waves soak up the uterus's active immune response so later sperm can get through. Failing at this may explain some infertility.

• Sperm take about 74 days to make, so changes show up months later

Turek's deuterated-water study found an average of 74 days from production to ejaculation (some men as fast as 42). That includes about two weeks maturing in the epididymis, a ~35 ft tube where sperm learn to swim forward and to 'smell' follicular fluid at one part per billion. Expect any intervention to take at least 2.5 months to show results, and about 90 days for a full turnover. After varicocele repair, the average time to conception was about seven months.

• Sperm drive evolution and carry the father's environment to the next generation

Sperm stem cells divide throughout life and pick up mutations and epigenetic changes, about 50 new mutations per generation on average, with many more from older fathers. Roughly half affect brain development. About 98% of normal sperm have the right number of chromosomes, and the epididymis seems to filter out defective ones: testicular sperm show 2–3 times more abnormalities than ejaculated sperm.

• Have sex in the days before ovulation, not after

Sperm can wait in the oviduct for days, but an ovulated egg survives only about 8 hours. In a NEJM diary study of about 700 couples, sex every other day before ovulation gave the best results, and waiting until ovulation produced only about 20% of conceptions. Turek says 80% of natural conceptions come from sex in the days leading up to ovulation. For conception he advises sex every other day. For a semen analysis, abstain 2–4 days: count rises with abstinence but motility falls.

• A male workup: thorough history, expert exam, two semen analyses, hormones

Only about 23% of men get a formal evaluation before couples go to IVF in North America. Turek uses a 200-question history, which he says matters most. On exam he checks for varicocele, cancer, and a congenitally absent vas deferens (about 1 in 500 men), which he can feel and which signals a likely cystic fibrosis carrier. Semen results vary 50–100% between samples, so get at least two about three weeks apart. He reads the results like a poker hand: low motility alone points to short-term exposures, while low count plus low motility suggests something more severe.

• Testosterone therapy usually wipes out sperm production

Exogenous testosterone shuts down LH and FSH. Turek puts the chance of zero sperm at 95% for a man on injections. Topical, nasal (three times daily) and oral (twice daily) forms are more physiologic and in his experience can preserve sperm counts. hCG and clomiphene/enclomiphene stimulate the body's own production and keep fertility. He adds clomiphene when hCG goes above about 1,500 units three times a week, which starts suppressing FSH. He has about 560 men on clomiphene and argues the FDA's rejection of enclomiphene reflects the backlash over direct-to-consumer testosterone ads.

• Thick blood is the main testosterone risk

Exogenous testosterone raises EPO and red-cell mass. Turek sees events begin around hemoglobin 18 and definitely at 19, and warns of clots on long, dehydrating flights. Pellets last about four to six months. Rough symptom thresholds Turek cites: erections ~290 ng/dL, fertility ~300, libido ~350.

• Getting off testosterone: taper, then stimulate

Recovery depends on dose, duration and form: continuous injections are worst, while cycling allows recovery. Turek worries that after 5–10 years function may not return; Peter's practice treats about two years as the ceiling. Turek tapers over about six weeks, with or without clomiphene, or uses hCG plus clomiphene for a faster restart. He checks testosterone about two weeks after the last dose, as the low point. Low-dose hCG (250–500 units twice weekly) alongside testosterone kept sperm normal in a 12-week study of bodybuilders, but miss doses over years and counts can crash.

• Hot tubs are among the worst things for sperm

The testes run about 3°F cooler than the body. When infertile men stopped hot baths, total motile sperm count rose about 300% by three to four months and 600% by six. Turek estimates that 20 minutes at 104°F three times a week could take a man to zero. Saunas have about a quarter to a third of the effect (so Peter's friend's ice packs make sense), steam rooms fall in between, and cold plunges and surfing are fine.

• Other common factors

Varicoceles (about 40% of cases) come from the left testicular vein draining uphill without valves, which Turek blames on humans standing up. Hormonal problems account for 10–15%. Genetic causes include Klinefelter syndrome and Y-chromosome deletions, which don't improve with varicocele repair and are passed to sons. Alcohol and THC act as direct toxins: THC stays in fat for weeks, and two epidemiological studies tie chronic use to testicular cancer. Type 2 diabetes and obesity also matter, and a third of type 2 diabetics have low testosterone.

EXAMPLES

• Extreme training cut counts by 40%

Going from moderate exercise to two hours a day above 80% of VO2 max for 12 weeks cut sperm counts by about 40% and testosterone by about 50%, and both recovered afterward. Military stress studies showed similar drops of about 50% in LH and testosterone.

• Peter's testosterone after residency

At 33 his total testosterone was about 220 ng/dL, which Turek attributes to stress and sleep loss. Chronic stress keeps cortisol up and shuts down reproduction.

• Just being cleared had results

In Turek's USC follow-up, 65% of men he cleared conceived naturally within a year, and another 15–20% with IUI or IVF, a higher rate than any treatment he's published.

• Semen quality and lifespan

A Copenhagen study of about 74,000 men over 50 years found those with normal semen quality lived about three years longer. Turek sees semen analysis as a way into preventive health for young men.

• Mumps, Zika, Ebola and COVID

Mumps after puberty can destroy the testes. One Ebola survivor transmitted the virus sexually a year later. Among men who died of COVID, only about 1 in 7–10 autopsies found virus in the testes. Turek has seen two unexplained cases of sterility after severe COVID.

OTHER RELEVANT

• Bank sperm before chemotherapy, and consider it as you age

Turek advises every man who might want children to bank before chemo. Three normal ejaculates give roughly one child's worth for IUI. About 10 give three chances at IUI, and three are plenty for IVF. About half of frozen sperm survive thawing.

• Older fathers carry risks too

Sperm-bank guidelines treat 40 as older paternal age. Turek sees a slow linear rise in offspring risk (miscarriage, autism, schizophrenia and similar) up to about 50–60, then a steep upturn. Unlike egg chromosome problems, these single-gene mutations can't be screened out.

• Choose a bike saddle with a center cutout

Commuting cyclists in a UK study had better fertility than average, but pelvic numbness signals nerve and artery compression. Get a saddle with a cutout middle, sized to your sit bones.

• Be skeptical of testicular stem-cell or PRP injections

Offshore clinics' claims lack real controls, and Turek has found nothing after such treatments in his own surgeries.

350 Injury prevention, recovery, and performance optimization for every decade

Guest: Kyler Brown
Date: 2025-05-26 · Duration: 1:50:55
URL: https://www.youtube.com/watch?v=CFXe36Bh4dQ

KEYPOINTS

• Prehab before surgery and a strong 'roll cage' around the joint allowed Attia out of a sling in 24 hours.

Attia's labrum was almost completely detached; it had been diagnosed by arthrogram in 2009 and was repaired by surgeon Alton Barron. With about eight weeks before surgery, Brown, a chiropractor turned rehab specialist, did aggressive supraspinatus and serratus work, used blood-flow restriction, and trained core and scapula–rib control. Barron didn't cinch the joint tight for liability's sake. Measurable stability plus Attia's strict rule-following let him skip the usual 4–6 weeks in a sling and use gentle isometrics instead of early rotation work.

• To be a capable 80-year-old you must be a robust 50-year-old, so train for the far target.

Attia's archery analogy: if you're accurate at 100 yards, 40 yards is easy, and difficulty rises non-linearly with distance. Training for the 'marginal decade' (the Centenarian Decathlon) builds strength, muscle and fat loss now. It also builds a buffer, so a strong person who rolls an ankle sprains it less. Stacked injuries, such as meniscus repairs, are how people lose hiking and then health.

• Most people lose capacities they stopped using—especially jumping and reactive footwork.

Attia jumped rope 25 minutes a day as a teenager, then didn't jump at all from 20 to his mid-40s. That's a setup for the classic middle-aged Achilles rupture. Kids jump off rocks and twist; adults stop. Brown wants people to keep playing reactive, randomised games and to rebuild jumping deliberately rather than suddenly.

• Rehab should build capacity under one coordinated plan, not deliver passive services.

Red flags: one therapist running four patients through the same insurance-coded routine, a room full of tables, ultrasound and stim instead of weights, 30 tedious exercises nobody sticks with, or a 30-year-old surgeon's handout with no follow-up. Good signs: one-on-one sessions, progressive loading, and a surgeon who refers to specific clinics based on their strengths. Even pro sports struggle with 'too many cooks' and contract-driven priorities.

• Pain often appears far from its cause.

Jill Attia, a marathoner, developed right knee pain after racing two marathons seven weeks apart. Running is a single-leg rotational movement (the 'spinal engine'). Mild scoliosis, pelvic rotation and a left proximal hamstring tendinopathy, confirmed by MRI, were 'dumping' load into the right knee. Treating only the knee usually means it comes back in 3–5 months.

• Real core stability is a pressurised cylinder that holds up in motion, not a six-pack.

Diaphragm, pelvic floor, transverse abdominis and multifidi must stiffen at the right time, then let the hips and shoulder blades move freely. When deep stabilisers fail, muscles like the biceps, traps or glutes guard and tighten. That's why needling or stretching gives about six hours of relief, while stabilisation training removes the guarding. One client's 'radicular' pain was actually referred from a gluteus minimus trigger point.

• Load tendons with heavy isometrics first, then progress to unloaded plyometrics, then full speed.

Train in three planes, not just straight-ahead calf raises. Long-hold and 'overcoming' isometrics, such as the isometric mid-thigh pull against a fixed bar, remodel tendons over weeks. Band-assisted pogos then train speed at less than bodyweight before full plyometrics. The test of readiness is the exercise itself, scored on numbers and quality, with double- versus single-leg gaps exposing balance deficits.

• Mobile feet and stiff feet fail in opposite ways.

Attia's swimmer feet are strong but too mobile to find stiffness. Rucking on uneven ground, and later an ill-advised pogo stick, flared tendons that are worst first thing in the morning—classic tendinopathy, which takes months to heal. His fix is a split squat with the front forefoot raised on a 45-lb plate, holding a calf raise. Rigid, weak feet in rocker shoes push force up to knees, hips and spine, so Brown checks foot and ankle first in any chronic knee case.

• Pain isn't the same as damage, and fear and stress amplify it.

Brown likens the brain to a contestant with a hand hovering over the Family Feud buzzer. Most MRIs over 30 show wear. He's seen 'thousands' of back flare-ups coincide with a partner's labour or job fears. Using scans to sell 40-visit packages makes people feel frail. Education and a plan empower them.

EXAMPLES

• Low back triage

Weakness or bowel or bladder changes mean immediate neuro or ortho referral. Otherwise, try conservative probes such as McKenzie extension work; symptoms 'centralising' from leg to hamstring is a good sign. Hot discs often settle in 4–10 weeks, and the better surgeons prefer to wait. One patient's disc herniation healed, but McKenzie work then aggravated an annular tear and had to be stopped.

• Attia's back flare-up fixed by isometric pressing

Barely able to limp in, he did supine 'leg press' isometrics with good intra-abdominal pressure, building to maximal effort against an immovable bar, and felt 'a million bucks' an hour later. Brown attributes this to reciprocal inhibition releasing the guarding muscles.

• Jill's PRP protocol

Two PRP injections about two weeks apart and around eight weeks of swimming instead of running. Meanwhile the team trained everything else hard, used BFR, and coordinated the PT, running coach and strength staff on a six-month plan.

• A 52-year-old executive

After a health scare, his testing showed very weak calves, poor balance and high Achilles and fall risk. So cardio and VO2 max work was designed around those risks rather than a running programme.

• A youth golf team

About 30% had lumbar stress fractures from heavy lifting with nobody watching technique. Brown says teens should get quick and coordinated first; strength can be added later.

OTHER RELEVANT

- **Prehab pregnancy and rehab postpartum**
  Brown argues that pregnant women should do foot strengthening and core work. Relaxin, weight and delivery change the feet, pelvis and pelvic floor, often showing up later as hamstring, sit-bone or knee pain.
- **Make your programme fit your life**
  Adherence beats perfection: swap exercises you hate, and adapt workouts to hotel gyms so two weeks of travel doesn't mean atrophy.
- **Treatments open a window; strength closes it**
  Adjustments, needling, cupping or even a cortisone shot are tools to lower pain so you can load and retrain. Strength is what makes improvements stick.
- **Keep doing barefoot work, but with care**
  Brown calls dropping barefoot training 'a pathway to frailty' but says to pair it with targeted stiffness and quickness work.

348 Women’s sexual health, menopause, and hormone replacement therapy (HRT)

Guest: Rachel Rubin
Date: 2025-05-12 · Duration: 2:24:37
URL: https://www.youtube.com/watch?v=W0XW6av2wLQ

KEYPOINTS

• Menopause is an empty gas tank, and perimenopause is the chaos before it

Rubin calls menopause a 'castration event'. Around 52 the ovaries largely stop making estrogen, progesterone and testosterone, while men's levels fall slowly. In a typical cycle estradiol runs from about 50 pg/mL at the low point to about 150 at ovulation (pregnancy is 3,000+). In perimenopause it can swing from 200 to 900 within ten days and then drop to zero, because the brain's FSH pushes a dwindling egg supply to overshoot.

• Women vary widely in how they respond to progesterone

Rubin suspects GABA-receptor effects; nobody can predict it. When she gives micronized progesterone, about a third of patients love it (better sleep, less anxiety), a third notice nothing, and a third are sensitive (sleepy, bloated, or worse). Peter puts the bad-reaction group at 10–20%.

• Going without hormones carries real risks too

Rubin says doctors talk about the risks of medication but rarely about the risks of not taking it. Without hormones, the genital and urinary tissue loses its acidity and protective bacteria, and UTIs rise sharply. Osteoporosis follows: about as many women die from hip fractures as from breast cancer, and Peter adds that half of survivors never regain their previous function. She adds heart disease and dementia, admitting the brain data is weak.

• The WHI scare came from a press conference and relative risk

The billion-dollar trial tested one old regimen at one dose (equine estrogen, plus medroxyprogesterone with a uterus). Results were announced at a press conference before the paper came out, and hormone use fell from roughly 40% of women to almost nothing. The headline was a 24% relative rise in breast-cancer incidence in the combined arm, with no rise in breast-cancer deaths. Peter says the absolute increase was about 0.1%, roughly one extra diagnosis per 1,000 women, and calls it the greatest injustice of modern medicine in his lifetime. Unreported: fewer fractures, colon cancers and diabetes cases, lower overall mortality, and lower breast-cancer incidence and death with estrogen alone.

• A generation of doctors never learned to prescribe hormones

Fewer than 6% of internists, OB-GYNs and family doctors get even an hour of menopause training. Fewer than 4% of eligible women now use hormone therapy, which is worse than ten years ago. Rubin works out about 84 million US women over 40 and about 3,000 clinicians listed on the Menopause Society site.

• Women's testosterone falls with age, not at menopause

The decline starts in the 30s. Testosterone receptors are found in the genitals, urethra and bladder, so low levels affect more than libido. There is global consensus that it treats low libido after menopause, but the US has no FDA-approved female product (Australia has one). Rubin says the FDA demanded a second five-year study after the first showed safety, and companies quit.

• Rubin's playbook adds one hormone at a time

Both doctors usually start with transdermal estradiol, because hot flashes are the most pressing symptom and stacking shows what each drug does. Then comes progesterone: 100 mg oral micronized nightly, or 200 mg for 12–14 days a month, with Peter often going up to 200 if tolerated. Taking it vaginally can reduce sedation. Testosterone is added last. Rubin uses about a tenth of a male dose: roughly 0.5 mL of 1% gel on the calf daily, with a 5 mL tube lasting about 7–10 days. She avoids pellets: supraphysiologic and irreversible.

• Oral, patch, gel and ring estrogen each have trade-offs

Oral estrogen passes through the liver, raises clotting proteins and SHBG, and so is avoided in smokers, people with obesity, or anyone at clotting risk. The KEEPS trial found transdermal estrogen better for sexual function. Patches can fail with sauna use or heavy sweat. The Femring (0.05/0.1) is systemic and needs progesterone. The 2 mg Estring is local only. Pharmacists sometimes mix them up, and Rubin often sees levels fade in a ring's third month.

• Use labs as a guide, but trust symptoms most

Both insist on sensitive LC-MS assays for estradiol and testosterone. Peter warns that ELISA tests can be thrown off by biotin and other interference, and the better test costs maybe $5–10 more. Symptoms come first. An FSH of 78 with estradiol of 40 nudges Peter to raise the dose, and breast tenderness is his clearest sign of too much.

• Local vaginal hormones are safe and cut UTIs by more than half

Estradiol cream (about $13 a tube), the Estring, or vaginal DHEA (Intrarosa) treats genitourinary syndrome of menopause: dryness, painful sex, urgency, leakage and UTIs. Rubin says these are safe at any age, including after blood clots or breast cancer, and don't raise blood estradiol, so women on systemic therapy can add them. Her group estimates that if Medicare patients used vaginal estrogen, Medicare would save $6–22 billion a year. Yet they still carry the systemic-estrogen boxed warning.

• Neither age nor ten years of use is a reason to stop

Rubin says the timing hypothesis rests on the WHI's old drugs, and Susan Davis has recently questioned even that. She calls osteoporosis prevention 'a green light' for offering therapy at any age. She sees no evidence for stopping after ten years. Bone gains disappear quickly when hormones stop, and stopping may destabilize plaque. The one reason she accepts is an active cancer being treated by blocking hormones.

EXAMPLES

• Rubin's mother in the ICU

Over six months in a Houston ICU after a transplant, with a catheter and on ECMO, Rubin had to persuade the transplant team, the ICU team and the pharmacy every week that vaginal estrogen doesn't cause clots. She also had to teach nurses to

apply it.

- **A gynecologist's advice to a woman in her 60s**
  The woman reported painful sex and asked for vaginal estrogen. She was told to 'think of other ways' to handle her relationship.
- **The ring that went missing**
  An ultramarathoner on a ring suddenly felt awful. Her estradiol was undetectable, and she couldn't find the ring, which had probably come out during a bowel movement.
- **The brain estrogen-receptor finding**
  Rubin cites Lisa Mosconi's work: receptor density in the brain rose rather than fell after menopause, up to age 65, and tracked brain fog. Peter compares this to muscles becoming insulin resistant during fasting to save glucose for the brain.
- **Biest as 'fancy lotion'**
  Patients using compounded biest (80% estriol, 20% estradiol) sometimes have estradiol below 5. Rubin moves them to FDA-approved products she can confirm are absorbed.

OTHER RELEVANT

- **Ask for every option, and watch for red flags**
  Be wary of a clinician who offers only one product, sells you compounded hormones they profit from, pushes pellets costing thousands, or requires expensive saliva tests.
- **Find a clinician through menopause.org or isswsh.org**
  Menopause Society listing means the clinician passed an exam. ISSWSH lists clinicians focused on sexual health.
- **Consider vaginal estrogen or DHEA even if your hormone dose is good**
  Rubin says systemic estrogen often doesn't fix urinary or vaginal symptoms. Peter notes this hasn't been tested in a randomized trial, so for now it rests on expert opinion.
- **With breast-cancer risk, weigh both sides with your care team**
  After risk-reducing surgery without cancer, skipping hormones may trade breast risk for worse bone and heart outcomes. After DCIS with no endocrine therapy, Rubin sees no barrier. Active cancer needs individual decisions, and she suggests rethinking it the way prostate cancer and testosterone have been rethought.

346 - Scaling biotech and improving global health: lessons from an extraordinary career in medicine

Guest: Susan Desmond-Hellmann
Date: 2025-04-28 · Duration: 2:28:18
URL: https://www.youtube.com/watch?v=ib88qkNY3LQ

KEYPOINTS

• Her career was shaped by the early AIDS epidemic.
Desmond-Hellmann, who went to Catholic school for 12 years in Reno, trained in San Francisco in 1982, a year after the first MMWR report, when the disease was a frightening mystery—she and colleagues even had blood drawn to check whether they'd been infected treating patients. Some patients sold their life insurance expecting to die soon, then regretted it once antiretroviral therapy arrived.

• Frontline work in Uganda showed the scale of the crisis.
With her husband, she worked on HIV in Uganda while still UCSF faculty. A 16-year-old girl attending an STD clinic had about a 50% chance of being HIV positive; Peter suggests sky-high viral loads drove heterosexual transmission rates far beyond what treated HIV produces today. She estimates a country of 16 million may have lost around a million people.

• Oncology in the mid-1980s offered little: durable remissions for perhaps 10%.
She describes patients with six months to live and few options, which drew her toward new mechanisms. At Bristol-Myers Squibb she taught herself SAS programming and, as the safety lead, helped make Taxol—a microtubule inhibitor with a new mechanism for drug-resistant cancers—safe to give, including managing reactions to its dissolving fluid.

• Genentech pioneered recombinant biologics and large simple trials.
In the late 1970s Genentech proved to the FDA its fermented human growth hormone was pure. It 'bet the farm' on TPA for heart attacks, proving benefit in 30-day outcomes and building large simple trials and postmarketing registries. When she arrived in 1995 the company was struggling, and oncology was its future.

• Herceptin made targeted oncology real, but only for some patients.
Herceptin targeted HER2-positive breast cancer; about three of four breast cancer patients weren't eligible, which motivated the search for more drugs.

• Rituxan rescued an antibody skeptics didn't believe in.
IDEC, which made an anti-CD20 antibody for lymphoma, was going to run out of money around 1995–96 when Genentech partnered. CD20 is on B cells; marrow reserves of immature cells replace depleted ones, so patients can be treated repeatedly. Surprisingly, lymphoma patients didn't develop antibodies against it.

• Avastin emerged from Judah Folkman's angiogenesis idea.
Napoleone Ferrara built an anti-VEGF antibody on the same backbone as Herceptin, about 93–94% human. A tough phase 2 in heavily pretreated metastatic breast cancer demanded at least 50% tumor shrinkage; colon cancer then became the phase 3 survival study.

• Drug development stages explained.
Phase 1 is dose escalation with an art to choosing the starting dose—'because we are greedy in oncology, we always look to see if anybody responds.' Phase 2 can cost in the tens of millions; phase 3 confirms benefit. Even then, 500 patients is very limited for safety—5–10% may have side effects that stop them taking the drug.

• Avastin's price tested the value debate.
At about $100,000 per course and roughly eight months' median survival gain, it failed the UK NHS's cost-per-QALY threshold. She acknowledges patient assistance programs didn't solve overall cost.

• Leading UCSF and the Gates Foundation required financial and cultural skill.
She became UCSF chancellor in 2009 amid recession and faculty skepticism of an outsider; grateful patients were the key donor base. As Gates Foundation CEO from 2014, she focused on strategy, decision frameworks and an empowering, values-driven culture.

• Public trust in science eroded during COVID.
She isn't convinced we're better prepared for a pandemic than in 2019. On ivermectin claims for stage 4 cancer, she says patients deserve data on dosing and harm; if a cheap drug cured cancer, pharma would modify and patent it immediately. She notes premature dismissal of the lab-leak question in May 2020 hurt credibility.

• AI could compress trials without cutting corners.
Desmond-Hellmann argues AI shouldn't change what a trial tests, but it can speed the pieces—site selection, enrollment, data cleaning, monitoring—so a six-year program shrinks. She suggests interim looks: at three years, you might already see the trend. And approvals made in emergencies aren't wrong if later data show less effect—'any port in a storm'.

EXAMPLES

• The 83-year-old pharmacist
A patient from her practice with low-grade lymphoma illustrated the need for gentler, repeatable therapies such as anti-CD20 antibodies.

• Elizabeth Glaser Pediatric AIDS Foundation
Her husband has worked with it for 15 years across about 12 sub-Saharan African countries.

• Viral load as a surrogate
Using viral load as an endpoint enabled about 20 HIV drugs in five years—a model for faster trials.

• OpenAI board
She joined after the November 2023 'blip' and argues AI should streamline clinical trials so delays happen only when they benefit humans, perhaps cutting trial time by up to 60%.

- **Fifteen breast cancers**
  With subtypes like ER+, HER2+ and triple-negative, precisely matched therapies could need only about 10 patients per trial because responses would be obvious.
- **Returning to UCSF**
  The institution that once wouldn't give her a clinical appointment after Uganda later made her chancellor—its highest post—reflecting what she had learned in a decade of biotech. Roche bought Genentech in 2009.

OTHER RELEVANT

- **Ask what a drug's benefit is worth.**
  Median survival gains measured in months, at six-figure prices, deserve scrutiny alongside quality of life.
- **Expect safety signals after approval.**
  A few hundred trial participants can't reveal rare harms; postmarketing surveillance matters. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Demand data, not clips.**
  For viral treatment claims, ask for dose, outcomes and side effects from real trials.
- **Use risk stratification in screening.**
  On prostate cancer, PSA density plus tools like PHI or 4K can guide who needs multiparametric MRI.
- **Leadership lesson: build trust with skeptics early.**
  Faculty were as nervous about money as she was; she won them over by showing she could fund their programs and by listening, a model for any outsider leader.

345 Chronic pain: pathways, treatment, and the path to physical and psychological recovery

Guest: Sean Mackey
Date: 2025-04-21 · Duration: 3:15:36
URL: https://www.youtube.com/watch?v=SsHdjDFNbp4

KEYPOINTS

• Pain is a biopsychosocial experience, not a simple wire to the brain.
Mackey, chief of pain medicine at Stanford, says Descartes' 17th-century model—injury sends a signal straight to the brain—stuck for centuries and lingers today. Only in the last 20 years or so have surgeons widely accepted that what patients bring to the operating table, including early-life experiences, shapes how much pain they feel.

• Different nerve fibers carry different pain, and referral explains odd symptoms.
Myelinated A-delta fibers transmit at about 10 m/s—roughly 10 times faster than unmyelinated C fibers—giving the sharp first pain before the dull ache. Bowel biopsies often don't hurt because those nociceptors don't respond to cutting; diaphragm irritation shows up as shoulder pain because both are served by C3–C5 ('C3, 4, 5 keeps the diaphragm alive').

• The spinal cord gates pain, so identical injuries feel different.
Melzack and Wall's 1965 gate control theory explains why ten people with the same injury report different pain, and why TENS and other neuromodulation can work. In a study applying a 48°C stimulus to about 500 people, ratings ranged from 0 to 10; Mackey's ice-water demo with medical students shows the same spread.

• Emotion, beliefs and sleep turn the volume up or down.
Mackey likens pain processing to a stereo amplifier set differently in each person. Peter notes his 42°F cold plunge sometimes feels like nothing for 10 minutes and sometimes makes his ankles scream after 30 seconds. Catastrophizing, a concept introduced by Albert Ellis in 1962, is a strong amplifier.

• Pain is evolutionarily essential.
People who can't feel pain make dangerous decisions and historically didn't pass on genes; Peter jokes he doesn't understand why more young males didn't die before 20. Cultural norms also reward stoicism—Mackey's father, one of 13 children, brought that ethic home.

• NSAIDs and acetaminophen work best thoughtfully combined.
NSAIDs and COX-2 inhibitors reduce the 'inflammatory soup' of swelling, redness and heat; Vioxx was withdrawn after FDA concerns. A combination of 400 mg ibuprofen and 500 mg acetaminophen three times daily worked well for Peter; naproxen at 500 mg twice daily is easier to line up. These are personal regimens discussed, not general prescriptions.

• Muscle relaxants and gabapentinoids have specific roles and side effects.
Peter uses 2–3 days of baclofen 20 mg with a little NSAID to abort back flares; Mackey generally goes up to 20 mg three times daily orally, with intrathecal pumps for severe spasticity. Gabapentin and pregabalin act on the alpha-2-delta calcium-channel subunit; gabapentin absorption saturates around 900–1,000 mg per dose, so he doses lower by day and higher at night (e.g., 300/300/600), and warns elderly patients about falls. Pregabalin can cause weight gain.

• Chronic pain is enormous in scale.
Mackey estimates 50–100 million Americans have chronic pain, about 8% (20+ million) with high-impact chronic pain; low back pain is the most common at about 28%.

• Opioids have a nuanced role, and the crisis had many parents.
Mackey criticizes how a brief letter to the New England Journal claiming little addiction was amplified by Purdue and others. Peter compares the crisis to the 2006–08 mortgage crisis: easy to blame one actor, but many contributed. Mackey's 2010 Institute of Medicine panel flagged the long-term effectiveness and safety of opioids for chronic pain as a top unanswered question.

• Low-dose naltrexone is a promising, cheap option for fibromyalgia and beyond.
At 50 mg naltrexone blocks opioid receptors; at about 4.5 mg it appears to block toll-like receptor 4 on microglia, calming neuroinflammation. Mackey has gone up to 13.5 mg in some patients. About 20–30% get vivid 'technicolor' dreams; if it's activating, take it in the morning. It must usually be compounded.

• Peter recovered from 320 mg/day of OxyContin to full function.
A 5 cm disc fragment sat on his S1 nerve root; he was taking about 320 mg of OxyContin daily—enough, he says, to kill two people today—to blunt emotional as well as physical pain. Mackey later gave him 400 mg of IV lidocaine over 20 minutes under EKG monitoring, followed by precise injections at T12–L1 facets over 3–4 months, and gabapentin he tapered off within 18 months.

EXAMPLES

• Peter's L5–S1
After multiple surgeries he has essentially no disc at L5–S1, leading to facet arthropathy higher up; his recovery is about '90% good', with a rare seconds-long flash of fire in the foot about once a year.

• Peripheral nerve blocks
A surgeon argued blocks were underused because nobody wants to wait 10 minutes for bupivacaine to work; even a 50% cut in post-op opioid needs would be huge. Stanford's acute pain service sees 30–50 patients a day.

• Acupuncture
Mackey's grant work is building a model predicting response to real versus sham acupuncture. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Cannabis

Few well-controlled trials show short-term benefit in neuropathic pain; UCSF researchers reportedly received study cannabis by armored truck.

- **Fibromyalgia criteria**

  The old 11 of 18 tender points have been replaced by multiple-site involvement plus a symptom severity score.

OTHER RELEVANT

- **Don't settle for 'cure' or 'give up'.**

  Mackey avoids promising cures but never gives up: there are 200+ analgesic drugs, 200+ procedures, mind-body and rehabilitative approaches to try.

- **Pair physical rehab with psychological recovery.**

  Breaking the pain cycle requires both; catastrophizing and fear can be treated. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Ask about low-dose naltrexone for centralized pain.**

  It has a benign side-effect profile and decades of safety data at higher doses, though evidence is still developing.

- **Use NSAIDs short-term and smartly.**

  Combinations and timing can limit doses; discuss GI, kidney and cardiovascular risks with a doctor. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

343–The evolving role of radiation: cancer treatment, low-dose treatments for arthritis, & much more

Guest: Dr. Sanjay Mehta
Date: 2025-04-07 · Duration: 2:25:06
URL: https://www.youtube.com/watch?v=xtgQUiBuGVI

KEYPOINTS

• Only ionizing radiation damages DNA, so cell phones and microwaves can't cause cancer that way.

Houston radiation oncologist Sanjay Mehta (more than 25 years in practice) explains the spectrum: radio waves, microwaves and visible light are non-ionizing. They can heat tissue but can't knock out electrons, so 'fallacies about your cell phone giving you brain cancer are just that'. Ionizing radiation starts at UV and X-rays. Diagnostic radiology uses kilovoltage X-rays, while the linear accelerators used to treat cancer use megavoltage.

• Everyday exposures are tiny next to the 50 mSv annual limit.

A gray is joules absorbed per kilogram of tissue. A sievert is the equivalent exposure measure, and one gray is roughly one sievert. Living at sea level gives about 1–2 mSv a year, Denver two to three times that, and a polar flight perhaps 3–4 mSv per trip. A chest X-ray or mammogram is under about 1 mSv. Modern cardiac CT angiograms are about 1–3 mSv (once about 25), and a whole-body PET-CT is perhaps 50–100. By contrast, prostate cancer treatment delivers 70–80 Gy, but only to the gland, split into daily 1.8–2 Gy doses. Mehta never skimps on dental X-rays, mammograms or cardiac imaging: 'the risk–benefit ratio is so heavily in favor'.

• Mehta believes the linear no-threshold model overstates the harm of very low doses.

LNT extrapolates cancer risk downward from high-dose data (atomic bombs, Chernobyl). Mehta notes it rests partly on a Nobel laureate's 1940s fruit-fly work and argues there's effectively a threshold. He cites animal data suggesting hormesis at single-digit mSv (better bone healing) and reports of lower leukemia and thyroid cancer rates among people a few miles from Hiroshima and Nagasaki. He calls these controversial and not widely accepted, but thinks fear of low doses is 'overblown'. The ALARA principle (as low as reasonably achievable) still guides practice.

• Breast-conserving surgery plus radiation replaced radical mastectomy, and today's courses are shorter and gentler.

Trials in the 1980s (Fisher) showed lumpectomy plus radiation matched mastectomy for survival. Today a typical course is about 40 Gy in 15 daily fractions over about 3 weeks, roughly biologically equivalent to the old 50 Gy in 25–28 fractions, plus an optional 10 Gy boost to the tumor bed. CT-based 3D planning, molded body casts, angled beams and deep-breath holds for left-sided tumors keep dose off the heart and lungs. Even dosing has replaced the old cobalt-era hot and cold spots, which caused severe skin burns or missed areas. Sessions take about 15 minutes, and patients often ask 'when do we start?' after it's already done.

• Mehta considers prostate radiation now as curative as surgery, with fewer urinary and sexual side effects.

Radiation used to be reserved for men who couldn't have surgery, which made older results look worse. Precise beam shaping (IMRT/IGRT), a full bladder, an empty rectum and daily imaging now keep dose to the rectum, bladder and penile bulb very low. Mehta says he can't recall a continent patient leaving incontinent. The trade-off is hormone therapy (ADT) for higher-risk disease, with hot flashes and low libido. AI pathology (ArteraAI) and genomic tests (Decipher) now spare perhaps a quarter of Gleason 7 patients from ADT, and PSMA PET lets him treat isolated recurrences directly.

• In the brain, focused radiosurgery has largely replaced whole-brain radiation.

Whole-brain radiation (30 Gy in 10 fractions) caused memory problems years later in metastasis patients who now live longer. Its use is perhaps 10% of what it was. Radiosurgery targets individual metastases, and when the whole brain must be treated, IMRT spares the hippocampi. Small-cell lung cancer patients with a complete response still get preventive cranial radiation (about 20 Gy in 5 fractions), which Mehta says cuts brain recurrences by roughly 70–80%. Glioblastoma gets about 60 Gy, and proton therapy limits the dose beyond the tumor, which matters for children.

• Low-dose radiation for arthritis and tendinopathy is routine in Germany but rare in the US.

Mehta says Germany treats some 20,000–50,000 patients a year for osteoarthritis, tendinitis, bursitis and plantar fasciitis. The usual protocol is 0.5 Gy × 6 (Monday, Wednesday, Friday for two weeks; 3 Gy total, about one cancer fraction), with an optional repeat after 12 weeks. He describes a cortisone-like anti-inflammatory effect, quoting 60–80% response after one course and 90%+ after a repeat. He has treated about 70 cases, including his own Achilles. The evidence is mostly observational: the two randomized trials were small and, he says, poorly run.

• Benign treatments use large fields and very low total doses, the opposite of cancer treatment.

The goal is to calm inflammatory cells across the whole painful region, so Mehta treats generously: for an Achilles, from the calf down to the heel and onto the sole. For superficial joints like hands, knuckles or the elbow he can use electron beams with the target removed, so dose stays shallow. With no vital organs nearby, the body-wide dose is about that of a CT scan. Patients keep training through the two weeks. Spine results are less reliable because nerve compression can't be fixed this way, though facet and SI joints respond.

EXAMPLES

• US fear of radiation has historical roots.

Mehta points to the Radium Girls, who licked radium-paint brushes, though he says only about 50 of roughly 1,500 suffered toxic effects, along with Cold War fears and oil-industry lobbying against nuclear power. Meanwhile 0.5–2 million American children had nasal radium treatments in the 1920s–40s with few reported problems.

• A PSA of 1,900.

A symptom-free 65-year-old whose bone scan 'looked like a Christmas tree' responded to chemotherapy and ADT, then had his prostate treated. He was still active about 12 years later, with no fractures.

• Mehta treated his own Achilles.

His left side had two cortisone shots plus PRP. A year later he radiated the right side only. Relief took about two months, and

both sides are holding up. Surgeons with plantar fasciitis who couldn't stand to operate improved within about a week.

- **Keloids and Dupuytren's.**
  Keloids get about 12 Gy in 3 fractions starting the same day as surgical removal. Radiating an intact keloid does little. Dupuytren's and Ledderhose fibrosis take higher doses (about 3 Gy × 5, repeated).

OTHER RELEVANT

- **Don't avoid indicated imaging because of radiation fears.**
  Dental X-rays, mammograms and a modern cardiac CT add only a few mSv.
- **For prostate cancer, see both a surgeon and a radiation oncologist.**
  Ask about genomic or AI risk tests that could spare you hormone therapy, and choose a high-volume specialist in your type of cancer.
- **For stubborn tendinopathy or arthritis, ask whether low-dose radiation is an option.**
  The evidence is mostly observational, but Mehta says US insurers, including Medicare for osteoarthritis codes, often cover it.
- **Ask to see your treatment plan.**
  Mehta walks interested patients through dose–volume charts showing how much each organ receives.

342 Aging well: Peter shares strategies for improving longevity with residents at senior living

Date: 2025-03-31 · Duration: 0:45:16
URL: https://www.youtube.com/watch?v=rRZs9xJ0ulo

KEYPOINTS

• Longevity means both lifespan and healthspan, and healthspan has three parts.

Speaking with residents of a senior living community, in a conversation hosted by his daughter Olivia, Peter defines longevity as maximizing how long and how well you live. Healthspan covers the physical (free of pain, able to garden, golf, hike or simply care for yourself), the cognitive (a sharp mind) and the emotional (purpose, happiness, connection). Asked to choose between living to 80 in good health with a quick end, or to 100 with 20 years of painful decline, he expects almost everyone would pick the first.

• It's never too late to start, and the biggest gains go to the least active.

Peter compares it to saving for retirement: earlier is better, but starting late still pays. Trials in older adults show people who first lift weights in their 60s and 70s benefit remarkably. Adding 3 hours a week of exercise barely changes things for someone who already trains, but taking a sedentary person to 3 hours (30 minutes, 6 days a week) has an 'enormous' impact.

• The four horsemen are heart disease, cancer, neurodegeneration and metabolic disease.

Cardiovascular and cerebrovascular disease is the leading cause of death for men and women, in the US and globally. Cancer is close behind and is many different diseases ('prostate and breast cancer are as different as a pickup truck and a Corolla'). Third is dementia, including Alzheimer's and vascular dementia. Fourth is the spectrum from insulin resistance and fatty liver to type 2 diabetes, which rarely kills directly but raises the risk of the other three by about 50%.

• Surviving a heart attack is a second chance to act on the controllable risks.

About half of heart attacks are immediately fatal. Survivors should target what drove the first event: cholesterol, blood pressure and smoking (the big three), plus exercise and metabolic health. Peter knows people who had a heart attack at 60, lost 30 lb, quit smoking, managed their numbers, started exercising and lived into their 90s.

• After 65, falls drive a five- to sixfold rise in accidental death.

At Olivia's age, accidental deaths are mostly car crashes and overdoses. At Peter's, overdoses. Over 65, almost all are falls. Three things drive it: loss of type 2 (fast-twitch) muscle fibers, which shrink from about age 25 and supply the reactive step that catches a stumble; lower muscle mass; and lower bone density. Women are more affected, partly because many didn't receive hormone therapy after menopause and estrogen is the most important hormone for bone. About half of hip-fracture survivors never regain their previous mobility.

• Heavy strength training can rebuild bone, even in frail older women.

Peter's favorite example is Belinda Beck's LIFTMOR trial in Australia. Women over 65 with very low bone density, who had only walked or done yoga, were randomized to supervised heavy training: squats, deadlifts, presses and pull-up progressions. Some ended up deadlifting their own body weight, and scans showed bone density increased, which was once thought impossible. Fast-twitch fibers also respond only to heavy loads plus reactive movement like bouncing, side-to-side steps and jumping rope. 'Lifting weights is something every person on this planet should be doing.'

• Older adults need about 1 g of protein per pound to fight anabolic resistance.

Peter's diet principles: don't eat too much or too little, and find a pattern you can stick to, whether vegetarian, Mediterranean or steak and potatoes. Aging muscles respond less to a given amount of protein (anabolic resistance), so needs rise just as many older people, especially women, eat like 'little birds'. If you weigh 150 lb, aim for about 150 g. Half that is clearly too little. Overweight people can base it on a reasonable goal weight. Track a week in an app to check.

• Sleep in later life: protect the wake time, cut naps, and time fluids, food and alcohol.

With age, sleep gets lighter and nighttime urination more common. Thirst also becomes a less reliable signal, so hydrate during the day but taper fluids before bed. Leave about 3 hours between dinner and bed, minimize alcohol, and keep the room dark and cold. The biggest lever is a fixed wake-up time with no daytime naps, which builds sleep pressure. If you still struggle to fall asleep, try the lowest-dose melatonin (about 300 mcg, no more than 1 mg), which helps start sleep but doesn't keep you asleep. Ashwagandha helps some people.

EXAMPLES

• 'Sitting is to lower back pain what bourbon is to alcoholism.'

Peter argues most people are less fragile than they think and that inactivity often worsens back pain. Bone-on-bone joints may need replacement, which he says has transformed quality of life, and a good physical therapist can sort out what training can fix.

• Klotho.

Neurologist Dena Dubal studies klotho, a brain-protective protein that exercise raises and age lowers (children make about six times more). In mice and monkeys it reverses cognitive decline. Human trials are starting, so a drug is perhaps 7–10 years away in the best case.

• APOE.

Two copies of APOE4 raise Alzheimer's risk about tenfold and one copy about twofold. About 60% of people are 3/3, Peter included, but he acts as if he's high risk. Women face nearly double men's risk.

• A hip fracture followed by decline.

An audience member's mother fell, broke her hip and then declined cognitively. Peter suspects the long physical and mental inactivity sped up decline by years, while noting this is hard to prove.

OTHER RELEVANT

• Start strength training now, with guidance.

Work up to heavy, supervised compound lifts and add balance and reactive drills to protect against falls.

- **Prioritize protein, ideally from dairy, beef and eggs.**
  For supplements, whey, casein or egg protein are best. Many people who can't tolerate dairy react to the sugar (lactose), not the protein.
- **Guard your social network and purpose.**
  Peter calls social support and a sense of purpose perhaps the most important emotional-health tools. He cites the familiar pattern of a long-married spouse dying within a year of the other.
- **If you've had a cardiac event, treat it as a turning point.**
  Work with your doctor on lipids, blood pressure, smoking and exercise.

341 - Overcoming insomnia: improving sleep hygiene and treating disordered sleep with CBT-I

Guest: Ashley Mason
Date: 2025-03-24 · Duration: 2:21:18
URL: https://www.youtube.com/watch?v=NneZHMv7VBU

KEYPOINTS

- **Insomnia is common, clinical and episodic, and what keeps it going isn't what started it.**
  Mason, a UCSF psychologist who trained where CBT-I co-inventor Richard Bootzin worked, estimates that about 90% of adults struggle with insomnia at some point. At any moment, 5–10% meet the definition: roughly three months of bad sleep that is distressing and impairs life. Predisposing traits plus a trigger such as job loss, divorce or a crash start it. Coping behaviours—Benadryl or Ambien, naps, scrolling or reading in bed—keep it going after the trigger is gone.
- **CBT-I treats current behaviour, not the original cause, so one recipe fits most types.**
  Trouble falling asleep, waking at night and waking too early all get the same intervention; for night waking, the racing mind just shows up later. Mason doesn't ask what caused the insomnia until the end of the first session. Done well, about 50% reach remission and about 70% improve meaningfully. Failure mostly comes from not doing it—or from distressed natural short sleepers who may not need fixing.
- **Stimulus control: the bed is only for sleep and sex.**
  This descends from a 1970s study in which struggling students could study in only one library carrel. People with insomnia often 'camp out' in bed—snacking, TV, podcasts—hoping to catch sleep, and break the bed–sleep association. Dismantling studies show CBT-I fails without stimulus control or time-in-bed restriction.
- **Time-in-bed restriction matches time in bed to the sleep your body actually produces.**
  From a 7-day paper sleep diary, average sleep plus 30 minutes sets the time in bed, with a floor of about 5.5 hours. If someone sleeps about 6 hours with a 7 a.m. wake time, bedtime becomes 12:30 a.m. When sleep efficiency (time asleep ÷ time in bed) exceeds 85%, bedtime moves 15 minutes earlier each week. Patients get worse for the first couple of weeks.
- **Fix the wake time first—a consistent wake time alone helps 1–2 of every 8 patients.**
  In Mason's 'democracy within a dictatorship,' she sets the wake time from what the diary shows the person can actually do, not their aspirational 5 a.m. She runs one week with that wake time and no naps before calculating a bedtime. You can force a wake time with an alarm, but not a bedtime. During treatment, every day that ends in 'day' has the same wake time.
- **Scheduled worry time keeps worries from 'demanding attention' at night.**
  Saying 'stop worrying' doesn't work. Instead, book a non-negotiable hour a day and jot down intrusive worries until then. Mason also has patients track how much they believe a 1 a.m. or 7 a.m. thought at different times of day. A patient with MS believed 'I'll never make it through today' at 7 a.m., but 0% by 5:30 p.m. She turned 7–9 a.m. into Italian-learning time.
- **Keep the body cool and the hands and feet warm.**
  Mason swaps down comforters and duvets for cotton blankets ('if I had five cents...') and recommends a room in the mid-60s °F. Warm hands and feet help the core dump heat for sleep onset; socks or a small auto-off heating pad are fine. She's wary of heated settings on mattress-cooling devices, citing the electric-blanket era. Avoid a cold plunge before bed, and test whether a sauna helps or overstimulates you.
- **Caffeine, including decaf, ends by 11 a.m.—but don't cut the amount.**
  Caffeine's half-life is about 4–6 hours. Decaf can carry about 15% or more of regular caffeine, and one outside test found a tall Starbucks with about 310 mg against a stated 155 mg. Mason keeps the total the same to avoid withdrawal and just moves it before 11. She doubts truly caffeine-immune people exist.
- **Melatonin is the starter's pistol, not a car in the race.**
  Supplements often don't contain what the label says, and taking melatonin at the wrong time can push sleep before the body is ready, leading to night waking. Mason stops supplements during treatment. Exception: beta-blockers suppress melatonin, and one patient on metoprolol for 30 years needed only a small nightly melatonin dose.
- **Taper hypnotics slowly, and only after stabilising.**
  First come one drug, one dose, one time, with no middle-of-the-night top-ups and no 'rotating' Ambien, trazodone and Benadryl. After CBT-I, patients reduce in steps they rate as 1 out of 10 on a stress scale—say, 12.5 to 12 mg—weighed on a jewellery scale and held about three weeks, often over a year. The taper pauses during life crises, always alongside the prescriber. Mason worries least about low-dose trazodone.

EXAMPLES

- **Middle-of-the-night reset**
  If you can't sleep, get up and do something 'embarrassing but boring'—trashy magazines, solitaire, a 20-minute sitcom. No email, news, social media or stressful trading, and don't make 3 a.m. into 'me time.'
- **Orange-lens glasses**
  For some patients with sleep-onset trouble who weren't using stimulating screens, wraparound orange glasses worn two hours before bed allowed them to quit Ambien. Attia finds that avoiding email matters more than filtering blue light.
- **Wine-glass swap**
  A patient drinking 16–20 oz of wine nightly moved to 2 oz plus a 'special' non-alcoholic drink in the same glass, keeping the routine consistent before treatment started.
- **Weekend rule**
  After a late Friday, sleep in by about an hour on only one day and hold your normal wake time the next. Attia's 2 a.m. flight return followed by sleeping until 8 pushed his bedtime late the following night.
- **The wearable-anxious 70-something**

An active volunteer was fine until her tracker kept warning her. The 'treatment' was taking the device away; Attia's clinic uses six-month tracker holidays.

OTHER RELEVANT

- **Low-hanging fixes to A/B test for two weeks**
  Older men waking to urinate can drink less at and after dinner (a light electrolyte tab may help). Use an eye mask for early waking, and take medications at consistent, appropriate times (not 450 mg bupropion at bedtime). Stop eating three hours before bed, and avoid podcasts in bed.
- **Do CBT-I yourself if you're stuck on a waitlist**
  Use 'Quiet Your Mind and Get to Sleep' (Manber and Carney) and a paper sleep diary. Find providers through the behavioural sleep medicine directory—telehealth makes access easier. Commit to weekly sessions over 5–8 weeks; four or more sessions predicts much better outcomes.
- **Rule out other sleep disorders**
  Snoring or gasping warrants evaluation, and if you have a CPAP, get it fitted and use it nightly.
- **Evening exercise depends on the person**
  Yoga or lifting late is usually fine. Late HIIT or hockey may keep heart rate up, especially in less fit people. A 5 a.m. class can cost sleep if your body won't sleep before 11.

339 - Unpacking trauma: How early wounds shape behavior and the path toward healing

Guest: Jeff English
Date: 2025-03-10 · Duration: 2:29:47
URL: https://www.youtube.com/watch?v=mE5vd98mohY

KEYPOINTS

- **Trauma isn't only 'big T' events like war.**
  English, a trauma-focused counselor at The Bridge to Recovery in Bowling Green, Kentucky, says people often picture Vietnam or 9/11-scale events. But trauma also includes chronic, highly stressful experiences in childhood—abuse, neglect, enmeshment—that shape how a person learns to survive. He cautions against both extremes: denying trauma and declaring that 'everything is trauma'.
- **The 'trauma tree': wounds are the roots, behaviors are the branches.**
  Roots are the wounding experiences (abuse, neglect, abandonment); branches are how they show up in adulthood—addiction, codependence, rage, people-pleasing, perfectionism. Abandonment is an 'umbrella wound': when a parent abuses you, they also abandon you. Treating only the branches, such as stopping drinking, leaves the roots driving new behaviors.
- **Childhood adaptations become adult maladaptations.**
  Strategies that helped a child survive—control, hypervigilance, caretaking, over-achieving—become liabilities later. Clients often resist healing because they fear losing traits they credit for success, a resistance Peter admits he felt. Socially rewarded behaviors like workaholism and perfectionism are hardest to address because everyone praises them.
- **Insecure attachment is the common denominator.**
  There are many unhealthy attachment styles, but English says the shared thread is insecurity, rooted in how caregivers responded.
- **Shame and guilt are different, and shame drives many behaviors.**
  Guilt says 'I did something bad'; shame says 'I am bad.' Shame can be passed down: one client said his father never had to get sober because the family carried the shame for him.
- **Healing requires surrender, fewer distractions and vulnerability.**
  Borrowing from 12-step language about powerlessness, The Bridge asks clients to give up control. The program removes distractions, and clients spend long days in group therapy plus evening 12-step meetings—even non-substance 'addicts' are told to substitute caretaking or work for alcohol in what they hear.
- **The program's rules exist to create emotional safety and surface patterns.**
  Examples: don't hand someone a tissue—a reflexive rescue can cut off emotion that 'may have been 25 years in the making'; adults ask for their own. Don't minimize others' experiences. Breaks happen about every 50 minutes. Group members are encouraged to 'take a risk' and name what they see, such as someone arriving late.
- **Storytelling and the 'no feedback to feedback' rule.**
  Each client gets about 45 minutes to tell their story, then must listen. They may not respond to feedback—undercutting the control many use to keep their polished narrative intact. Peers typically share feelings like 'when you described that at 8 years old, I felt angry,' showing they were present.
- **Immersion works differently from weekly therapy.**
  English compares it to language learning: two hours of Portuguese lessons a week works eventually, but moving to Brazil works faster. Residential programs aren't required to heal, though, and he warns against implying otherwise.
- **Trauma is transmitted across generations unless someone breaks the cycle.**
  A wound in generation minus two can manifest differently in minus one and become a blind spot in the current generation. 'I don't drink, so I'm not as bad as my parents' can mask work still to be done.
- **Insight alone isn't change; breakthroughs rewire beliefs.**
  English describes moments that shatter a belief and make change possible, but insists new patterns must be practiced. He distinguishes deep-seated trauma from simple bad habits by whether behaviors resist ordinary effort and are tied to emotional wounds.
- **Therapists must do their own work.**
  English says The Bridge doesn't operate from 'therapy hill': staff are expected to keep working on their own healing, which is why some clinicians won't work there. His own codependence taught him he expected others to rescue him. He sees his purpose as coming from both pain and hope, and says he heals a little each time he helps a client—while still knowing when to take the therapist hat off with his own family.

EXAMPLES

- **Peter at The Bridge, December 2017**
  Peter, one of 12 in his group, describes arriving feeling they were 'a collection of losers' who had lost everything and came because they had no choice. He said almost nothing for the first days because of the discomfort of opening up; morning runs at 5:30 helped him cope.
- **A reaction 16–18 hours later**
  English describes a client still having a strong reaction many hours after a schedule detail wasn't written on the board—showing how control needs link to old wounds.
- **The bullied boy**
  A client who spent three years being bullied daily while no adult noticed carried that neglect into his 30s.
- **English's own story**
  He was a client in 2016 before becoming a therapist there; his sister, raised in the same home, died in 2014, and his 87-year-

old mother lives with dementia in a nursing home.

- **'Higher dose' isn't the answer**
  Peter reflects that if you keep 'upping the dose' of a coping strategy you'd end up comatose—there's no dose at which a breakthrough happens without addressing the wound.

OTHER RELEVANT

- **Look beyond the behavior to the wound.**
  If a pattern persists despite willpower, explore what it protected you from as a child. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Vet 'trauma-informed' therapists.**
  A 45-minute seminar doesn't make someone trauma-informed; ask about depth of training and experience rather than a long list of modalities.
- **Expect the work to be uncomfortable.**
  Good therapists keep you grounded in the present while you revisit the past—'feel a little of the temperature' without drowning.
- **Parents: prioritize safety and connection.**
  English says his most important job is that his children go to bed and wake up feeling safe—the best way to stop generational transmission.
- **Be patient with change after intensive work.**
  English notes clients sometimes leave a great session and return a week later seemingly transformed—or backslid. Follow-up support, ideally with someone familiar with the program you attended, helps integrate breakthroughs into daily life.

337- Insulin resistance masterclass: The full body impact of metabolic dysfunction, treatment & more

Guest: Ralph DeFronzo
Date: 2025-02-24 · Duration: 2:42:18
URL: https://www.youtube.com/watch?v=vYQaLV3Fm00

KEYPOINTS

• 'Insulin resistance' only means something once you name the tissue and the process

DeFronzo developed the euglycemic insulin clamp. Insulin is raised by about 100 µU/mL and held there for two hours, while glucose is infused to keep blood sugar near 80–90. Under those conditions about 80–90% of glucose goes into muscle, about 10% into fat, and essentially none into the liver. Different tissues switch off at different insulin levels. A rise of only about 10 µU/mL stops fat breakdown, the liver needs about 50 to stop releasing glucose, and muscle uptake still climbs 20–25% between 100 and 200.

• Type 2 diabetes needs two defects

Insulin resistance on its own doesn't cause diabetes as long as the beta cells can keep up. Diabetes appears when genetically vulnerable beta cells wear out from constant overwork. DeFronzo says about 10–15% of people already have clinically significant heart disease when diagnosed, and 'virtually 100%' do if you look carefully. The same blocked signaling step (IRS-1/PI3-kinase) that keeps glucose out of muscle also stops nitric oxide production, which ties insulin resistance directly to atherosclerosis.

• Too much insulin causes insulin resistance

When his group raised healthy lean young adults' fasting insulin from about 8 to 20 µU/mL, still below a normal meal spike, they became as insulin resistant as people with type 2 diabetes within 48–72 hours, because the signaling pathway turns itself down. Healthy beta cells make about 35 units of insulin a day, while many patients inject 100–150. He thinks that level is atherogenic, so diet, exercise and other drugs should aim to bring doses back toward a normal range. Those who need insulin should still get it.

• The 'ominous octet': eight organs drive the disease

He started from a triad of beta cell, muscle and liver, and added five more. Fat cells stop responding to insulin and release free fatty acids. The gut's incretins (GLP-1 and GIP) are released normally, but the beta cell ignores them, even though they drive about 70% of meal-time insulin. Alpha cells overproduce glucagon. The kidneys increase SGLT2 and hold on to more glucose. The brain becomes resistant to GLP-1, amylin and leptin. Eight faults, so one drug can't be enough.

• Raised fatty acids are toxic

Infusing a fat emulsion causes severe insulin resistance in muscle and liver and impairs beta cells within 2–4 hours. Lowering fatty acids for 12 days with acipimox (sold in Europe) sharply reduced muscle fat, greatly improved insulin sensitivity, and raised mitochondrial ATP production by about 50%. So much of the mitochondrial problem follows from fat overload.

• SGLT2 inhibitors came out of DeFronzo's kidney research

As a kidney fellow he used phlorizin to show glucose and phosphate transport are linked. The kidneys filter about 180 g of glucose a day, with SGLT2 recovering about 90%. In diabetic animals, blocking this improved beta cells and insulin sensitivity. In people, 14 days of dapagliflozin raised insulin sensitivity by about 35%, the first human evidence that high glucose itself is toxic. He never patented it.

• Pioglitazone is the only true insulin sensitizer and is heavily underused

It fixes the signaling defect and moves fat out of muscle, liver and beta cells into tissue under the skin. In a 2017 study it improved heart insulin sensitivity by about 75% and muscle by 74%, and ejection fraction rose 5–10%. Weight gain (about 2–2.5 kg at 15–30 mg, partly from appetite effects in the hypothalamus) and fluid retention put people off. Yet in PROactive (5,238 patients), weight gain was the strongest predictor of survival. He calls it the best drug for NASH.

• Metformin is useful, but it isn't an insulin sensitizer

DeFronzo brought it to the US in 1995. Clamp studies never showed that it improves insulin sensitivity. Its transporter isn't present in skeletal or heart muscle, and labeled-tracer scans show it only in the liver, kidney and bladder. It works by reducing glucose production in the liver. The sensitizer myth likely came from ~3 kg weight loss driven by GI side effects. It costs about $5 a month and is fine to add, but it ranks fourth on his list.

• Start with combination therapy built on the biology

In EDICT (315 patients, six years), metformin plus exenatide plus pioglitazone from the start kept about 70% of patients below an A1c of 6.5% and produced large gains in insulin sensitivity and beta-cell function. The stepwise ADA approach (metformin, then sulfonylurea, then insulin capped at 60 units) failed in about 71%, with no improvement in either. The NIH's GRADE study found that every single drug added to metformin had stopped working by about year five.

• His ranking of drugs

If he could use only one: a modern GLP-1 drug. Two: add pioglitazone, since GLP-1 weight loss cancels its weight gain and fluid retention. Three: add an SGLT2 inhibitor, especially with kidney or heart disease, and he expects the same protection in newly diagnosed patients. Heart-event reductions are about 20% across old and new GLP-1 drugs, which he takes as a sign the benefit levels off.

• Damaged eating circuits in the brain drive the epidemic

Processed, calorie-dense food and inactivity are the trigger, he says, but they reshape the brain's reward circuitry. Gray matter shrinks in reward areas, and in obese people those areas take up excess glucose during a clamp, in proportion to how resistant their muscle is.

EXAMPLES

• Qatar study

About 220 people failing on metformin and a sulfonylurea, average A1c about 10%. After three years, split-dose insulin had

reached 7.1%, held back by low-sugar episodes, while exenatide plus pioglitazone reached 6.1%. Symptomatic patients starting at 12.2% also got to 6.1%.

• Lean children of diabetic parents

Lean Hispanic children with two diabetic parents (a 70–80% lifetime risk) were as insulin resistant as their parents despite normal glucose, with insulin about double normal and the same IRS-1 defect in muscle.

• Gastric bypass and muscle

After losing about 33% of body weight, absolute strength fell about 25%, but strength per kilogram rose about 50%. Walking distance went from 200 yards to two miles, and chair-rise counts went up three- to fourfold. He thinks worries about GLP-1 muscle loss are overstated.

• Cahill's starvation studies

DeFronzo was paid $50 to fast for three days as a Harvard student. Even weeks in, glucose still supplied about a third of brain energy.

• Young people with type 2

In San Antonio perhaps 1 in 20 teenagers has type 2 diabetes. Those in the RISE study respond poorly to drugs, and some had heart attacks in their twenties.

OTHER RELEVANT

• Ask for an OGTT with insulin, not just an A1c

DeFronzo's group showed a one-hour glucose above 155 mg/dL predicts diabetes. Peter's targets: under 90/6 fasting, 140/40 at 30 minutes, 130/30 at 60, 110/20 at 90 (glucose/insulin). DeFronzo: maybe 'overly aggressive.' A large insulin spike with normal glucose, or a weak 30-minute insulin rise, are both warning signs.

• Measure C-peptide, and compare it to glucose

The liver clears about half of secreted insulin, and insulin breakdown slows in resistant people, so insulin levels mislead. C-peptide relative to the rise in glucose, ideally adjusted for insulin resistance (the disposition index), shows real beta-cell function.

• If you need lots of insulin, work to need less

Weight loss, exercise and insulin sensitizers can bring doses toward a normal 35 units a day.

• GLP-1 drugs depend on adherence

About half of patients stop within a year because of cost (around $1,000 a month), GI effects, or missing food. Weight usually returns when the drug stops.

335 The science of resistance training, building muscle, and anabolic steroid use in bodybuilding

Guest: Mike Israetel
Date: 2025-02-10 · Duration: 3:06:54
URL: https://www.youtube.com/watch?v=VhkxTq-fxJc

KEYPOINTS

• Most of the health benefit takes 1–3 hours a week

Israetel says the best return for most people is about 30 minutes of hard resistance training twice a week, for example Monday and Thursday. Even full-time bodybuilders top out around 8–10 hours a week. Lifting works through high force and fatigue, so it has no real equivalent of zone 2 cardio. Each session causes so much disruption that more volume quickly becomes something you can't recover from.

• Fatigue rises steeply with force

Using a whiffle ball versus a .50-cal round as his comparison, Israetel says damage climbs exponentially as force rises. Fast-twitch fibers take more damage, have less blood supply and heal slower. Nerves fatigue too: ion pumps and channel proteins wear down and neurotransmitter stores run low. Strength can take hours to days to return. Much of that fatigue is local, so you can train back the day after a hard chest session.

• More sets give smaller and smaller gains

Israetel's rough figures: one all-out set per muscle per week gives about 30% of the growth that five sets would. Three sets give clearly more than one but not three times as much, and 7–8 sets in one session add little statistically. About 14–15 hard sets per muscle per week (roughly what Dorian Yates did) gets perhaps 70–85% of a muscle's potential. Specializing in a few muscles can push those to 25–35+ sets if you cut back elsewhere.

• Stop 1–2 reps short of failure most of the time

In studies, sets ending 1–2 reps from failure grow about as much muscle as sets to true failure. That last stretch costs about 10 units of fatigue for each unit of stimulus, compared with 1:1 to 5:1 earlier in the set, and it raises injury risk. You need roughly 30 sets at 4 reps short, 22 at 1–2 short, or 20 to failure for similar growth. He says people who always train to failure 'emoted their way' into it.

• A twice-weekly beginner plan

Train the whole body each session, spaced evenly. Use compound lifts: rows and pulldowns, close-grip bench or push-ups, overhead presses, upright rows, squats, leg presses or lunges, and RDLs, which work the spinal erectors, glutes, hamstrings and more. Spend the first sessions practicing technique with light weights (3–4 easy sets per lift). Add load and reps over 3–4 weeks, then build from one to 3–6 working sets per lift. He says beginners should never max out.

• Pairing lifts gives you cardio as well

Alternate lifts that use unrelated muscles, such as a seated dumbbell press with goblet squats or deadlifts, or close-grip bench with rows, resting only 5–10 seconds between them. Use 15–30 working sets per session in the 10–30 rep range, staying below your 10-rep max. Add two zone 2–3 cardio sessions and you're getting about 2–3 hours a week of hard activity. He's honest that it 'is going to hurt.'

• To get past a plateau, work through a checklist

Pick exercises that match your goal: bigger arms need curls and extensions, not only pull-ups. Use technique that puts muscles under high force at long lengths. Push hard enough, because people regularly leave 4 reps in the tank. Use logged numbers instead of feel, adding a rep or 2.5–5 lb each week until you actually fail. Below 5–10 sets per muscle per week is too little. Above 20, if you're always sore and stalling, is probably too much.

• Take a deload every 6–8 weeks

Recovery between sessions may be only about 90–95%, so fatigue builds up (0.95 multiplied over many weeks). Take one easy week every two months and two full weeks off once a year. When you return, start back at 2–3 sets because your muscles will respond more strongly again.

• Age, genetics and life circumstances limit results more than the plan does

Gains slow sharply over time: if three years got you 10 lb of muscle, the next three might get you 5. He has told 150 lb clients in their sixties that their goal of reaching the 200s was impossible without drugs. Nutrition is simple: about 1 g of protein per pound of body weight across 3–4 meals, and gain about 0.5 lb a week when building. Consistency is the usual problem: good weekdays followed by a weekend 'throwing up a lot in the toilet' will cancel the effort.

• Bodybuilding steroid doses are far beyond replacement

Peter's TRT doses typically run about 80 mg a week, never above about 140. Israetel describes bodybuilders taking 250–1,000+ mg of testosterone a week, often with primobolan or masteron to manage estrogen instead of aromatase inhibitors, which he calls very toxic. Side effects he lists: less empathy and fluent communication, more irritability and focus on status, water retention, and erectile dysfunction from nandrolone. He reached just over 2,000 mg a week and got about the same gains at 1,000. Above 1,500 he felt 'mentally insane.'

• Muscle gained on steroids partly stays, and the health costs are real

Israetel estimates he would be about 200 lb rather than 230–235 without steroids, and would keep about half of that extra muscle if he came off, because the added myonuclei appear to stay. He thinks drug-tested federations should ban anyone who has ever used. He controls his blood pressure with medication and reports total cholesterol around 79, but believes he has thickened his left ventricle, lost some fluid intelligence, and probably cut 5–20 years from his life. He is betting on AI-driven biology in the 2030s. Peter is far more skeptical and prefers to stay as healthy as possible in the meantime.

EXAMPLES

• Dorian Yates' low volume

About one all-out set per exercise and each muscle once a week. It worked because hard sets close to failure recruit every

motor unit. Israetel thinks Yates could have grown bigger arms and shoulders by specializing.

- **Israetel's own numbers**
  He is 5'6". Drug-free in his master's program he had about 175–185 lb of fat-free mass. He started high-dose steroids at 27 and is now about 235 lb at roughly 8% body fat. After 13 years with no breaks he reports no testicular shrinkage.
- **His wife on a GLP-1**
  A doctor who once nearly failed medical school while dieting hard, she reached almost 200 lb by 41 despite huge willpower. On Ozempic she described feeling 'this is how normal people live.' He argues GLP-1s free up willpower for the rest of life.
- **The trainer who called the diet 'stupid'**
  A client asked why and got an answer so incoherent that she switched trainers, and loved the new one.

OTHER RELEVANT

- **Choose a trainer for knowledge and rapport, not looks**
  Israetel points to Menno Henselmans' PT certification and a kinesiology degree as good signs. Ask the trainer to explain their reasoning, then check it with an AI 'steelman and red team.' Ignore how ripped they are, since that's mostly genetics.
- **Treat high blood pressure first**
  'It just doesn't matter why your blood pressure is high, control it with drugs' and then work on lifestyle. Modern drugs have few side effects.
- **Think hard before starting steroids or TRT if you want children**
  Israetel guesses about 90% of men recover natural production after stopping, and knows men who can't have children. Peter doubts recovery is that common after long use.
- **GLP-1 drugs don't remove hunger, and drug-tested sports should ban them**
  Bodybuilders still get cravings and heartburn. Peter argues cycling and drug-tested federations should test for them, since weight matters as much as power.

334 - Cardiovascular disease, the number one killer: development, biomarkers, apoB, and more

Guest: Thomas Dayspring
Date: 2025-02-03 · Duration: 2:24:02
URL: https://www.youtube.com/watch?v=5hiLY5oFprY

KEYPOINTS

• Atherosclerosis is cholesterol deposited in the artery wall, delivered by apoB particles.

Dayspring, a lipidologist, calls it 'a dump job': the artery isn't making the cholesterol. Coronary and cerebral arteries matter most because their lumens are pencil-dot small and the tissue is oxygen-hungry. Narrowing usually causes no symptoms until about 75–80% blockage. Plaque rupture triggers clotting that can kill in minutes; Attia notes that close to half of first heart attacks are fatal.

• The disease starts in childhood and takes decades.

Autopsy studies show fatty streaks in the aortas of children aged 4–8 and subclinical disease in young soldiers. Fetal studies of mothers with high cholesterol show early lesions. About 50% of men's and 33% of women's first major cardiac events happen before 65. Hence the push for pediatric lipid testing around age 8–9 and 'primordial prevention.'

• Separate causal risk factors from risk markers.

Causal: age, smoking, apoB-containing lipoproteins and high blood pressure. Diabetes and kidney disease act largely through dyslipidemia and hypertension, plus other circulating irritants such as homocysteine, ADMA blocking nitric oxide, and uric acid. Markers include calcium scores, hs-CRP and homocysteine. Attia notes that a cause can be neither necessary nor sufficient: smoking raises lung cancer risk enormously, yet about 15% of lung cancer patients never smoked.

• ApoB counts the particles, and particle number drives entry into the artery wall.

Each LDL, VLDL, IDL and Lp(a) particle carries exactly one apoB, so the standardised immunoassay is a direct particle count. About 95% are LDL. Once inside, particles stick to proteoglycans, aggregate and oxidise. Monocytes become macrophages and then foam cells (first seen in Anichkov's 1913 cholesterol-fed rabbits). Smooth muscle caps the plaque, and calcium comes late. Smoking, hypertension, high insulin and homocysteine make the endothelium leakier.

• Insulin resistance shows up in lipoproteins years before glucose rises.

A 1990s NMR study found big VLDLs, small LDLs and small HDLs in clamp-confirmed insulin resistance, before post-meal insulin, fasting insulin or glucose rose. Dayspring considers insulin resistance and lipoprotein abnormalities inseparable. Attia leans toward some independent harm from hyperinsulinemia, citing diabetes trials where insulin-driven glucose control seemed to damage large vessels.

• Triglycerides above about 100 mg/dL quietly raise apoB.

In insulin resistance, the liver makes large apoC-III-laden VLDLs that linger. CETP swaps their triglycerides into LDL and HDL. Lipases then shrink those particles: HDL breaks apart (hence low HDL-C), and small LDLs change apoB shape so LDL receptors clear them poorly. That spreads cholesterol over more particles, which is why LDL-C and apoB disagree. Dayspring calls the 150 mg/dL 'normal' cutoff the 75th percentile and gets nervous above 80–100. His own triglycerides of 102–105 hid a high particle count.

• Remnants and Lp(a) pack more punch per particle than LDL.

Lp(a) is an LDL with apo(a) attached, carrying oxidised phospholipids—'gasoline on the fire.' Dayspring says it's about 7–8 times more atherogenic per particle. About 20% inherit it, so test once in life. Remnant VLDLs carry 5–7 times more cholesterol per particle. If apoB looks fine but non-HDL cholesterol (total minus HDL) is high, suspect remnants.

• HDL cholesterol tells you nothing about HDL function.

HDL function depends on more than 150 associated proteins and its surface phospholipids, neither measurable clinically. Low HDL-C with disease nearly always comes with high apoB and triglycerides. Very high HDL-C can be dysfunctional. Attia's friend had HDL-C over 100 and LDL-C under 100, yet a high calcium score; he's now on two drugs with apoB at 20–30.

• Lowering apoB through diet works best through triglycerides and saturated fat.

Saturated fat signals the liver to make fewer LDL receptors, raising apoB. Dietary cholesterol matters less. Reducing calories and refined carbs lowers triglycerides. Attia reserves drastic fat cuts for people who clearly overeat saturated fat. Fibrates lowered triglycerides in trials but didn't reduce events because they didn't lower apoB—so apoB is the goal.

• The brain makes all its own cholesterol, and desmosterol may flag over-suppression.

The brain is the most cholesterol-rich organ, with a half-life of about five years. No plasma lipoprotein crosses into it. In adults, astrocytes make cholesterol via the desmosterol pathway and ship it to neurons on apoE particles; apoE4 versions work worse. Neurons export excess as 24S-hydroxycholesterol. Low serum desmosterol has been associated with cognitive impairment, so Dayspring watches it in E4 carriers on statins.

EXAMPLES

• Attia's own early calcium

At 35, he had coronary calcium with LDL-C around the 50th percentile, normal Lp(a), normal blood pressure and no insulin resistance. That points to non-lipid family risk. He's seen no progression in 16 years of treatment.

• hs-CRP's limits

Dayspring treats over 2 as concerning and over 4 as serious. Attia sees people with CRP under 1 who already have a calcium score of 10 in their 40s, so inflammation markers are neither sensitive nor specific enough to rule disease out.

• Statins and dementia

Across more than a dozen trials with dementia as a secondary outcome, statins were neutral or protective, and the lipophilic-versus-hydrophilic difference didn't hold up. Dayspring says it began as marketing between simvastatin and pravastatin.

• Low-dose statin plus add-ons

Most LDL lowering comes from the lowest dose; each doubling adds about 6%. Dayspring prefers a 'baby statin' plus ezetimibe, bempedoic acid or PCSK9 inhibitors, none of which enter the brain.

OTHER RELEVANT

- **Get apoB, triglycerides and Lp(a) tested**

  Dayspring says apoB and triglycerides are the only blood measurements truly needed, plus a one-time Lp(a). Bring the results to someone who understands them; many doctors and some insurers resist.

- **Don't wait for calcium**

  No validated test detects pre-calcified plaque cheaply. Dayspring argues for treating modestly elevated apoB rather than waiting for the 80th–90th percentile.

- **Lp(a) drugs are still unproven**

  Outcome trials are pending. For now, high Lp(a) means controlling every other risk factor more aggressively.

- **Nobody needs to tolerate lipid-drug side effects**

  With statins, ezetimibe, bempedoic acid, PCSK9 inhibitors and more coming, apoB can be lowered without side effects in almost everyone.

333 Longevity roundtable—the science of aging, geroprotective molecules, & lifestyle interventions

Guest: Steven Austad, Richard Miller & Matt Kaeberlein
Date: 2025-01-27 · Duration: 2:55:00
URL: https://www.youtube.com/watch?v=NU98SXBCjz4

KEYPOINTS

• Healthspan and lifespan aren't a seesaw when you target aging itself.

Miller, who runs the NIA's Interventions Testing Program (ITP), says every drug that extends mouse lifespan does so by delaying both fatal and non-fatal diseases, much like exercise or avoiding insulin resistance. Austad counters that in humans the gap between healthspan and lifespan is widening fastest in the US and in women, because medicine keeps sick people alive longer. Kaeberlein reconciles the two: slowing aging moves both together, while disease-by-disease care stretches the sick years.

• US life expectancy lags because of deaths in middle age, not old age.

Attia notes the US spends about 80% more than peer countries yet ranks lowest among OECD nations. That's because of maternal and infant deaths, overdoses, guns and suicide. Past about 65, Americans jump to the top, reflecting 'medicine 2.0' extending life with chronic disease. With 60% of Americans having a chronic disease, many spend decades in 'sickspan.'

• Aging research gets a sliver of funding despite driving nearly every leading killer.

Nine of the top 10 US causes of death have aging as their biggest risk factor. Yet biology-of-aging research gets about 0.5% of the NIH budget (about $350 million). Disease lobbies guard their turf: when NIA council members floated diverting a few percent of Alzheimer's money, appropriations staff called the next day. Miller's talks showing anti-aging drugs cut age-adjusted cancer in mice tenfold draw no follow-up from cancer centres.

• Calling aging a disease is the wrong framing.

Miller calls it a 'fundamental error' because aging is a risk factor for diseases. Austad says the label is a marketing ploy for funding. Kaeberlein says the FDA doesn't require it—Austad's TAME team got metformin trial interest by framing the endpoint as multimorbidity. Austad estimates privately funded aging research now outspends public money at least 2:1.

• Consumer epigenetic age tests aren't reliable.

Kaeberlein sent duplicate samples from one day to four companies. At age 53.7, results ranged from 42 to 63; one company's duplicates were 20 years apart. Biological aging is real—dogs age about seven times faster, and single genes like daf-2 shift the rate—but Miller and Attia say no single number beats a rich clinical picture. Life insurers don't use the tests.

• The 'hallmarks of aging' both helped and harmed the field.

Miller says the list became 'biblically sacrosanct,' letting grant writers skip proving causation and starving ideas off the list. Kaeberlein agrees it narrowed the field prematurely—we may understand 'about 0.005%' of aging—but says it gave the field mechanistic credibility. Austad notes reviewers punish 'fishing expeditions' and breakthrough ideas.

• Speed-type aging-rate indicators could make human trials feasible.

Biomarkers are like an odometer and change only by old age. Miller's lab found about 12 markers that shift early in every slow-aging mouse model, across drugs, caloric restriction and five gene mutants. Examples include fat macrophage shifts, UCP1, and the enzyme GPLD1, which exercise also raises and which boosts neurogenesis in mice. A new grant tests whether they stay unchanged with ineffective drugs. Austad warns that mouse findings may not carry over to humans.

• Senescent cells are hotly disputed.

Miller argues the concept grew from Hayflick taking a lunchtime joke seriously, and that 'senescent cell' and 'SASP' lump unrelated phenomena together. The ITP found fisetin had no lifespan effect and no change on six senescence markers. His group went 0 for 7 replicating senescent-cell clearance in the Mayo genetic model. Austad and Kaeberlein point to evidence that clearing p16-positive cells improves health, and to NIH's roughly $600 million senescence network.

• Rapamycin works as cancer prevention even where it fails as chemotherapy.

Kaeberlein: established tumours evolve around the mTOR brake, so disease-stage biology differs from aging biology. ITP rapamycin is mixed into food daily. Weekly human dosing of about 3–10 mg traces to Joan Mannick's everolimus vaccine trials, where 5 mg weekly worked best. The idea that side effects come from mTORC2 is less proven than assumed. Partridge's lab found a MEK/ERK inhibitor adds to rapamycin through a separate pathway.

EXAMPLES

• Resveratrol's coconut-oil mice

The 'first drug to extend mouse lifespan' worked only in mice on a 60% coconut-oil diet. Their fatty livers were compressing their lungs, as a later paper quietly noted. Nobody at the table defends resveratrol for aging.

• NAD precursors

The ITP's negative result is the strongest evidence. Oral NR and NMN appear to be broken down to nicotinamide in the gut. One mouse study found kidney inflammation from NMN in aged mice, which Kaeberlein flags given NMN sold for pets.

• Metformin

Miller co-wrote a review arguing that the famous Bannister diabetic-survival study is methodologically flawed; metformin didn't extend ITP mouse lifespan. Austad finds the observational signals worth a trial, and TAME has finally begun enrolling on a small budget.

• Canagliflozin and GLP-1 drugs

The SGLT2 inhibitor canagliflozin extended male mouse lifespan, mechanism unclear. GLP-1 drugs await an easy oral form for ITP testing; oral semaglutide requires laborious fasting protocols.

• Parabiosis and plasma exchange

Austad and Kaeberlein are cautiously optimistic, since plasma exchange is existing technology. Miller wants the specific harmful or helpful factors identified rather than 'medieval' mixtures. Parabiosis surgery itself shortens rodent lifespan, a possible

confounder.

OTHER RELEVANT

- **Define your own healthspan**
  Austad says health means being able to do what you love. Attia's 'marginal decade' exercise covers physical, cognitive, emotional and social goals.
- **Immune aging matters**
  Attia would add immune decline as a fifth 'horseman.' Young patients survive pneumonias that would kill a 75-year-old, and flu or pneumonia remains a top-10 cause of death.
- **Be sceptical of longevity products**
  Miller blames a profitable industry selling untested products 'with a wink and a nod and a lawyer.' Kaeberlein urges caution about stacking supplements without evidence.
- **The economics are enormous**
  Austad cites an analysis by economist Andrew Scott valuing one extra year of healthy life at about $38 trillion.

331 Optimizing endurance performance: metrics, nutrition, lactate, & insights from elite performers

Guest: Olav Aleksander Bu
Date: 2025-01-13 · Duration: 2:41:05
URL: https://www.youtube.com/watch?v=QpK3jXLwz_Y

KEYPOINTS

• Threshold numbers are approximations, so test the same way every time

FTP was originally a 5-minute all-out effort followed by a 20-minute all-out effort, minus 5%. Many people now skip the first part, which changes the result. Critical power comes from several all-out efforts fitted to a curve, and usually sits between maximal lactate steady state and VO2 max. The various thresholds are often only a few percent apart, and the gap is bigger in power athletes than in endurance athletes. Bu says a single number throws away how long you can hold each power. Track your 1-, 5- and 15-minute bests and watch how the balance between them changes.

• Blood lactate depends on dilution as well as production

Lactate is produced all the time, even during sleep. A test only shows a 'threshold' once muscles release more than they clear. Hematocrit can change by more than 10% within a session from dehydration, and elite athletes have larger plasma volumes, so they may produce more lactate and still show lower concentrations. In elite marathoners and triathletes, the second inflection point (confirmed by maximal lactate steady state) can be below 2 mmol/L. The most useful definition is the point where lactate keeps rising at a constant pace.

• Elite endurance depends on how much of your VO2 max you can sustain

Utilization is oxygen use at maximal lactate steady state, or at race pace, as a share of VO2 max. About 80% is unremarkable. Elite marathoners reach 94–95%, and Bu's triathletes are about there in Ironman racing. VO2 max itself falls over a long race, so the aim is to lose as little as possible. Keeping a very high VO2 max is costly: training 1- and 5-minute power takes away from race-specific work, and an oversized heart is less efficient at the effort that matters.

• Elite VO2 max is highly trainable

Bu calls VO2 max the best practical single measure of health and performance, and says endurance capacity is better but impractical to test. Kristian Blummenfelt has exceeded 7.7–7.8 L/min at about 80 kg (about 100 mL/kg/min), and Gustav Iden reached about 94. Their VO2 max dropped when they moved from Olympic-distance training to Ironman training. Values across swimming, cycling and running started out clearly different and became almost identical as they trained to recruit more muscle in each.

• A good VO2 max test needs preparation and a set warm-up

Eat as you would before a key session (carbohydrate), hydrate, sleep well, avoid soreness, and test at the same time of day because of circadian temperature changes. Bu's warm-up: 6 minutes very easy, 6 minutes at long-session effort, about 3 minutes near threshold by feel, then 2–3 efforts of 10–15 seconds with equal rest, for about 20 minutes in total. Then start the test without much delay. Peter adds that you have to be completely exhausted at the end, and many people aren't.

• Breath-holding can inflate a VO2 max reading

Briefly restricting breathing near the end builds up an oxygen debt and can push a trained person's reading from 60 to over 70. Bu calls this cheating the protocol, not improved fitness. He also checks his metabolic carts against a lung simulator with reference gas, and in his lab the highest values often come on a second or third test about 10 minutes later.

• RQ tables mislead at high intensity

Lactate can supply about 13–14% of energy if an athlete stays near threshold, while standard substrate tables assume it contributes nothing up to an RQ of 1.0. Bu is skeptical of them for endurance athletes from the low 0.90s. Threshold RQ also varies with athlete type: 0.96 is a common estimate, but extreme endurance athletes can be at 0.92–0.94.

• Fueling has advanced more than training

Kristian and Gustav routinely absorb about 160 g of carbohydrate an hour, measured with carbon-13 tracers, and Bu has measured over 240 g. They drink about 1.4–2+ L an hour of a roughly 12% glucose-fructose mix (about 40:60) in a hydrogel, double the old 5–6% guideline. Bu says the gut is trainable and even honey can get you past published limits. They take no fat or protein during races, because carbohydrate gives the most work per unit of oxygen. Exogenous ketones can't be dosed high enough to fuel racing without making athletes feel as if they're bonking.

• Two elite athletes can respond very differently to the same aid

Encapsulated bicarbonate (about 19–22 g, in a hydrogel to get past the stomach) produced Gustav's highest VO2 max. Some athletes nearly double their blood lactate on it, while Kristian's barely changes. Bu points to their very different blood and plasma volumes and stroke volumes: Kristian has more hemoglobin mass, and Gustav's maximum heart rate is about 200 versus about 170–180. At the elite level, one system ends up compensating for another.

• Bu prefers adapting the athlete to masking a limit

He doesn't use high-dose acetaminophen for heat or pain, preferring that the body adapt to heat. Peter suggests testing it against placebo in alternating training weeks. Bu says the same oxygen logic applies to heat: every inefficiency adds heat and costs you late in the race. On cycling's post-doping speeds, both credit nutrition first, and Bu expects riders to get heavier again as underfueling is shown to limit adaptation.

EXAMPLES

• A beetroot-related supplement

Nitrate concentrate didn't measurably help these elite athletes. After a pine-bark extract that is said to aid conversion to nitric oxide, Kristian set record VO2 values with lower RQ (about 1.05 down to about 0.95). His efficiency also fell, and core temperature showed more heat for the same power.

• Swimming efficiency

In a laminar-flow flume at the same speed, a retired elite swimmer close to 100 kg used about 25% less oxygen than Kristian

at about 80 kg. Peter thinks swimming has the most to gain from reducing drag.

• Paris versus Tokyo

Kristian won Tokyo. In Paris, after a swim in a strong, uneven current, he had to ride about 30% harder for roughly three-fifths of the bike leg to rejoin the group and lost about 4 seconds per km on the 10 km run, finishing 12th. Bu says they got careless with intensity control in the final year, the same mistake they made in 2017–18.

• Formula 1 heart rates

Peter at first thought drivers' telemetry was faulty because heart rate jumped with every hard braking zone and fast corner. They discuss high g-forces cutting venous return to the heart, and how muscle contractions above roughly 30% of a one-rep max start squeezing off blood flow.

OTHER RELEVANT

• Use running power and pace together

Footpods and insoles from companies such as Stryd now track force curves closely against force plates. Bu works from raw positive and negative mechanical power, not modeled metabolic power. Peter plans to add running power to his wife's Boston training.

• Use RPE, but remember fatigue builds over time

A pace Kipchoge might rate 6 out of 10 when fresh feels like 9–10 at the end of a marathon. In races Bu's athletes rely mostly on perceived effort, and in training they use many more sensors.

• Expect AI to improve consistency more than workouts

Bu's team uses its own agent-based system, with language models as the interface, to flag what matters in its data, so the team can adjust earlier. He thinks it will do for training what ski technology did for Norway, while coaches still make the decisions.

330 – Autism, ADHD, and Anxiety: the rise in autism & an approach to diagnosing & treating children

Guest: Trenna Sutcliffe
Date: 2025-01-06 · Duration: 2:15:31
URL: https://www.youtube.com/watch?v=Az1oycmlpec

KEYPOINTS

• Anxiety, ADHD and autism are clinical diagnoses based on impairment, not biomarkers.
Sutcliffe, a developmental-behavioural paediatrician who founded a multidisciplinary Bay Area clinic, stresses there's no blood test or scan for any of them. Clinicians use DSM checklists, parent and teacher rating forms, history, clinic assessment and ideally school observation. The key question is whether traits impair a child's 'job'—learning, making friends, communicating, contributing at school. Anxiety itself is a normal emotion; it's about severity and pervasiveness.

• Each condition has its own diagnostic age window.
Autism can be confidently diagnosed from about 18 months (rarely 15 months in obvious cases), though the typical age is 3–4 and half of cases are diagnosed after 6. ADHD can technically be diagnosed at 4, but Sutcliffe usually waits until 5–6 because preschoolers are a 'moving target,' while starting behavioural support earlier. Anxiety conditions—separation anxiety, selective mutism, phobias, OCD—appear in preschoolers.

• Self-esteem is the impairment Sutcliffe watches most closely.
Children with ADHD get constant correction for forgetting, losing things and not finishing tasks, often from well-meaning adults. With elementary-age children, she asks about a 'third person'—why might another child come home crying?—because kids find it easier to describe others, and their stories reveal their own experience.

• Autism diagnosis requires differences in three social areas plus restricted or repetitive behaviours.
The three areas are social reciprocity (back-and-forth, initiating and responding), nonverbal communication (eye contact, gestures, reading others' cues), and understanding relationships and group context. Since the 2013 DSM-5, Asperger's and PDD-NOS fall under one autism spectrum, specified with or without intellectual disability or language impairment. Severe cases can be diagnosed quickly; milder ones need multiple visits and outside perspectives.

• Autism prevalence has risen far beyond what criteria changes explain.
CDC figures went from about 1 in 150–169 before 2013 to about 1 in 36 by 2020. Heritability is about 70–98%, higher than any other DSM condition, but it involves hundreds to roughly a thousand genes with a different 'fingerprint' in each child. Sutcliffe describes a multiple-hit gene–environment–epigenetic model, where timing and order matter. Implicated factors include pollution, maternal infection or prolonged fever, placental health, stress and parental age. Whether epigenetic marks pass across generations remains controversial.

• Level 1 autism is the blurriest category and often goes unsupported.
Levels 1–3 range from 'requires support' to 'very substantial support.' Level 1 children have strong cognition and language but social and coping difficulties. One clinician may call it autism while another calls it ADHD plus anxiety. They often miss services despite responding very well to coaching on coping, change and social skills. Sutcliffe wonders whether the next DSM will swing back.

• The conditions overlap heavily.
About half of autistic children also have ADHD (reports range 40–70%), a dual diagnosis only allowed since 2013, and about 40% have anxiety. ADHD 'frequently has a partner'—anxiety or mood issues, learning disabilities or oppositional behaviour. Imaging implicates frontal lobes, amygdala, cerebellum and temporal lobes.

• An 'ODD' label doesn't tell you what to do—find the function behind the behaviour.
Arguing, lying and defiance may come from anxiety or embarrassment (very common), untreated impulsivity, social misunderstanding, or sensory overload. Each needs a different plan. Sutcliffe left the traditional model in 2014 because it amounted to 'you have autism, here's a list of 15 recommendations, good luck.'

• ADHD treatment: behavioural parent training first under 6, medication plus training from 6.
Stimulants raise dopamine and norepinephrine in prefrontal synapses. Sutcliffe starts young children on methylphenidate (Ritalin, Focalin, Concerta), which meta-analyses show is slightly better tolerated. Amphetamines (Adderall, Vyvanse) give 'a bit more bang for your buck.' Formulations differ mainly in release mechanism, so switching brands can help. Common side effects are reduced lunchtime appetite and delayed sleep onset; some teens feel less funny or spontaneous, which calls for adjusting the dose or brand. Most families say 'I wish we'd started sooner.'

EXAMPLES

• ABA, from discrete trials to naturalistic methods
Applied behaviour analysis breaks skills like greeting someone—eye contact, turning toward them, speaking—into reinforced steps. Classic table-based discrete trials are controversial. Naturalistic methods use the child's motivators, such as requiring a glance before a swing push. Pivotal response treatment trains parents to do this everywhere. Sutcliffe recommends ABA, but quality varies as the industry scales.

• Non-stimulants and autism medications
Atomoxetine, guanfacine and clonidine must be taken daily and help emotional dysregulation, sometimes combined with stimulants. No drug treats autism's core features. Symptoms are targeted instead: stimulants for attention, SSRIs for anxiety and rigidity, and atypical antipsychotics, usually with a psychiatrist, for self-injury or aggression.

• Parents recognising themselves
While their child is being evaluated, many parents realise they share the traits. That can be validating ('it wasn't my fault'), and those with ADHD traits affecting work often seek their own assessment.

• Coming off medication
Stimulants clear daily, so there's no lingering effect. Sutcliffe won't promise lifelong or temporary use. Many patients develop

strategies, using neuroplasticity built through practice while medicated, and eventually stop as teens or young adults.

OTHER RELEVANT

- **How to choose providers**
  Look for individualised, flexible plans rather than one-size-fits-all; proactive coordination with teachers and therapists (for example, seasonal team meetings); and real parent training, not just education. Start with your paediatrician and build a team around a 'quarterback.'
- **Siblings carry risk and gifts**
  Siblings of autistic children have higher rates of autism traits, language delay, ADHD and anxiety, but often develop unusual empathy. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Strengths are real, especially at level 1**
  Memory, attention to detail and the ability to hyperfocus often suit STEM and technical careers. Autistic adults have successful careers and marriages.
- **Bridge health care and school**
  Sutcliffe attends IEP meetings and observes classrooms because insurers and schools each push responsibility onto the other. In California, an autism diagnosis is what unlocks insurance coverage for ABA.

327 - Choices, costs, and challenges in US healthcare: insurance, drug pricing, & potential reforms

Guest: Dr. Saum Sutaria
Date: 2024-12-02 · Duration: 2:45:38
URL: https://www.youtube.com/watch?v=QqrpFICtqpQ

KEYPOINTS

• US healthcare is a roughly $4 trillion system, close to a fifth of the economy.

Saum Sutaria, CEO of Tenet Healthcare and formerly a leader in McKinsey's healthcare practice, puts US healthcare at about 17–18% of a roughly $28 trillion GDP, or about $12,000 per person. Consumers pay about a quarter (around $1 trillion), employers another quarter, and federal and state government roughly half, counting direct spending plus the tax subsidy for employer insurance. For scale, he notes total post-tax US corporate profits are just under $4 trillion, and federal health spending of about $1.8 trillion exceeds defense (about $1 trillion) and Social Security (about $1.2 trillion).

• A simple map of where the money goes: administration, then thirds.

Saum estimates administration takes 10–15% of spending, which he calls one of the biggest gaps between the US and other countries. Of the rest, roughly a third goes to hospitals and facility-based care, a third to physicians and clinics, and a third to drugs and devices, including drugs given in hospitals. He prefers this to the older 'half facilities' framing, which hides the physician pay and pharmaceuticals inside hospital spending. Peter adds that administration is partly the price of choice: other countries have administration too, but it sits in one government payer and skips line-by-line adjudication.

• The shift to third-party payment removed price sensitivity and drove consumption.

In 1950 the US spent under 5% of GDP on health, and more than half was paid out of pocket. Today direct out-of-pocket exposure is about 15%, so about 85% of spending is paid by a third party. A 1954 law made employer insurance a pre-tax benefit and entrenched it. Medicare and Medicaid followed in 1965, when health spending was around 6% of GDP. Combined with a wave of innovation in drugs, devices and procedures, this created what Saum calls a 'virtuous cycle' of rising spending, which has grown about 2% per year faster than GDP.

• Health insurance has become a 'discount card' for predictable chronic care.

Insurance is designed for 'random, infrequent and unpredictable events' such as heart attacks, accidents and appendicitis. Today spending is driven by chronic and often multiple illnesses, including diabetes, heart disease, and even HIV and cancer, which are now managed long term. 'You don't use your car insurance to get an oil change,' yet we route checkups and lifelong prescriptions through insurance. Insurers succeed by understanding concentrated risk pools, where about 5% of members may account for half of costs.

• Other rich countries control cost by restricting supply, not by better 'value-based care.'

Universal coverage creates the same moral-hazard demand, so systems like Canada's limit capacity. Emergency care is fast, but elective care such as hip and knee replacements, cataracts and scheduled heart surgery involves long waits. Peter frames it as four variables: quality, access, choice and cost. The US fixes the first three at the maximum and lets cost float, while others cap cost and give up access and choice. Their spending still rose from about 4% to 11–12% of GDP.

• Drug pricing is distorted by negotiation rules and pharmacy benefit manager (PBM) rebates.

Saum says the Medicare Modernization Act of the early 2000s barred HHS from negotiating drug prices, and the Inflation Reduction Act 'cracked that door open.' Medicare already acts as a monopsony that sets prices for doctors and hospitals. PBMs, mostly owned by insurers, earn rebates for formulary placement, which can reward higher list prices. Peter recounts a pharma CEO who wanted to launch a drug cheaply and was told by PBMs to triple the price first and recoup the difference through rebates. Saum hopes that isn't the norm. He favors curbing price inflation over imposing OECD-level prices, which he warns would chill innovation.

• US life expectancy lags because of deaths before 65, not because of the medical system.

The US moves from near-last to first among rich countries in life expectancy over roughly ages 60–75, which Peter credits to its strength at treating chronic disease. Saum attributes the earlier gap to infant mortality two to three times higher than peers, homicide about seven times higher, injuries, overdoses (more than 100,000 a year) and obesity-driven disease. Meanwhile the US does better on vaccination, cancer screening, blood pressure and cholesterol treatment, and smoking. 'This isn't a coverage problem,' and public health has been ineffective against these behavior-driven conditions.

• The real squeeze is demographic: fewer workers per Medicare beneficiary.

Medicare covers about 65 million people and may reach about 90 million around 2032, when the inflow of new retirees peaks. Medicaid already covers about 90 million. In the 1980s there were about two people aged 40–65 for every Medicare beneficiary, and that ratio is heading toward one to one. Because commercial insurance cross-subsidizes government payment rates that are often below cost, a shrinking working-age base strains the whole system. Saum sees the next decade as the hard part.

EXAMPLES

• Colonoscopy moving out of hospitals.

Moving the procedure from hospital stays to outpatient centers cut the cost per procedure and made it easy enough that far more people got screened. Saum credits ambulatory surgery with preventing more colon cancers than any gastroenterology innovation, even though total spending probably rose.

• Joint replacement in a surgery center.

Hip and knee replacements that once meant four hospital days can now be done same-day at an ambulatory surgery center for about half the payment.

• The $16 gauze myth.

Hospitals must keep a 'chargemaster' list price for every item, but insurers pay one bundled diagnosis-related group (DRG) rate. In Saum's illustrative example of bypass plus valve replacement, the surgeon's own fee, which covers days of inpatient care, might be only around $1,000–2,000. Inflated charges mainly hurt uninsured patients, though hospitals usually discount steeply.

- **GLP-1 drugs.**
  Saum agrees they work but worries about muscle loss in the elderly. He argues the economic return is greatest in working-age people, calls current prices too high, and expects them to fall as competitors and political pressure grow.

OTHER RELEVANT

- **PPO versus HMO is a choice-versus-cost tradeoff.**
  PPOs give open networks at higher cost. HMOs such as Kaiser narrow choice to cut cost. Saum notes Kaiser still referred his mother to UCSF for a rare brain cancer.
- **The ACA mainly expanded coverage, not affordability.**
  Medicaid expansion and the exchanges raised coverage and spending. Weakening the individual mandate invited adverse selection.
- **Long-term care and dementia are the next big frontier.**
  Families absorb much of this care, often women leaving work. Saum expects device and engineering solutions to matter because drugs struggle to cross the blood–brain barrier.
- **Bending the trend beats cutting it.**
  A 25% cut would mean massive job losses. Saum's goal is health spending growing no faster than GDP, through a 10-year national push on nutrition and physical activity.

324 Metabolism, energy balance, and aging: the impact of diet, calorie restriction & macronutrients

Guest: Eric Ravussin
Date: 2024-11-04 · Duration: 2:18:52
URL: https://www.youtube.com/watch?v=UVGBfrfPq98

KEYPOINTS

• Metabolic chambers measure energy expenditure with remarkable precision.

Ravussin, who spent 15 years at the NIH intramural program and 2.5 years at Eli Lilly before 24 years at Pennington Biomedical Research Center in Baton Rouge (about 500 researchers, roughly $80 million a year), explains indirect calorimetry: measuring oxygen consumed and CO2 produced reveals total calories burned, and the ratio (respiratory quotient) shows fuel—about 1.0 for carbohydrate, 0.7 for fat, ~0.82 for protein. Pennington validates its chambers against each other within 3% for O2 and CO2.

• Body weight is regulated, and energy intake dominates.

As weight creeps up, resting metabolic rate and the cost of moving rise, partly braking further gain. Ravussin himself went from 69 kg when he married in 1975 to about 77 kg. Still, from the 1980s to 2010 the average American gained about 10 kg (22 lb)—a tiny daily imbalance compounded over 30 years. He sees intake, not expenditure, as the main driver.

• People differ substantially in metabolic rate even after adjusting for size.

In measurements of about 150 people's 24-hour energy expenditure and resting metabolic rate, large variability remained after accounting for body composition—one reason identical diets yield different results.

• Exercise alone is a weak weight-loss tool because appetite compensates.

Peter notes an hour of hard cycling burns about 750–800 kcal, but eating quickly afterward can easily add 1,000 kcal in 20–30 minutes. Ravussin says generic advice like 150 minutes a week of moderate-to-vigorous activity 'doesn't work in general' for weight loss, though exercise has other major benefits and early-life habits matter.

• Macronutrient swaps barely change energy expenditure.

In a tightly controlled metabolic-ward study discussed in the episode (~16 people housed for a month with frequent chamber stays), switching from roughly 45–50% to under 10% carbohydrate at equal calories increased expenditure by only around 100 kcal/day—statistically significant but below the ~150 kcal hypothesized. Ravussin notes the body holds only about 500 g of glycogen (~100 g in liver, 300–500 g in muscle).

• Ultra-processed food may drive overeating via protein dilution.

Ravussin notes ultra-processed foods are about 12–13% protein versus the 15–18% we need. Under the protein-leverage hypothesis—first shown in insects and rodents—we keep eating until we hit a protein target, overshooting calories when protein is diluted.

• Biosphere 2 sparked the CALERIE study.

From 1991–93 eight people lived sealed in Biosphere 2; food ran short and they lost about 15% of body weight, with physician Roy Walford—author of a calorie-restriction textbook—among them. Ravussin found their energy expenditure stayed about 200 kcal/day below predicted, evidence of metabolic adaptation, and later partnered with Walford.

• CALERIE tested 25% calorie restriction for two years in non-obese adults.

Participants were women 21–47 and men 21–50 with BMI 22–27.9. More than 5,000 were screened to enroll about 225, randomized 2:1 to 25% restriction or ad libitum. Retention was spectacular: about 95% in controls and 82–85% in the restriction group. The main grant was $10.4 million in 2003, later about $13 million.

• Actual restriction fell short of 25% but still produced meaningful weight loss.

Measured with doubly labeled water, restriction was about 20% for the first 6 months, about 15% at one year and about 12% averaged over two years—cutting roughly 500–600 kcal from about 2,400. Weight loss averaged about 12% at one year and 10.4% at two.

• CR improved markers of 'secondary aging', with hints on primary aging.

Healthy participants saw remarkable improvements in cardiometabolic risk markers, inflammation (including hs-CRP) and other measures, plus signs of more efficient mitochondria and reduced thymic fat. Whether primary aging slows is uncertain.

• Open questions: muscle, sarcopenia and lasting effects.

Peter asks what happens to muscle mass decades later if lean people stay 10–12% lighter into their 70s and 80s; Ravussin says we don't have an answer. A CALERIE Legacy study is following participants from 2005–08 to see if any benefit persisted; many still use what they learned.

• Self-reported diet data are a core weakness of nutrition science.

Ravussin and Peter discuss how food-frequency questionnaires and recall are unreliable. Newer studies use tools such as a small camera mounted on glasses to record what people eat; one module of a large study involves about 10,000 people, with daily records over 10-day periods. Peter asks whether samples are banked for future biomarkers; Ravussin sees AI and better tools transforming how intake is measured and enabling more personalized nutrition and public policy.

EXAMPLES

• The six-month pilot

Four arms: ad libitum, 25% CR, 25% deficit split between 12.5% CR and 12.5% more exercise, and a low-calorie diet (about 800 kcal) to lose 10% then maintain.

• Peter's view on CR

Peter says no health benefit would justify the unhappiness of cutting calories 20–25% for him personally; Ravussin notes some participants loved watching body fat fall, e.g., from 15% to 12% on DEXA.

• The CR Society

About 200 self-imposed calorie restrictors exist; Ravussin is familiar with but hasn't studied them.

- **A cheap study**
  $13 million on a roughly $28 billion NIH budget is under a tenth of a percent, Peter notes, for one of the most important human CR trials.

- **Living in 2024**
  Peter: he'd rather be the most average person in 2024 than the most important person in 1400—our obesogenic environment is the cost of abundance.

OTHER RELEVANT

- **Focus on intake for weight; exercise for health.**
  Exercise is invaluable but easily out-eaten; plan post-workout meals rather than eating fast.

- **Prioritize protein.**
  Aiming for adequate protein may curb overeating, particularly in diets heavy in ultra-processed food.

- **Don't expect metabolic magic from low-carb.**
  Macronutrient shifts move expenditure by perhaps 100 kcal/day; adherence and total intake matter more.

- **Consider moderate, sustainable restriction.**
  Even ~12% CR improved markers in healthy people, but watch muscle mass and quality of life.

- **Expect metabolic adaptation after weight loss.**
  Biosphere 2 and CALERIE both showed expenditure falling more than body-size changes predict; maintaining loss requires planning for that lower budget.

323 - CRISPR and the future of gene editing: scientific advances, genetic therapies, & more

Guest: Feng Zhang
Date: 2024-10-28 · Duration: 2:18:46
URL: https://www.youtube.com/watch?v=aOl0IDhzLCo

KEYPOINTS

• Zhang came to gene editing from optogenetics and a need to target specific cells.
Zhang, who finished his PhD in 2009 and started his lab at MIT and the Broad Institute in 2011, helped develop optogenetics—inserting light-sensitive genes into specific brain cells. That worked only in genetically modified mice, which took one to two years to engineer, motivating a faster, more general way to edit genomes.

• CRISPR began as a curiosity in bacterial DNA in the 1980s.
Japanese researchers studying E. coli noticed unusual repeating sequences; the acronym CRISPR came in the early 2000s, and Francisco Mojica found that the spacer sequences between repeats matched viruses. Scientists initially focused on the repeats—the strongest signal—before realizing the spacers were an immune memory.

• How bacterial CRISPR works: a guide RNA directs a Cas enzyme to cut.
After infection, bacteria store a snippet of viral DNA. On reinfection, the CRISPR region produces RNA carrying a roughly 20–30 letter guide that matches the virus; Cas proteins (numbered Cas1, Cas2… roughly by order of discovery) bind it, find the matching sequence next to a PAM motif, and cut. Viral genomes range from about 10,000 to 100,000+ letters.

• Earlier tools—meganucleases, zinc fingers, TALENs—were cumbersome.
Each zinc finger recognizes three DNA letters, so six fingers recognize 18—enough for uniqueness because 4^18 exceeds the human genome's 3 billion letters. TALENs recognize single letters via 12–20 repeats. But both required engineering a new protein for each target, whereas CRISPR needs only a new guide RNA.

• Over 5,000 single-gene disease mutations make editing a powerful therapeutic idea.
Since the Human Genome Project, researchers have identified more than 5,000 mutations directly causing disease, usually affecting small populations. In a dish, editing efficiency can approach 100%.

• Delivery is now the main bottleneck.
Cas9 is about 1,300 amino acids and other Cas proteins around 1,000, too large for some vehicles. Ideally the system would be around 300 amino acids. The liver is robust—80–90% editing is achievable—while other tissues are harder. Solving delivery wouldn't solve cancer, Zhang notes, because cancers arise from many different mutations.

• Sickle cell disease is the first approved CRISPR therapy.
Cells are edited outside the body and returned, reactivating fetal hemoglobin—an ex vivo approach that avoids the delivery problem but is costly and demanding.

• Base editing and AI-designed proteins are expanding the toolkit.
Base editors change single letters without cutting both strands. DeepMind's AlphaFold 2 (2020–21) allows predicting structure from sequence, helping engineer proteins; Zhang's lab studies IscB, an ancestral Cas9 form only about 450 amino acids—roughly a third the size.

• Cas13 targets RNA and enabled diagnostics.
Cas13, the RNA analog of Cas9, cleaves the target RNA and then indiscriminately cuts nearby RNA—a 'suicide' feature that makes a signal. Zhang's team used it for diagnostics during COVID.

• Germline editing for enhancement is far off and ethically fraught.
Zhang discusses He Jiankui's 2018 editing of embryos for HIV resistance, done without proper consent and with little rationale since transmission could be prevented otherwise. Nobody knows how to make a child '30 IQ points smarter'; huge risks need huge payoffs.

• Gene therapy's long-promised revolution is finally becoming practical.
Peter recalls that when the human genome was sequenced nearly 25 years ago, gene therapy was hailed as imminent, then disappointed. Zhang says the difference now is the ability to go to a precise address and fix it—something impossible 10–15 years ago. Still, therapies must be manufactured at clinical scale: his lab makes its own Cas9 and Cas13, and commercial supply is mostly laboratory-scale, while a human may need thousands of times the dose of a 10 g mouse.

• Efficiency multiplies, which limits benefit outside the liver.
In the eye or brain, delivery may reach only some cells, and editing may work in only some of those; multiplied together, the fraction corrected can be small. That's one reason partial vision restoration in LCA trials was modest, and why age of treatment and neuroplasticity windows may also matter.

EXAMPLES

• Eye therapies
Editas developed a CRISPR treatment for LCA10, a form of inherited blindness, delivered by a single eye injection to inactivate a mutant gene; phase 1/2 showed some vision improvement. Partial cell coverage times partial editing efficiency limits benefit.

• Editing PCSK9
One-time liver editing to disable PCSK9 could permanently lower cholesterol. PCSK9 antibodies launched around $15,000 a year and now cost far less—Peter estimates about $6,000–10,000—so editing might be worth tens of thousands.

• A Jurassic Park moment
Zhang moved to Des Moines, Iowa at 11 after his mother came as an exchange scholar; seeing Jurassic Park in the mid-1990s and a 10th-grade gene-therapy lab experience made him want to do science.

• Biofuels detour

Around 2007–08, during his PhD in Karl Deisseroth's lab and amid the oil crisis, he explored biofuels as a side project; the financial crisis ended plans to raise venture money.

- **CRISPR transformed basic research by making transgenic mice in one step.**
  Rather than breeding mosaics over generations, researchers can edit embryos and have a modified mouse in one 21-day gestation, saving years of a PhD.

OTHER RELEVANT

- **Single-gene diseases are where editing will help first.**
  Expect progress in liver, eye and blood disorders before complex diseases. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch delivery, not just editing.**
  Breakthroughs in small editors and vehicles will determine which organs become treatable.
- **Be skeptical of enhancement claims.**
  Polygenic traits like intelligence are poorly understood; editing for them is not near-term.
- **Support basic science.**
  Zhang stresses that payoffs from science can take 10–20 years, and today's tools came from curiosity research on bacteria.
- **Costs should fall as tools mature.**
  Zhang expects one-time edits to become relatively inexpensive compared with lifelong drug costs once development costs are absorbed and manufacturing scales—though early prices will reflect a decade of R&D.

322 - Bone health for life: building strong bones, preventing age-related loss, osteoporosis, & more

Guest: Belinda Beck
Date: 2024-10-21 · Duration: 1:48:48
URL: https://www.youtube.com/watch?v=bFvPbXC1lpQ

KEYPOINTS

- **Bone adapts to mechanical loading—its structure literally aligns with force.**
  Beck, an Australian bone researcher, notes that in 1882 scientists described trabecular struts aligning with the forces placed on them. Bone is a 'use it or lose it' tissue: it needs brief, high-magnitude loading, not endurance—'you don't need to run a marathon, just one sprint' to stimulate bone cells.
- **Peak bone mass is built in childhood and adolescence, and then it's a glider.**
  The growth spurt comes around 12 in girls and 13–14 in boys; bone accrual ends around 18 in girls and as late as 25 in boys when growth plates fuse, with most people done by 30. Peter's glider analogy: you reach maximum altitude about 20 years into life, and afterward the best you can do is slow the descent. Genetics explain an estimated 70–80% of bone density, per twin studies, so family history matters.
- **Women start with less bone and lose it faster, especially after menopause.**
  In their 20s women have less bone than men, and at menopause (average around 52–54) circulating estrogen nearly vanishes, accelerating loss for perhaps 5–8 years. By late life the gap is substantial.
- **Kids need calcium, vitamin D and diverse, load-bearing sport.**
  Teenagers need about 1,000 mg of calcium daily; a 250 ml glass of milk has about 300 mg, so about 750 ml of milk or equivalent (yogurt, cheese) covers most of it. In Australia sun before 10 a.m. and after 2 p.m. can supply vitamin D without burning. Swimming and cycling don't load bone enough—a 1992 Stanford study of varsity athletes found gymnasts 'off the scale' while swimmers resembled sedentary controls, though it was observational.
- **Vitamin D thresholds are debated.**
  Beck cites 30 ng/mL as a common deficiency cutoff and 50 as sufficient, with some arguing for 75; she defers to others on specifics. Peter supplements 5,000 IU daily to stay around 50–60 ng/mL, admitting he has no clear indication beyond a hope of being better off later.
- **Corticosteroids harm growing bones.**
  Beck advises keeping children off steroid inhalers where possible or titrating to the lowest dose, and making sure kids who need them get ample milk, sun and loading.
- **Inactivity rapidly causes anabolic resistance.**
  In cast-immobilization studies, after two weeks the casted leg showed about 40–50% anabolic resistance versus the other leg—not aging, just disuse. Movement throughout life matters.
- **DEXA T-scores and Z-scores mean different things.**
  Osteoporosis is a hip T-score of " 2.5 or lower (WHO), with " 1 to " 2.5 being osteopenia. A T-score compares you to an average 20–30-year-old of the same sex and race; a Z-score compares you to people your age—a Z of 0 is the 50th percentile, +1 about the 84th. Total hip is preferred over femoral neck because of analysis variability.
- **LIFTMOR showed heavy lifting is safe and effective for women with low bone mass.**
  About 100 postmenopausal women with low bone mass were randomized to high-intensity resistance and impact training—30 minutes twice weekly, four compound exercises (including deadlifts and squats) at about 85% of one-rep max, with jumping—or a low-intensity program, over eight months. Everyone had said their bones were too fragile; with expert coaching, it was safe.
- **The results rival drugs.**
  The training group gained a net benefit of a bit over 4% at the spine and about 6% at the femoral neck (controls lost about 2.5%). 3D hip analysis showed about a 13% net gain in femoral-neck cortical thickness. Function improved too: sit-to-stand, timed up-and-go, jumping, posture and grip strength.
- **The WHI scare left a generation of women untreated.**
  Peter calls the Women's Health Initiative's effect on hormone therapy one of the great tragedies of the past 25 years for bone health.
- **Middle age is about preserving bone before the menopause cliff.**
  For men and women in their 30s and 40s, Beck says most are on a plateau, so the goal is maintaining loading and avoiding the long sedentary stretches that drive loss. Women should build reserves before menopause. She acknowledges others may disagree given limited long-term data, but sees no downside to continued heavy, varied loading.

EXAMPLES

- **Women deadlifting 70 kg**
  Beck was puzzled how women lifting about 70 kg improved so much until geometric analysis revealed cortical thickening.
- **The 90-year-old deadlifter**
  Peter says he could watch a video of a 90-year-old woman deadlifting for days—the algorithm knows him well.
- **The Onero program**
  LIFTMOR became a clinic-based program, Onero, with accreditation via the Onero Academy, because Beck didn't think high-risk people should do it unsupervised; baseline testing takes 2.5 hours with yearly retests.
- **Masters athletes**
  Beck's long-term data on masters athletes support lifelong loading, though true lifelong trials are almost impossible.
- **From animal lab to humans**

Beck did an animal study for her PhD and quickly realized she didn't want to do that forever, steering her toward human trials and ultimately LIFTMOR.

- **Hearing, posture and falls**

  Peter notes hearing loss is a dementia risk via reduced sensory input; Beck argues posture and sensory awareness similarly matter for falls, alongside strength.

OTHER RELEVANT

- **Parents: maximize peak bone mass.**

  Ask what your 10-, 12- and 15-year-olds are doing: varied impact sports, weight training, calcium and sun.

- **Adults: lift heavy with coaching.**

  Brief, heavy compound lifts and impact twice weekly can build bone even after menopause.

- **Know your family history and get a DEXA.**

  Osteoporotic parents or grandparents signal high risk; check total hip T- and Z-scores. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Train balance and posture for fall prevention.**

  A startle from a neighbor's dog causes falls; strength, posture and grip all reduce risk.

- **Don't rely on swimming or cycling for bones.**

  They're great for fitness but low in bone loading; add weight training and impact work, as many endurance athletes now do compared with the early 1990s.

321 – Dopamine and addiction: navigating pleasure, pain, and the path to recovery

Guest: Anna Lembke
Date: 2024-10-14 · Duration: 2:32:01
URL: https://www.youtube.com/watch?v=ZTxpIBk2F4c

KEYPOINTS

• Dopamine evolved for movement toward reward, which is why it drives motivation.
Lembke, a Stanford addiction psychiatrist and author of Dopamine Nation, notes that dopamine first helped simple organisms locomote toward food—probably no coincidence that the neurotransmitter for movement also governs pleasure, reward and motivation. The prefrontal cortex, which weighs consequences, is still maturing until about 25, so habits laid down earlier are harder to change later.

• Pleasure and pain sit on opposite sides of a balance.
One of neuroscience's key findings of the past 75 years, she says, is that pleasure and pain are co-located and work like a seesaw. Each hit of pleasure is followed by a compensatory tilt toward pain; with repeated use, the brain sets the balance toward pain, so people need the drug just to feel normal—craving, anxiety, irritability and depression between uses.

• Addiction is defined by behavior: continued compulsive use despite harm.
Diagnosis relies on behavioral criteria (loss of control, compulsion, consequences), which is why ten psychiatrists might give ten diagnoses—true of all mental health disorders. Harms include subtle opportunity costs, such as working so much you don't know your children. Someone losing $1 million a year gambling while earning ten times that may not meet criteria if it isn't affecting their life.

• Measure alcohol precisely with standard drinks and a timeline.
A standard drink is a 12 oz beer, 5 oz wine or 1–1.5 oz of liquor. The timeline follow-back method—reconstructing each day for a week—often surprises patients ('I'm drinking 21 drinks a week'). For adult men, more than 14 drinks a week or more than four on any day signals risk, based on epidemiology.

• Risk factors: nature, nurture and neighborhood.
Heritability of addiction is about 50–60% from family and twin studies. Nurture includes trauma and family dynamics. 'Neighborhood' means access—one of the biggest risk factors; easy access to a drug increases addiction risk regardless of other vulnerabilities.

• A four-week 'dopamine fast' resets the reward system for most people.
Lembke asks patients to abstain from their drug of choice for about four weeks. The first 10–14 days usually feel worse; by about four weeks roughly 80% feel better, showing the drug was driving their anxiety and depression. The 20% who don't improve reveal something else is going on, which is equally useful information.

• Some withdrawals need medical supervision.
Alcohol and benzodiazepine withdrawal can be life-threatening; and in the last 20 years, tapering people off very high prescribed opioid doses has revealed severe withdrawal. People who have repeatedly failed to stop alone should seek day or residential treatment rather than self-directed abstinence.

• Addiction is rising, with new demographics and digital drugs.
The male-to-female ratio for alcohol addiction was 5:1, then 2:1 30 years ago, and is now 1:1 among millennials. Cannabis use shifted from weekend recreation to daily high-potency use. Where online sports betting became legal, calls to gambling hotlines rose 300–500%. Cigarette use has fallen, but a 'whack-a-mole' effect shifts addiction to new substances.

• Medications help, and GLP-1s may become addiction treatments.
Gabapentin, typically 600 mg three times daily, helps alcohol withdrawal and sometimes maintenance, though some become dependent. Lembke occasionally recommends semaglutide off-label; small trials show effects, and she wouldn't be surprised if it's approved for addiction within 5–10 years. Naltrexone at 50 mg can blunt reward enough to keep some people free of alcohol and opioids.

• Twelve-step programs work for many and deserve less bashing.
Lembke credits easy access, low barriers, community and 'pro-social shame'—honest sharing that builds connection. She says don't force them or claim they're the only way, but don't malign something clearly effective; Peter mentions a devout Christian theologian friend who now attends 12-step meetings instead of church.

• Causality is hard to prove, which slows policy on screens and cannabis.
Peter notes tobacco's harms were established without RCTs, via Bradford Hill criteria plus mechanism—leading to a 50-year decline. Lembke is divided on cannabis legalization: criminalization caused harm, but access drives addiction.

EXAMPLES

• Peter's 300 mg/day of OxyContin
Peter describes reaching 300 mg a day of OxyContin for back pain—a dose that could kill a naive person. An anesthesiology resident he was dating told him he was crazy; years later, after two days of Percocet for a tooth, he noticed the pull and stopped.

• The cannabis patient
A longtime patient came for anxiety and depression, not cannabis. Twenty years ago Lembke would have prescribed for the mood symptoms; now she first suggests an abstinence trial, and most patients feel much better.

• The marshmallow test revisited
When children were lied to about whether the researcher would return, they were much more likely to eat the marshmallow early—untrustworthy environments make waiting irrational, which may raise later addiction risk.

• Gamblers who want to lose
Some gamblers want to lose because losing justifies staying in the game—revealing that the activity itself, not the money, is

the reward.

- **Pornography escalation**
  Lembke describes patients whose compulsive use escalated over years to extreme content; getting them out of the cycle can remove preferences that seemed fixed.

OTHER RELEVANT

- **Try a 30-day abstinence experiment.**
  Pick your drug of choice—alcohol, cannabis, phone, gambling—push through the first two weeks, and assess how you feel.
- **Count your drinks honestly.**
  Use standard-drink math and a seven-day timeline to see your real intake. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Delay kids' unsupervised digital access.**
  Lembke recommends no unsupervised internet-connected devices for children under 13; talk with teens frankly about drug biochemistry and risk.
- **Get medical help to stop alcohol, benzos or high-dose opioids.**
  Withdrawal can be dangerous; repeated failed attempts warrant a higher level of care. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

318 - The Meteoric Rise of Tadej Poga Ö : From Prodigy to Cycling Legend

Guest: Tadej Poga Ö
Date: 2024-09-23 · Duration: 0:49:44
URL: https://www.youtube.com/watch?v=m9yjbJJBjHU

KEYPOINTS

• His 2020 Tour de France win came as a complete surprise, decided in the final time trial.

In the Covid year, with few races, Poga Ö " pent to the Tour as co-leader with Fabio Aru. After the queen stage to the Col de la Loze, where he finished just behind Primož Rogli ÒÂ †R pas sure he'd be second. The team was preparing a white bike for the young rider's ceremony. He'd scouted the final time trial course in advance and rode it relaxed, with 'no tension, no stress,' and turned the race around. He rode about 380–390 W on the flat. For the climb he used a 6.8 kg bike with no power meter or radio he could hear over the crowds, and simply went 'full gas.' He weighed about 66 kg.

• His 2022 Galibier collapse came from answering too many attacks, not from poor fuelling.

On the Télégraphe–Galibier–Granon stage, Jumbo-Visma attacked relentlessly. He answered eight or nine accelerations, then tried to drop everyone himself, which he now calls 'stupid,' with Wout van Aert up the road anyway. 'If you do eight sprints… it takes too much.' His view: the nutrition plan was fine, but you can't replace that much output by eating more.

• He trains by copying race courses.

Since he was a junior, Poga Ö " † 2 `ound climbs near home that resemble upcoming race climbs and repeated them as many times as they appear in the race. Before Montreal, that meant 4–5 minute efforts plus two short ones. He prefers climbs of about 20 minutes steeper than 9%, because at today's speeds 7–8% gradients give too much drafting advantage. Heat has always been a weakness, so in the last two or three years he has deliberately overheated himself in training, including on a home trainer.

• His stronger 2024 came from work off the bike and closer attention to nutrition.

He added core and strength work for legs, glutes and hips, kept at lower loads through the season, plus more detailed nutrition. As a younger rider he 'could eat what you want.' He never bans foods like chocolate, arguing that six months of restriction ends in a binge. He raced the 2024 Tour at about 64.5–65.5 kg and peaks at about 69–70 kg in the off-season.

• He takes in about 120 g of carbohydrate per hour on hard stages.

Easier stages need 60–90 g/hour. Bottles hold 30 g or 60 g; he prefers 30 g so he can eat more, but uses 60 g on hard days. Five years ago 120 g/hour seemed 'impossible' and he regularly had stomach problems. He credits gels designed by the team nutritionist with the right glucose–fructose ratio, plus gut adaptation.

• Heart rate is his main gauge; power meters need cross-checking.

He's trained with a heart-rate monitor since he was 10–12 and could train on heart rate alone. He finds power meters affected by temperature and calibration, so on home roads he checks heart rate, power, speed and VAM. All-out efforts of about 15 minutes at 7.5% reach roughly 1,700–1,800 m/hour of VAM; Attia says he's happy to hit 1,000.

• His zone 2 is about 320–340 W at 140–155 bpm, but he adjusts it for duration.

Heart rate is 140–145 when fatigued and 150–155 when fresh. Monaco's terrain forces high zone 2 on 20–40-minute climbs with recovery on descents. Five flat hours at 320–340 W would wipe out the next day, so on long flat rides he drops to 290–300 W, because zone 2 'after 5 hours may not be your zone 2 anymore.'

• He tracks overnight HRV and heart rate cautiously, because the numbers can get in your head.

His HRV ranges from about 35 (for example, after alcohol) to 120–130, occasionally 150. It was steady at 80–110 during the Giro and Tour. His resting heart rate averages 42–43 overnight (lowest 37), and 48–50+ means fatigue or illness. His max was 213 as a junior and is still 203. His partner, also a pro cyclist, checks her morning HRV only after a race so a low number can't affect her.

• He treats defeat as a team matter.

After cracking on the Col de la Loze in 2023, he thanked his team. 'It's a team sport… the guys sacrifice everything.' He felt he'd let them down, was devastated and angry, but 'you cannot change nothing,' and dinner with teammates helped. He traced that Tour back to a crash at Liège that hurt his preparation, then rebuilt confidence with a stage 20 win, a third place at the Worlds and victory at Il Lombardia.

EXAMPLES

• Ranking the mythic climbs

With equal freshness, he rates the Galibier easiest, Mont Ventoux second, and Alpe d'Huez hardest (partly because of wind and heat on Ventoux). He calls Alpe d'Huez 'mythical' but says there are much harder climbs, and the Col de la Loze is the hardest of all.

• Off-season training

He never uses a stationary trainer in the off-season. He mixes in running, padel and swimming, rarely takes more than about three days fully off, and is back on the road bike by mid-November. Cross-country skiing and running up a mountain near Ljubljana were his junior winter training.

• Lab testing

He hasn't done a VO2 max or a true 20-minute FTP test in a while. Instead he does a December step test of about 1 hour 20 minutes on a trainer, with 10-minute steps and lactate checks, plus fatigue tests of repeated rising 8-minute efforts.

• Fans on the road

Flags waved in the middle of the road are the biggest danger. He may ease off slightly, but adrenaline and noise mean 'you don't lose momentum.'

OTHER RELEVANT

• Goals ahead

He wants a world title and Milan–San Remo ('the one that is going to send me to grave'), maybe Paris–Roubaix, and a Vuelta

win. A hilly Los Angeles Olympic course would raise its priority. Of the five Monuments, he says Lombardia suits a Grand Tour rider best.

• Records and criticism

He won 12 Grand Tour stages in 2024 and takes every chance to win 'because you never know when is your last win.' He won't chase Cavendish's 35 Tour stage wins, and says the hour record no longer appeals after Ganna.

• Time-trial power

When it matters, he can produce about the same power on the TT bike as on the road bike, thanks to biomechanics work, wind-tunnel testing and a lot of TT intervals, though his TT days are less consistent.

• Rivalry with Vingegaard

He thinks Jonas Vingegaard's 2024 crash didn't cost him peak power but did cost him three-week durability. He'll keep racing the Tour as long as he enjoys the stress.

317 Reforming medicine: uncovering blind spots, challenging the norm, and embracing innovation

Guest: Marty Makary
Date: 2024-09-16 · Duration: 2:11:30
URL: https://www.youtube.com/watch?v=Dzz_tO4Gu3A

KEYPOINTS

• Groupthink in medicine runs on cognitive dissonance and effort justification

Makary draws on Leon Festinger: the brain dislikes holding conflicting ideas, so it reshapes or dismisses new evidence to protect what it heard first. Festinger joined a Chicago cult awaiting an alien rescue before a flood. When the noon pickup failed, the committed members dug in deeper. One physician member admitted he had too much invested to let go. Aronson and Mills showed the same pull: people who passed the hardest entrance test rated a deliberately dull talk the most enjoyable.

• Most uncomplicated appendicitis can be treated without surgery

Before treatment, appendicitis killed more than 60% of those who got it, and lifetime risk is roughly 5–7%. Randomized trials found that a short course of antibiotics cures about two-thirds of patients without a rupture or a fecalith (a small stone in the appendix). About 12% come back with symptoms within a month and then have surgery, with no worse outcome for waiting. It also avoids anesthesia and frees operating-room time.

• Peanut avoidance advice likely helped create a US allergy epidemic

In 1999 a Mount Sinai study put peanut allergy at about 0.5%, and most cases were mild. Around 2000 the American Academy of Pediatrics told parents to keep all peanut products from children aged 0–3, and from pregnant and breastfeeding mothers. This became the '1-2-3' rule. Allergy rates and ER visits climbed, and severe anaphylactic cases appeared. Makary cites an estimate of about 1 in 18 children now, and about 20% of US schools ban peanuts.

• Reversals rarely get the same megaphone as the original warning

Gideon Lack's 2015 NEJM trial of about 640 infants found that early peanut introduction (around 4–6 months, as a supplement to breastfeeding and not as whole nuts) gave about an eightfold difference in allergy rates. NIAID took about two more years to issue guidance, about 17 years after the original advice. Peter says the HRT breast-cancer scare is worse: more than 20 million women went without therapy, and the correction never got the same publicity.

• The HRT scare was announced before investigators could object

Makary says the roughly 40 WHI investigators were told at a meeting to drop the agenda because the paper was already submitted. Investigator Bob Langer warned that the 'genie' could never be put back in the bottle. Makary says the lead investigator acknowledged to him that there was no increase in breast cancer deaths. He says that held at publication and at follow-ups about 9 and about 20 years later.

• Think in probabilities to avoid both blind faith and blanket rejection

Peter worries about a bimodal public: some reject all of medicine, others trust it completely. His fix is to train doctors in statistics and probability theory and treat beliefs as probabilities that get updated. For COVID's origin, that might mean 90% wet market at first, then 80/20, then 50/50 as evidence came in. That makes it easier to change your mind.

• Antibiotic overuse drives resistance and may harm the gut microbiome

Makary estimates about 100,000 US deaths a year from resistant bacteria. The time it takes bacteria to develop resistance has fallen from about 23 years to 14 years to about one year. About 60% of outpatient antibiotics are unnecessary. He no longer gives routine antibiotics before minor laparoscopic procedures. The evidence came from open abdominal surgery. University of Chicago work suggests some surgical infections start in the gut, not on the skin.

• Most 'ovarian' cancer appears to start in the fallopian tube

Makary says the most common lethal type, high-grade serous carcinoma, starts in the fimbriated end of the fallopian tube and the cells move onto the ovary. A large UK screening study found that ultrasound and CT didn't improve outcomes. Lifetime risk is about 1 in 78, and fatality is over 50%. Johns Hopkins now removes the tubes instead of tying them. Germany and most of Canada offer tube removal, with the ovaries left in place, during other elective abdominal surgery for women who are done having children.

• Tube removal is offered only alongside another operation

Peter asks about the risk of damaging the ovaries. Makary agrees this is the main unknown: if one surgeon in 20 had a 5% complication rate, a broad stand-alone recommendation could cancel out the public-health gain. So Hopkins offers it only during other procedures, mostly to women below the mid-60s (the average age at ovarian cancer diagnosis is about 67). Canadian data show lower long-term ovarian cancer rates.

• Medical education and funding reward memorization and narrow ideas

A recent graduate estimated that about half of his medical training was rote memorization, including about 20% on enzyme names. Makary criticizes the AAMC's control over curricula and licensing exams, and the paid board-recertification requirements. NIH spends about $80 billion in siloed institutes, while trials no one profits from go unfunded. Peter's counterpoint: memorizing still matters, but students need to know why it matters.

EXAMPLES

• A wedding-day appendix

A 19-year-old with early appendicitis needed to fly to his sister's wedding in Boston the next morning. Offered surgery or antibiotics, he chose antibiotics and danced at the wedding. A colleague asked for two, then three randomized trials. When they arrived, he still preferred surgery.

• Early antibiotics in Olmsted County children

Mayo Clinic data on about 14,000 children (about 10,000 exposed to antibiotics before age 2) found associations with obesity (+20%), learning disabilities (+21%), ADHD (+32%), asthma (+90%) and celiac disease (about 2.9×). Peter points out possible confounders. Makary points to a Danish study of about a million children and a dose-response pattern, which are Bradford Hill-

style signals. These are associations, not proof.

• C-sections and the newborn microbiome

US C-section rates are about 30%, and Brazilian private hospitals reach about 90%. Individual doctors range from 12% to 100%. Respected obstetricians run at about 12–15%. A spring 2024 JAMA Surgery database study from Sweden linked C-section birth to colon cancer before age 50, which Makary calls a signal only.

• Ritual at birth

As a student, Makary was told to cut a still-pulsing cord and watch the baby be warmed under a lamp. Evidence now favors skin-to-skin contact, which gives the baby steadier heart rate, blood pressure and glucose. It also favors waiting to bathe the baby for 24 hours and delayed cord clamping: a trial found 90 seconds better than 45.

OTHER RELEVANT

• Be wary of absolute certainty

Makary says to be suspicious when health advice is presented as settled 'evidence-based' fact without data. Peter adds that most outlandish ideas turn out to be wrong, so you still need a testable hypothesis.

• Question routine antibiotics

Ask whether a course is really needed, especially for children under 3, whose microbiomes Makary considers most vulnerable. Antibiotics still save lives when they are needed.

• Ask about tube removal during other surgery

Women done having children who are having elective abdominal surgery can ask about removing the fallopian tubes while keeping the ovaries, and should weigh the surgeon's experience.

• Ask questions about the practice pattern

You can ask about non-operative appendicitis care, skin-to-skin contact, delayed cord clamping and a doctor's C-section rate. Watch for one-sided nudges like 'bone on bone, nothing else will help.'

315 Life after near-death: a new perspective on living, dying, and the afterlife

Guest: Sebastian Junger
Date: 2024-08-26 · Duration: 2:19:13
URL: https://www.youtube.com/watch?v=lekPcBKAA-0

KEYPOINTS

• A hidden aneurysm nearly killed a fit, healthy 58-year-old.
In June 2020, Junger—author and journalist, a lifelong athlete in his 50s in excellent health—suffered a ruptured pancreatic artery aneurysm that had probably been growing for decades. He was losing perhaps a pint of blood every 10–15 minutes into his abdomen; of roughly 10 units in the body, losing about two-thirds becomes very hard to survive, and he estimates he lost around 60%.

• He survived because of a long chain of improbable events.
Peter and Junger use the Swiss-cheese model: about ten things all had to go right, from getting to a hospital in time to having the right interventional radiologist on duty. Another physician later told him the radiologist was one of maybe 5% of IR doctors who could have saved him—like Captain Sullenberger being the one pilot in 50 who could land on the Hudson.

• The numbers show how close he came.
His hemoglobin had fallen to a level his doctor said he'd almost never seen (normal is about 14; hematocrit in the mid-40s fell to perhaps 10). His blood pressure was around 60/40. He received about 10 people's donated blood, and spent five days in the ICU before recovering quickly.

• His body may have warned him 36 hours earlier.
The only symptom was intermittent abdominal pain that came and went. Thirty-six hours before nearly dying, he was woken by a disturbing dream that he discussed with his wife—he wonders if some part of him sensed a 'five-alarm fire' coming. He became a father late, at 55, and had daughters aged 3 and 6 months.

• He experienced a near-death vision of a black pit and his dead father.
He felt a sudden, unfamiliar pull, like standing at the edge of a cliff and feeling the void—'I'm getting pulled into this hole.' As he grew scared, he 'saw' his father, an atheist physicist who had died eight years earlier, above him, clearly inviting him to join. Junger, also an atheist, felt the stark dichotomy: the black pit and his dead father meant nothingness, a journey he wouldn't return from. He was almost offended his father would think he'd choose that over staying with his wife and two little girls—'I'm only 58, for God's sake.'

• The experience didn't make him religious, but it unsettled his materialism.
A rationalist journalist, Junger couldn't explain the vision away, yet resists claiming it proves an afterlife. He wrestles with the 'god problem': he doesn't understand how any of us exist, and the fine-tuning of the universe's ~30 physical constants makes existence seem wildly improbable—he cites odds of 1 in 10^230 for a universe like ours. His father had trained him in precise, rationalist questioning—he used to needle Junger's mother about what 'bad energy' even meant—which makes the vision harder for Junger to dismiss or to embrace.

• Quantum physics frames his openness to mystery.
His father, a physicist, was close to Erwin Schrödinger. Junger explains Schrödinger's cat (an isotope with a 50/50 chance of decaying in an hour) and entanglement experiments, where particles seem to coordinate faster than light. Physicists a century ago found Newtonian physics broke down at the atomic level; Junger draws from them humility about what we can know.

• An infinite afterlife might drain life of meaning.
Junger argues that if eternity follows our 70–80 years, it strips the dignity, struggle and victory out of life; conversely, the black pit of nothingness may be so troubling that we struggle to live those years with dignity.

• Married men live longer, and he watched why.
Junger recalls the statistic flashing through his mind as his wife pushed for urgent action—her insistence on getting him to the hospital was part of what saved him. She couldn't accompany him because of COVID rules.

• The aftermath brought psychological fallout.
After recovering physically, he was haunted by how close he came—statistically his wife 'should be grieving me right now by odds of 100 to one'—and spun into what-ifs and gratitude. He felt reverence for medicine: the team in the room and decades of researchers and inventors.

EXAMPLES

• Running obsession
As a young man Junger ran a 4:12 mile, 30 minutes for 10K and a 2:21 marathon on 100–120 miles a week—a maniacal focus he later channeled into journalism.

• War reporting
He recalls being shot at from about 500 meters by AK-47 or PKM fire in Afghanistan, and how a second's luck reshaped his life.

• His father's escape
His father, born in Dresden in 1923 to a Jewish father and Catholic mother, fled Germany for Spain, then France, then the U.S. as fascism spread.

• Schrödinger and the twins
Schrödinger tutored twin girls failing math, related to Junger's family, and had an affair with one of them—a story preserved in a biography where his father kept a bookmark.

• Dostoevsky's mock execution
In the 1840s Dostoevsky was sentenced to death for radical politics, reprieved at the last moment by Tsar Nicholas I—a story Junger uses to illustrate facing infinity 30 seconds away.

OTHER RELEVANT

- **Take recurring, unexplained pain seriously.**
  Junger's only warning was intermittent abdominal pain; prompt evaluation matters even in fit people.
- **Get to an ER fast when something feels catastrophically wrong.**
  Scoop-and-run beats on-site stabilization in some emergencies; minutes mattered.
- **Let mortality sharpen reverence.**
  Junger came away with gratitude and a sense that life's finite struggle gives it meaning.
- **Keep the people who'll push for you close.**
  His wife's insistence was a crucial link in the chain.
- **Medicine's progress is a collective gift.**
  Junger stresses he's alive because of the specific team and because of decades of doctors, researchers and inventors who built interventional radiology—and the roughly ten strangers who donated blood. Donating blood is one way to be a link in someone else's chain.

314 Rethinking nutrition science: obesity treatment, GLP-1 agonists, protein, & better research

Guest: David Allison
Date: 2024-08-19 · Duration: 2:06:56
URL: https://www.youtube.com/watch?v=ilMWQBb_qVY

KEYPOINTS

• Decades of obesity research have produced little public-health progress.
Allison, a statistician and obesity researcher who began his career around 1991 at the New York Obesity Research Center, says clinical treatment improved moderately but public-health efforts achieved virtually nothing. Peter uses an aviation analogy: if planes fell from the sky more often every decade, nobody would claim we understood aerodynamics—yet obesity has risen steadily despite enormous effort.

• The 'epidemic' was declared from NHANES data in the early 1990s.
NHANES III (roughly 1988–94) midpoint data released around 1991 showed what looked like a jump and the word 'epidemic' took hold. Allison notes skinfold data show less of a jump and an earlier, more gradual rise; historical data on 18th-century British naval cadets, French cadets and Civil War soldiers help show long-run trends.

• The environment changed, not our genes.
People ate ad libitum 50, 100 or 200 years ago without today's obesity rates, so something environmental shifted. Peter notes type 2 diabetes rose by roughly a log-fold in his lifetime. Allison points to multiple plausible contributors, including air conditioning—a buffet is more tempting at 110°F in Austin if you're cool indoors—and is wary of single-cause zealotry, including from low-carb advocates.

• Classic public-health tools like 'nudges' have shaky evidence.
Eat-less-move-more messaging, school programs and nudges have weak data. Cluster-randomized school-based childhood obesity trials tend to be quite poor in quality. After repeated failures, Allison argues, we should say 'enough' and change approach.

• GLP-1 success forces a paradigm shift—but we didn't get fat from a GLP-1 shortage.
The drugs work, which some in public health resist because it seems to imply lifestyle doesn't matter. Allison wants a balanced approach: pharmacology plus realistic environmental change, while studying the mechanisms we still don't fully understand. Long-term safety is uncertain because no one has taken them for 40 years.

• Risk means uncertainty, not just known probabilities.
Following FDA thinking, Allison stresses safety involves unknowns. That shapes the debate over whether someone 'subjectively 10 pounds overweight' should take GLP-1s versus someone with a BMI of 40 and diabetes, where benefits clearly outweigh unknowns.

• Peter declines GLP-1s for himself despite their appeal.
He'd love to be 10 pounds lighter and never hungry, and the drugs improve glycemic control, but after watching many patients he doesn't accept side effects like the heart-rate increase for a cosmetic goal; for 40 pounds of medically significant excess, he'd take it 'any day of the week'.

• 'Healthy food' depends on the goal.
Someone wanting to be 10 pounds thinner, lift 10 more pounds or live 10 years longer may need different diets, so Allison dislikes blanket healthy/unhealthy labels.

• Protein needs are probably above the RDA, but thresholds are uncertain.
The RDA of 0.8 g/kg probably isn't optimal. Allison questions claims that 20–30 g per sitting is required to be anabolic—a sigmoid curve is plausible but not proven. A study co-authored by Luc van Loon using up to 100 g suggested the old 40 g ceiling may apply only to fast-digesting whey.

• Upper limits for protein are poorly established.
Claims that more than about 3 g/kg risks kidney damage in healthy people rest on thin evidence. 'Rabbit starvation' reports go back a century; one or two men ate only meat for 6–12 months and were fine, and a 1928 study put two Polish men on nothing but potatoes for six months, also fine—'semi-anecdotes', not RCTs.

• Physics-style humility: we may not understand obesity mechanisms for decades.
Allison compares obesity science to other fields where progress was steady because the underlying science (physics, chemistry) kept improving and being applied. He imagines a future, perhaps 30 years out, where obesity rates fall back toward levels of 50–100 years ago—driven partly by drugs—even while we still don't fully understand the mechanisms, much as the 1970s 'population bomb' fears were defused by agricultural advances rather than by the solutions people then proposed.

• Bias in trials is subtle and often misunderstood.
Allison distinguishes genuine bias from selection inherent in a goal—being cut from a basketball team for being short isn't 'bias' because height is intrinsic to basketball. In nutrition RCTs, he urges clear definitions before labeling a study biased, and notes funding source alone doesn't determine quality.

EXAMPLES

• Danish conscripts
Denmark recorded heights and weights of virtually every 18-year-old male conscript for over 100 years—a rare long-run dataset on obesity trends.

• Feeding-tube experiments
Classic 1960s studies by Theodore Van Itallie and Sami Hashim let people feed themselves through a tube without seeing how much they ate; obese and lean participants responded differently, informing ideas of appetite regulation.

• Viagra's origin

Allison recalls sildenafil was developed for something else, and erections were noticed as a side effect—an example of serendipity in drug discovery.

- **Trial costs and CROs**

  An RCT can cost from over $100,000 to far more; pharma studies are usually run by hired contract research organizations, not the company itself.

- **Obesity and Energetics Offerings**

  Allison's free weekly curated list of about 100 links reaches over 100,000 people, accepts no commercial support and flags when findings are 'in mice'.

OTHER RELEVANT

- **Judge obesity interventions by data, not ideology.**

  Allison urges openness to drugs and to environmental change, and skepticism about cherished programs that haven't worked.

- **Match medication decisions to medical need.**

  The case for GLP-1s is strongest for significant obesity and metabolic disease; for small cosmetic goals, unknown long-term risks weigh more.

- **Aim above the protein RDA, spread across meals.**

  Higher intakes appear safe for healthy people, though minimal per-meal thresholds aren't firmly proven. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Read nutrition headlines skeptically.**

  Ask whether it was in mice, observational or a well-run randomized trial. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

312 - A masterclass in lactate: metabolic fuel, implications for diseases, and therapeutic potential

Guest: George Brooks
Date: 2024-08-05 · Duration: 2:20:56
URL: https://www.youtube.com/watch?v=TGuPXGak5GI

KEYPOINTS

- **Lactate is a fuel, not a waste product—a '100-year mistake'.**
  Brooks, a Berkeley exercise physiologist who proposed the lactate shuttle, says lactate is not an innocent bystander but a participant in powering muscle and all cells. Otto Meyerhof's work—Nobel Prize in 1922, shared with A.V. Hill—led to teaching that lactate is a dead-end byproduct of oxygen-poor glycolysis; Brooks argues we've taught glycolysis wrong for a century.
- **Glycolysis normally ends in lactate, which is then shuttled and oxidized.**
  Lactate is produced continuously, even at rest, and moves between cells and tissues to be burned in mitochondria or converted to glucose in the liver (gluconeogenesis, the Cori cycle). In his tracer studies, about 75–80% of lactate disposal during exercise is oxidation.
- **Most carbon for lactate comes from muscle glycogen.**
  About 80% of the body's glycogen sits in skeletal muscle and roughly 20% in the liver. During exercise, glycogen-derived lactate becomes a major fuel distributed to heart, brain, liver and other muscles.
- **Lactate transporters (MCTs) and mitochondrial machinery enable the shuttle.**
  Monocarboxylate transporters move lactate across membranes; there are now more than four known, the first characterized around 2000. Brooks published finding MCTs on mitochondrial membranes around 1995. Training roughly doubles transporter and mitochondrial capacity—the 'cartoon' muscle cell going from 50 to 100 MCTs.
- **Training expands mitochondria far more than VO2 max.**
  Training can increase mitochondrial mass perhaps 100% while VO2 max rises only 10–15%—a 1967 study in rats by John Holloszy showed this. Mitochondria form a branched network ('reticulum'), so mass and volume matter more than counting individual organelles.
- **Lactate thresholds reflect clearance capacity, not just production.**
  A brisk walk keeps lactate around 1–1.5 mmol; about 4 mmol is the classic threshold a fit person can sustain 30–40 minutes. Elite athletes produce lots of lactate at a given relative intensity but clear it rapidly. Venous lactate from a hard-working muscle might hit 10–12 mmol.
- **Lactate fuels the brain, especially when it's stressed.**
  George Cahill's fasting studies showed people with glucose around 55 mg/dL got about half their brain's fuel from BHB. Brooks's group studies lactate for traumatic brain injury; colleagues in Switzerland give hypertonic lactate to TBI patients who appear to do better, and people can be clamped at about 4 mmol safely, with some reaching 6–8 mmol.
- **In disease, lactate signals metabolic inflexibility.**
  In insulin resistance, muscle struggles to take up glucose via GLUT4, so lactate patterns change. Sepsis lactate of 10 mmol is bad news—but standard assays measure only L-lactate, and Peter wonders whether D-lactate might also matter. Metformin users face increased lactic-acidosis risk when dehydrated.
- **After an oral glucose load, the liver buffers most of the sugar and lactate rises.**
  With a 75 g oral glucose tolerance test, blood glucose may double from ~75 to ~150 mg/dL—only about 5 g more glucose in circulation—so ~70 g must go elsewhere. Studies with 13C-labeled glucose and grain show the liver sequesters about 80% and releases it later; lactate spikes within 5 minutes and peaks around 15.
- **Lactate is also a signaling molecule.**
  Brooks says lactate can activate hundreds of genes (he cites about 500), affecting mitochondrial biogenesis and other adaptations—part of why exercise is so broadly beneficial.
- **The Warburg effect: cancer cells make lactate even with plenty of oxygen.**
  Otto Warburg, Meyerhof's professor in Germany, observed that cancer cells break down glucose to lactate under fully aerobic conditions—room air, with more oxygen than tissues ever see. Brooks reframes this as cancers exploiting lactate's roles as fuel and signal, rather than simply 'avoiding' mitochondria, a point Peter challenges him to explain.
- **Fiber recruitment and clearance explain everyday fatigue.**
  Light work like writing uses type I fibers, which oxidize lactate well. Lifting heavier loads or working overhead recruits type II fibers that produce more lactate and clear it less well, which is why something as simple as changing a light bulb overhead can feel surprisingly fatiguing. Ketones such as BHB enter cells through the same MCT transporters as lactate, so fuels compete—more glucose means less fat, and vice versa.

EXAMPLES

- **A pH of 6.9**
  Peter recalls trauma patients arriving with pH 6.9 rarely survived, though he remembers one miraculous exception. Normal pH is about 7.38–7.4.
- **The elite masters cyclist**
  A friend in his late 40s holds about 5.3 W/kg for an hour—420–430 W at about 80 kg—likely top 10 among U.S. amateur cyclists. His capacity to produce and dispose of lactate, not just generate it, explains it; when lifting with Peter, his strength was unexpectedly low.
- **400-meter runners aren't hungry**
  Brooks notes that after a 400 m sprint, high lactate suppresses appetite for about three hours until cleared.
- **Lactate infusions without acidosis**

In infusion studies, blood pH stayed essentially unchanged (around 7.38–7.4), with even slight alkalosis—undercutting the idea lactate itself causes acidosis.

- **Peter versus his cyclist friend**

Peter rides 3–4 hours a week; his friend rides 15–20. Over a week, the friend both produces and consumes far more lactate—illustrating that trained bodies are high-flux lactate systems, not low-lactate ones.

OTHER RELEVANT

- **Think of zone 2 as training lactate clearance.**

Building mitochondrial capacity improves your ability to oxidize lactate and stay metabolically flexible.

- **Don't fear lactate.**

The 'burn' and fatigue involve multiple factors; lactate itself is useful fuel and a signal.

- **Watch for lactate in medical contexts.**

High lactate in sepsis or with metformin and dehydration is a warning sign needing care.

- **Expect research on lactate therapies.**

TBI and other uses are promising but need multicenter trials. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Measure lactate thoughtfully if you train by it.**

Where you sample (venous versus capillary) and what you're doing matter; values reflect the balance of production and disposal, so use them to track trends rather than as absolute markers.

311 Longevity 101: a foundational guide to Peter's frameworks for longevity

Date: 2024-07-29 · Duration: 1:30:02
URL: https://www.youtube.com/watch?v=B94rbrZkXPI

KEYPOINTS

• Longevity has two parts: lifespan and healthspan

Peter describes longevity as a function of two vectors. Lifespan is binary and objective: you are either alive or dead. Healthspan is analog and subjective, with physical, cognitive and emotional parts. His working goal is to live years or a decade longer, not double lifespan, and to slow the decline of healthspan. Someone who wants to reach 95 presumably wants to function like a healthy 75-year-old at the end, not suffer like Tithonus, who was granted immortality without eternal youth.

• Physical and cognitive health decline with age, but emotional health doesn't have to

Peter says he is clearly past his physical and mental prime, but he has gained in some areas: he moves more intelligently, and his intelligence has shifted from fluid toward crystallized. Emotional health roughly follows a shallow U-shaped curve with a dip around the late 40s. That means it can keep improving: he says he is better off emotionally than a decade ago and expects to be better still in another decade, provided he does the work.

• About three-quarters of the lifespan gain comes from pursuing health

Peter's 'bold', untested belief is that if you only pursued strength, endurance, balance, processing speed, emotional health and relationships, and never thought about heart disease, cancer or Alzheimer's, you would get about three-quarters of the way to an optimized lifespan. Healthspan work is a 'two-fer': it pays off on its own and very likely extends life more than the disease-specific efforts of conventional medicine.

• Medicine 3.0 adds to Medicine 2.0 rather than replacing it

Medicine 1.0 relied on gods, spirits and humors, and life expectancy was in the late 30s to early 40s. Francis Bacon's scientific method, the microscope, germ theory, sanitation and antibiotics roughly doubled lifespan in about 100 years, and RCTs then supercharged this Medicine 2.0. But lifespan has stalled against chronic disease. Medicine 3.0 prevents disease early and aggressively, tailors care to the individual, and gives healthspan equal weight. Peter illustrates the split: of 100 units of health spending, perhaps only 60 are needed, split 30/30.

• Atherosclerotic disease is the most preventable of the Four Horsemen

Atherosclerotic disease needs three things: apoB-carrying lipoproteins entering the artery wall, endothelial damage, and inflammation after those particles oxidize. Peter says genetics and environment drive it with little role for chance. RCTs, Mendelian randomization and epidemiology all show a log-linear drop in risk as apoB falls. Smoking, blood pressure and insulin-resistance markers (glucose, insulin, homocysteine, uric acid) weaken the endothelium. About 50% of first heart attacks are fatal, and he calls the roughly 19 million deaths a year a 'bizarre tragedy' given the tools available.

• Cancer has fewer known levers and depends partly on chance

Clear genetic drivers exist (BRCA1/2, Lynch syndrome), but most family risk is polygenic and unidentified. Smoking and obesity are the clear environmental triggers, and about two-thirds of cancers are strongly tied to obesity. He thinks growth factors such as insulin and IGF matter more than the fat itself. At equal calories, evidence that specific foods such as red meat or soy cause cancer is 'scant'. Much of the rest may be bad luck from acquired mutations (Vogelstein). Metastatic solid tumors have about the same 10-year survival as 50 years ago, which is why he favors early, aggressive screening.

• For dementia, prevention comes first, second and third

'What's good for the heart is good for the brain': every measure that lowers atherosclerotic risk (lower apoB and blood pressure, better metabolic health, not smoking) also lowers dementia risk. Exercise has an even larger and more certain effect on neurodegeneration. With almost no effective treatments, building cognitive and movement reserve is the main defense. Metabolic disease, driven mainly by overnutrition and insulin resistance, adds roughly 25–50% to the risk of the other three Horsemen.

• Two nutrition claims are highly certain: energy balance and protein

Peter admits he spoke with unwarranted certainty about nutrition 12 years ago. He is now confident of only two things. Total energy intake matters most, though quality and processing still count (1,000 calories of Tic Tacs isn't broccoli). Protein is the macronutrient not to compromise on: about 1.6 g/kg/day as a default, perhaps 1.2 or even 1.0 g/kg with high-quality protein in less active people, and more with age because of anabolic resistance. To eat less, you can restrict calories, restrict foods or restrict eating windows.

• Exercise has the biggest single effect

Exercise beats every other tool for both lifespan and healthspan, with the possible exception of emotional health when it is severely broken. Training for the Centenarian Decathlon has four parts: stability (bracing, rib position, foot mechanics, controlled force), strength and power, aerobic efficiency (all-day pace, fat oxidation), and VO2 max (engine size). You set late-life goals, work out what each requires (for example a VO2 max of about 31 mL/kg/min), and work backward to today's training to allow for decline.

• Every supplement should pass a set of questions

Is it meant to extend lifespan or improve healthspan? If lifespan, does it target a specific disease or aging broadly? If healthspan, does it help cognition, physical performance or emotional health? Are there human or relevant animal data on safety and efficacy? How is purity verified? He treats drugs as tools: refusing all of them is like telling a contractor not to use a hammer.

EXAMPLES

• The funeral that started the Decathlon

At a 2018 funeral for his best friend's mother, who died at about 89, Peter realized she had lost golf, gardening and playing with her grandkids a decade earlier and later developed dementia. He had trained without purpose since quitting competitive cycling at the end of 2014, and resolved to train for the last decade of his life instead.

• Specific goals versus the Decathlon

His wife's Boston Marathon training, or a jiu-jitsu tournament in six months, needs specific training. Most people have no such

event, so he says the Centenarian Decathlon is the best default framework he knows.

- **Late starters**
  He writes about people who started committing to their health in their 70s and in their 80s are doing better than in their 60s. He compares it to braking before a red light: earlier is easier, but it's rarely too late.
- **Three first-visit questions**
  Using a DEXA scan and blood work, Peter checks whether a patient is over- or undernourished, adequately muscled, and metabolically healthy. He estimates about 70% of people are overnourished.

OTHER RELEVANT

- **A short list of sleep basics**
  Keep consistent bed and wake times, allow about 8 hours in bed, keep the room dark and cold, avoid work, social media and upsetting stimuli for 2 hours before bed, and stop food and alcohol 3 hours before. He estimates 80 of 100 poor sleepers would improve.
- **Treat emotional health as foundational**
  Even if misery somehow added years, few would choose it. Peter calls this pillar possibly the most important, because without it the others don't matter, and says your mental 'software' can be modified.
- **Start with one pillar**
  If you feel overwhelmed, pick the area where you're most likely to succeed, such as sleep, and change nothing else. Early success makes the other changes easier and builds a sense of control.

310 - The relationship between testosterone and prostate cancer, TRT, and more

Guest: Dr. Ted Schaeffer
Date: 2024-07-22 · Duration: 0:48:20
URL: https://www.youtube.com/watch?v=fiVCsm4dNh0

KEYPOINTS

• TRAVERSE found no increase in prostate cancer with testosterone, but its limits matter.

TRAVERSE was designed mainly to test whether testosterone replacement raises cardiovascular risk, and it found it did not. Urologist Ted Schaeffer walks through its pre-specified prostate analysis. The roughly 5,300 men were symptomatic and hypogonadal, averaged in their 60s, and had a low median PSA of about 0.9, making them a low-risk group. Treatment raised testosterone only modestly, about 140 ng/dL, and more than 60% had dropped out by five years. Only about 23 prostate cancers were diagnosed, with no difference between testosterone and placebo. Peter notes the incidence curves diverged slightly, and both agree the trial was likely too small and short to rule out a small effect.

• In the trial, PSA kept working as a warning signal on testosterone.

Most men's PSA changed by less than half a point during the trial. The men diagnosed with cancer had higher PSAs at entry and larger rises over time. Ted's takeaways: men with low PSA have low prostate cancer risk, and PSA changes can be interpreted much as usual in men taking exogenous testosterone.

• The saturation model: prostate androgen receptors max out at low testosterone levels.

Androgens bind the androgen receptor, which moves to the nucleus and switches on androgen-responsive genes. Once a tissue's receptors are saturated, extra hormone does little more. Saturation thresholds vary by organ. Modeling by former Drive guest Abraham Morgentaler put prostate saturation at a serum testosterone of roughly 200–250 ng/dL, about the 10th percentile for adult men, according to Peter. Prostate and hair follicles are rich in 5-alpha reductase, which converts testosterone to DHT, about 10 times more potent, amplifying the effect. Muscle needs much higher levels for anabolic benefit. That's why raising a man from 300 to 800 ng/dL can visibly build muscle while barely moving PSA.

• Benign prostate cells are more sensitive to testosterone than cancer cells.

Benign prostate cells carry higher densities of androgen receptors. Ted says studies of testosterone supplementation more often show mild worsening of BPH (enlarged prostate) and urinary symptoms than any effect on cancer. He describes this as consistent with TRAVERSE and several smaller studies over two to three decades.

• Aggressive prostate cancers tend to rely less on androgen signaling.

An early-2000s New England Journal paper Peter and Ted discussed on Ted's first appearance linked lower testosterone to higher-grade cancer. Ted's lab built a nine-gene androgen receptor activity (ARA) signature from mRNA in tumor tissue. Larger signatures of 250 or 600 genes tell the same story: tumors with low androgen receptor output are more aggressive, spread more and resist standard therapy, using other pathways such as PTEN loss or MYC. Ted's garden analogy: high-AR tumors are big weeds with thin roots, while low-AR tumors look nothing like normal gland and are the dangerous ones.

• Genomic testing can sharpen treatment for higher-grade disease.

Ted collaborated on Decipher, a clinically certified mRNA test from biopsy or surgical tissue that scores aggressiveness from about 22 genes. A broader genomic panel from the same test reports the ARA score and tumor subtype. In low-grade (Gleason 3+3) cancer, Decipher flags an aggressive outlier only about 7% of the time, and surveillance usually catches those anyway. In phase 3 trial analyses, low-ARA tumors responded especially well when standard hormone therapy was intensified with drugs like enzalutamide, apalutamide or darolutamide. NRG radiation trials, fully enrolled, are testing this, with results expected in about two years.

• Ted rarely advises against testosterone replacement for symptomatic low testosterone.

For a cancer-free, symptomatic, hypogonadal man, Ted can't think of a case where he'd advise against it, because low testosterone threatens cardiovascular, bone, muscle and cognitive health. Strikingly, if a man on replacement at about 800 ng/dL is diagnosed with low-grade cancer on surveillance, Ted keeps him on it. He says there's no evidence it accelerates prostate cancer, and about 30% of men naturally run that high. He wouldn't encourage going above that, and he monitors both men the same way.

• Low-AR, intermediate-risk tumors may favor surgery over radiation.

Radiation for higher-grade cancer is paired with androgen deprivation, which takes testosterone to near zero, sensitizes cells and adds DNA damage. Ted calls that deprivation 'incredibly morbid.' Only about 50–60% of men recover normal testosterone after two years of it. Because benign tissue remains after radiation, restarting testosterone can create false-positive PSA rises. After surgery with favorable pathology, Ted can keep men on testosterone, perhaps around 400 ng/dL.

EXAMPLES

• Two men, same cancer.

Ted's thought experiment: one man naturally at 800 ng/dL and one supplemented to 800 both have Gleason 3+3 cancer. He would follow both identically and not force either to stop or have surgery.

• Testosterone as a differentiation factor.

In the normal prostate, testosterone pushes cells toward a mature, benign state. So high testosterone tends to accompany better-differentiated tumors, while tumors that arise in low-testosterone environments are more worrisome and harder to target.

• A sniper, not a bazooka.

After prostatectomy, men aren't routinely given preventive hormone therapy the way women with ER-positive breast cancer get anti-estrogens. PSA can detect recurrence from just a few hundred cells, so doctors can treat early recurrences only when they appear.

• A hope for breast cancer.

Peter and Ted hope cell-free DNA liquid biopsies can give breast cancer a similar monitoring tool, sparing the many women who don't need years of hormone suppression.

OTHER RELEVANT

- **Watch PSA trends on testosterone therapy.**
  A stable PSA is reassuring. Rising values warrant workup, typically MRI and possibly biopsy.
- **Ask about genomic profiling for higher-grade cancer.**
  Decipher and the ARA score are available through physicians and may inform surgery versus radiation and hormone-therapy intensity.
- **Weigh hormone-deprivation morbidity in treatment choice.**
  When surgery and radiation are equally effective, avoiding androgen deprivation can be a major quality-of-life advantage.
- **These are one expert's practices.**
  Ted's comfort with testosterone in low-grade cancer is his clinical approach. Individual decisions belong with a urologist.

309 AI in medicine: its potential to revolutionize disease prediction, diagnosis, and outcomes

Guest: Isaac 'Zak' Kohane
Date: 2024-07-15 · Duration: 2:16:15
URL: https://www.youtube.com/watch?v=Xa5396tnCIQ

KEYPOINTS

• AI's near-term promise: lift the bottom half of doctors to the level of the top half.
Kohane, a physician and computer scientist who chairs biomedical informatics at Harvard Medical School, says merely making the bottom 50% of doctors as good as the top 50% would be transformative—before even counting 'superhuman' capabilities.

• AI has come in waves.
Kohane majored in biology, got 'nerd-sniped' by computing in the late 1970s and did a computer science PhD in the early 1980s—AI's second wave of rule-based 'expert systems' written in English-like rules, such as Digital Equipment Corporation's R1, which configured minicomputers. These were brittle and lacked data, so the field stalled.

• Gaming GPUs and data made deep learning work.
Video games' need to render high-resolution, 24-bit color at 60 frames per second produced cheap, massively parallel chips that could train multi-layer neural networks. Around 2012, deep networks on GPUs crushed competitors in an annual image-recognition contest—when 'everybody woke up'.

• Transformers and scale produced large language models.
Google's 2017 'Attention Is All You Need' paper introduced the transformer, noticed mainly by computer scientists. Kohane wrote a 2018 JAMA editorial on Google's diabetic-retinopathy AI. Researchers saw performance keep scaling with data and model size, and GPT-3.5 (ChatGPT, December 2022) and GPT-4 became the tipping point—like when everyone knew what Google was by 2000.

• He saw GPT-4 early and was stunned.
In October 2022, Peter Lee emailed him about GPT-4 before ChatGPT's public release, leading to their book on AI in medicine.

• Visual specialties will be augmented first, then language-heavy work.
Radiology, dermatology, pathology and ophthalmology—fields interpreting images—are most easily augmented, followed by work combining language and visual data. Geoffrey Hinton predicted around 2016 that radiologists would soon be replaced; that hasn't happened, and the real future job of doctors in 10 years is an open question.

• Doctor shortages make AI urgent.
The Association of American Medical Colleges estimates a shortfall on the order of 50,000 primary care doctors by 2035. Patients are already using GPT-4, Gemini and Claude in unanticipated ways. Kohane imagines low-cost AI-assisted concierge-like care versus the $5,000–$20,000 a year concierge services cost in Boston.

• Better prediction needs long-horizon data, which is scarce.
Peter calls 10-year cardiovascular risk 'ridiculous', preferring lifetime or at least 30-year risk models with many more inputs. Kohane notes Framingham and its offspring cohort followed LDL over decades; systems like Kaiser Permanente have 20–25 years of detailed records, enough to approximate such models now—don't let perfect be the enemy of good.

• Novel signals—retina, gait, voice—could predict disease.
Peter would take a retinal exam over HbA1c 'all day every day'. AI might analyze eye movements or gait to predict neurodegenerative disease 20 years early, and cameras can detect hypoglycemia risk. Kohane contributed to a 2005 Nature study showing about a 30% drop in gene transcription after age 40, with one 90-year-old who looked young.

• Patients now have a legal right to their data, enabling AI tools.
The 21st Century Cures Act requires programmatic patient access; Apple Health connects to about 800 hospitals. With consent, GPT can extract data from years of lab reports—Epic is using GPT-4 with Stanford—replacing clumsy optical character recognition. Still, Kohane pays hundreds of dollars to extract records for rare-disease patients.

• Why AI suddenly felt different from past hype.
Kohane notes that in the 1980s nobody worried about AI threats because it simply wasn't powerful enough; the Terminator's Skynet was fiction. With GPT-3.5 and GPT-4, AI became a household noun almost overnight. He sees data as one of three key ingredients—alongside compute and algorithms—and electronic health records now supply medical data at scale, though it's messy and fragmented across systems.

• AI can settle old clinical debates quickly when data exist.
Kohane recalls 1990s arguments over how often and at what dose to give certain drugs; with enough real-world data, such questions can be answered rapidly. He also describes an NEJM 'image of the week' of a 72-year-old's back that AI could plausibly interpret—examples of pattern problems that are fundamentally data problems.

EXAMPLES

• Overnight overseas reads
Kohane describes EKG and imaging reads done 12 hours away overnight—early evidence that interpretation can be decoupled from location.

• ELIZA
A 1960s pattern-matching program mimicking a Rogerian therapist; people still found nonjudgmental sessions with it valuable—foreshadowing chatbot therapy.

• Robot surgery bet
Peter offers better than 50% odds that a robot will perform prostatectomies autonomously within 10 years; Kohane calls 10

years 'a very safe bet'.

- **Bots on social media**
  Peter cites estimates that 75–90% of some social media 'individuals' aren't people.
- **Recording a life**
  Kohane describes a man recording his life 24/7—including arguments with family—to create a data legacy for an AI model, accepting the risks.
- **Mark Cuban's early interest**
  Kohane mentions briefly discussing with Mark Cuban an early business plan generated shortly after GPT-4 came out—an illustration of how fast entrepreneurs moved to apply it to health care.

OTHER RELEVANT

- **Get your data.**
  Use your Cures Act rights and tools like Apple Health to gather records, and consider AI to summarize them—with privacy in mind.
- **Use chatbots as a second opinion, not a doctor.**
  They can help prepare questions and interpret results, but verify with clinicians.
- **Push for long-horizon risk thinking.**
  Ask about 30-year or lifetime risk, not just 10-year scores. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Expect imaging-heavy care to change first.**
  AI reads may soon accompany radiology, retinal and skin exams. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Expect AI to democratize expertise, but mind the risks.**
  Kohane imagines patients and primary-care doctors accessing specialist-level interpretation cheaply. The flipside is privacy, bots and misinformation, so build habits of verifying sources and protecting personal data.

307 Exercise for aging people: where to begin, and how to minimize risk while maximizing potential

Date: 2024-06-24 · Duration: 1:45:25
URL: https://www.youtube.com/watch?v=Yz0W-P0UaKE

KEYPOINTS

• It's never too late to start, but waiting raises the cost

Peter compares exercise to saving for retirement. Someone who puts savings into an index fund at 22 barely has to think about it. Starting later means saving more and taking more risk. Fitness works the same way. He sees 50 as one turning point and 65 as a bigger one, when strength loss becomes noticeable and changes in the inner-ear balance system start to raise fall risk.

• Muscle and activity both drop sharply around 75, and individual losses come in steps

Fat-free mass rises until about 25, declines slowly until about 75, then falls steeply, especially in men. Physical activity follows the same pattern, and Peter thinks each drives the other. Luke van Loon pointed out that the smooth population curves hide what happens to individuals: a series of large, discrete drops, because after a certain age minor setbacks become permanent. A broken hip after 65 carries a 15–30% one-year death rate, and about half of survivors never regain their previous function.

• Aim to have VO2 max in the elite range for someone two decades younger

The elite cutoff (top 2.3%) for women falls from over 53 mL/kg/min in the late teens to about 30 at age 80. Most people's late-life goals in the Centenarian Decathlon exercise need a VO2 max in the high 20s to about 30 in their final decade, and daily activities become limited in the high teens. A personal goal: keep VO2 max above your age for as long as possible.

• Fitness is a stronger mortality marker than most diseases

In the large cohort Peter cites, smoking raised one-year all-cause mortality by 41%, type 2 diabetes by 40%, coronary disease by 29%, high blood pressure by 21% and end-stage kidney disease by 178%. Going from below-average to above-average VO2 max for your age also cuts risk by a hazard ratio of about 1.41, the same as smoking. Below-average to high is about a doubling, and even high to elite is about 29%.

• Older bodies still respond to training, but they also lose gains faster

In a 6-week cycling study, people averaging 80 and 24 years old both improved VO2 max by about 13%, maximal workload by about 34% and endurance about 2.4-fold. Absolute values stayed far apart. In the 8-week detraining period that followed, the older group lost gains faster, so consistency matters more than intensity. His big goals for patients are two- to three-year projects.

• Variety and movement quality come before volume, load and intensity

Even with a high 'training age' since 13, Peter, now over 50, prioritizes varied, multi-plane movement because he is more prone to injury. For beginners that means body-weight step-back lunges rather than only heavy leg presses. The most important outcome is that after 3 months the person sees it as positive, feels fitter and wants to do more.

• Build an aerobic base before adding VO2 max work

Start with walking (as little as 5,000 steps a day on flat ground), incline walking, rucking with about 20 lb, or a recumbent bike. For beginners, a reasonable starting point is twice a week for 30 minutes. After 8–12 weeks, increase frequency first (3–4 sessions), then duration (at least 45 minutes). Peter defines zone 2 as the highest steady output with lactate under about 2 mmol. Use the talk test, or Phil Maffetone's 180 minus age, minus another 10 for beginners. Lactate isn't useful for deconditioned people, whose resting levels can be near 2.

• Introduce intensity gradually, then use 3–8-minute intervals

A first step is ending a treadmill walk (for example 3 mph at 5% incline) with five 1-minute bursts at 10% incline. Later, do a weekly session of 3–8-minute intervals with 1:1 passive rest, building from 4 to about 8 rounds. Peter's favorite is 4 minutes: barely noticeable at minute 1, about 50% of maximum pain at three-quarters of the way through, brutal at the end. Choose activities where form won't break down under fatigue.

• Everyone should lift weights

In a 6-week study, people in their late 70s and early 80s increased 3-rep-max leg extension by 78%, versus 83–84% in 20-somethings, even though their absolute strength was far lower (22 kg vs about 178 kg). Type II fiber atrophy is a hallmark of aging (Andy Galpin), and 13 weeks of training increased type II fiber cross-sectional area by 27% in men aged 60–73. Beginners should start with volume over load: 12–15 or more reps per set.

• Most falls come from weak feet, ankles and fast-twitch fibers

About 25% of people over 65 (over 14 million in the US) report falling each year, and at least 50% of people in their 80s and 90s fall. US fall deaths rose about 30% from 2007 to 2016, and the projection is seven an hour by 2030. Contributors include lower-limb weakness, vision and inner-ear balance loss, poor footwear, clutter, and overtreated blood pressure causing dizziness on standing. Falls cause about 95% of hip fractures and are the leading cause of brain injury after 65. Recovering after stepping off an unexpected curb is a power movement that depends on type II fibers.

EXAMPLES

• Courtney Conley's toe and ankle tests

The big toe should press down at least 10% of body weight on a card-pull dynamometer, and toes 2–5 together about 7%. Peter calls toe strength the biggest predictor of falls after 65. In the forward-lean test you should travel roughly 4.5–5 inches. Almost no one passes her calf tests at first, so Peter added heavier calf training (soleus and gastrocnemius). Dorsiflexion check: walk down normal stairs with your toes pointed straight ahead.

• The LIFTMOR trial

Postmenopausal women with low bone mass did two 30-minute supervised sessions a week for 8 months: 5×5 at more than 85% of one-rep max. Lumbar spine bone density rose almost 3% while controls lost more than 1%, and the femoral neck showed a similar split (controls about " 2%).

• Tabata deadlifts

Peter used to do 225 lb for 20 seconds on and 10 off, for 8 rounds. It boosted his VO2 max, but he now calls it too risky because form breaks down in the late rounds.

• Injury costs more with age

A back injury at 27 left Peter unable to walk for 3 months and limited for 9 months, with no lasting effect. He believes the same injury at 70 could have been permanent. After shoulder surgery he did about a year of floor presses before going back to the bench.

OTHER RELEVANT

• For people new to lifting after 65, start on machines

Use machines and body weight before dumbbells (except carries), practice getting down to and up from the floor, and progress faster only with a good trainer. Single-leg variations and single-arm floor presses can replace heavy squats, deadlifts and bench presses.

• Progress in order: frequency, then duration, then intensity

Rushing intensity is the most common cause of injury. Add balance and agility drills and controlled lowering phases for neuromuscular control.

• Ask for hip and lumbar spine scores on your DEXA

Total-body scores aren't enough. A T-score below " 1 is osteopenia, and below " 2.5 is osteoporosis.

• Support training with protein

Aim for at least 1.6 g/kg/day, more with age because of anabolic resistance, and at least 20 g per serving.

305 Heart rate variability: measure, interpret, & utilize HRV for training and health optimization

Guest: Joel Jamieson
Date: 2024-06-10 · Duration: 1:53:50
URL: https://www.youtube.com/watch?v=3TClfAvj2-Q

KEYPOINTS

• HRV measures how strongly the vagus nerve is acting on the heart

Without input from the nervous system, the heart would beat at roughly 100 bpm. At rest, the parasympathetic system (via the vagus nerve) slows it, and that input rises and falls with breathing: inhaling briefly reduces it, exhaling lets it return. That breathing-linked variation between beats is what HRV captures. After a heart transplant the vagus nerve is cut, and the heart beats almost like a metronome. Jamieson says to think of the sympathetic and parasympathetic systems as dials the brain constantly adjusts, not on/off switches.

• Signal quality depends on where you measure

ECG (3- or 6-lead) is the gold standard. A good chest strap finds the peak of each beat (the R wave) to within about 1–2 milliseconds, and over 90% of the research used ECG or chest straps. Optical sensors measure blood volume, technically 'pulse rate variability', and are thrown off by motion, high heart rates, darker skin and tattoos. The forearm is much better than the wrist because wrist bones move. Peter's forearm optical sensor tracks his chest strap within a beat on the bike, while he calls his $700 wrist GPS watch a 'random number generator' for heart rate.

• Different HRV metrics can't be compared

Most devices report RMSSD, a time-based measure of beat-to-beat variability. Apple uses SDNN, a standard deviation taken at random times, which mixes rest and activity. Morpheus applies a natural-log transform and a multiplier to RMSSD to make the skewed distribution close to a 100-point scale: lower values are 50s–60s, moderate 60s–70s, higher 70s–80s and elite athletes 90–100. Compare trends within one system, not raw numbers across devices.

• HRV falls steeply with age, and fitness is the main lever

A typical 50-year-old's HRV is less than half a 15-year-old's. Jamieson ties the drop to declines in mitochondrial, immune and hormonal function, and frames aging as a loss of adaptability, consistent with 'loss of resilience' in the Hallmarks of Aging. Cardiovascular fitness, especially frequent lower-intensity volume, is most closely linked to higher average HRV. Lifestyle also counts: hours of work stress, poor sleep, alcohol and stimulants keep the sympathetic dial turned up.

• HRV is more genetic and less predictive than VO2 max

Studies put the genetic share of HRV anywhere from about 15% to over 70%. Peter has patients who average about 100 ms RMSSD for years and others who average 15. A VO2 max of 70 tells you someone has trained hard for years. A high HRV with no training history tells you much less. Their shared conclusion: worry more about VO2 max, which is more controllable and a better predictor of all-cause mortality, and use HRV for daily guidance.

• A standardized morning reading beats an overnight average for training decisions

About 95% of HRV research uses spot measurements taken under the same conditions each time. That's like weighing yourself first thing every morning: it captures the previous 24 hours of stress and recovery. Overnight averages run higher, and an evening workout, wine or mental strain depresses the first half of the night. People with very high HRV (Morpheus 90s, resting heart rate in the low-to-mid 40s) should measure seated so the lying position doesn't hide changes. Getting up to use the bathroom first is fine.

• Read HRV against your own 7-day baseline and normal variability

Morpheus compares each reading with your rolling 7-day average and typical day-to-day swing, and flags changes larger than one standard deviation as a sign of greater stress. After easy aerobic work, HRV dips and then often rebounds above baseline (about 110–120%) within hours. Hard or long efforts (for example 3 hours in heat) cause a deeper, longer dip. Less fit people may never rise above baseline. So the trend matters more than a single day's number.

• Heart rate recovery is a simple output metric

Peter counts how many beats his heart rate drops in the 60 seconds after each VO2 max hill interval: normally 30–35, 40–45 on great days, and 19–21 after a sleepless night. The drop reflects the sympathetic system easing off and the vagus nerve coming back. New research suggests vagal input doesn't fully switch off above 100 bpm. Faster recovery also points to a more aerobic energy mix.

• GLP-1 drugs consistently raised resting heart rate in Peter's patients

In roughly 25 patients with overnight wearable data, resting heart rate rose by about 10 bpm (range 8–12) with no exceptions, and HRV fell. Both returned to normal within weeks to a month of stopping. Jamieson speculates that suppressing appetite involves suppressing the vagus nerve and says a sustained shift of this size probably carries a cost. Peter notes that for someone going from 250 to 200 lb with HbA1c falling from 7% to 5.5%, the benefit clearly outweighs the unknowns. The question is marginal cosmetic use. He stresses the sample is small. Jamieson sees similar patterns with ADHD stimulants and heavy caffeine use.

EXAMPLES

• A Soviet origin

Jamieson was introduced to HRV over 20 years ago by a Russian engineer, recommended by jumps coach Randy Huntington, who wired him to a laptop in an airport hotel. Soviet scientists had studied Yuri Gagarin's ECG from orbit (his HRV rose in space) and gathered norms from thousands of athletes. The resulting system cost $35,000.

• Finals week versus playoffs

College women soccer players who normally scored in the low-to-mid 80s on Morpheus dropped to the 50s–60s during finals week, lower than during tournaments, from poor sleep and study stress.

• Fighters between rounds

Jamieson wanted UFC fighters coming off 160–180 bpm in sparring to reach the 130s during the 1-minute seated break. Fighters stuck at 150–160 after round one relied too heavily on anaerobic energy and tired quickly.

• Zone 2 on a bad day

Morpheus set Peter's zone 2 at about 139–140 bpm. He felt off and rode by feel at about 132 bpm, and his lactate was 1.1 mmol, well under his limit. His daily targets usually range from about 121 to 141.

• A warning from a very low reading

A well-known sports scientist and author of Supertraining, who had already had a heart attack, showed an RMSSD of about 5. He dismissed it and died of a heart attack months later. Jamieson says persistent Morpheus readings in the 30s–40s are worth looking into.

OTHER RELEVANT

• Wear the sensor in the right place

Use a chest strap for intervals and lifting. If you use an optical sensor, wear it snug (not tourniquet-tight) on the forearm, for example just below the inner elbow.

• Take a 2–3-minute reading lying down after waking

Log sleep, soreness and how much you want to train. A low score doesn't mean you can't train; it tells you what a hard session will cost.

• Treat HRV as a check on direction

A sustained downward trend means you're not adapting well, so adjust training or lifestyle. Unusual jumps can come a few days before a cold, or reflect an arrhythmia or a medication effect.

• Find the right weekly dose of training

Jamieson's closing point: there's an individual weekly amount and intensity that works best, and it shifts week to week. Too little wastes time, and too much brings injury and burnout. With age, the margin for error shrinks.

303-A breakthrough in Alzheimer’s disease: potential of klotho for brain health & as a therapeutic

Guest: Dena Dubal
Date: 2024-05-27 · Duration: 2:23:23
URL: https://www.youtube.com/watch?v=qsA5MBLoeGI

KEYPOINTS

• Klotho was discovered by accident and behaves like a true longevity factor.

In 1997, Japanese scientist Makoto Kuro-o was studying hypertension. A transgene insertion disrupted a gene in one mouse line, and those mice aged prematurely from about two weeks old (osteoporosis, atherosclerosis, emphysema) and lived about three months instead of about 30. He mapped the disrupted gene and named it after Clotho, the Fate who spins the thread of life. The decisive test was the reverse: mice engineered to overexpress klotho lived about 30% longer.

• Most klotho circulates as a hormone cut from a membrane protein.

Klotho is a roughly 1,000-amino-acid (about 130 kDa) transmembrane protein, made mainly in the kidney and also in the brain's choroid plexus. Enzymes (ADAM10/17) clip off most of its outer portion into the blood or spinal fluid, where it acts on many organs. Dubal calls this the 'klotho hormone.'

• Levels fall with age, through the day, and with chronic stress; exercise raises them.

Cord blood has about six times adult levels, and levels can halve from age 40 onward. Fabrisia Ambrosio's lab linked the age-related decline to methylation of the klotho promoter. Levels also fall up to about 40% from morning to midnight. In Dubal's study with Elissa Epel and Aric Prather, highly stressed mothers of children with autism had lower klotho, which tracked shorter telomeres. Across about 12 studies, 12 weeks of regular exercise raised klotho about 30%. Rapamycin raises it in mice, and in mouse data a 45-minute treadmill run may nearly double it acutely.

• Extra klotho made mice smarter, which surprised Dubal.

Her lab crossed Alzheimer's-model mice with klotho overexpressers. The biggest surprise was in normal mice: those with more klotho learned and remembered better across many tasks and ages, with nearly non-overlapping data, not because they swam faster or saw better. The effect replicated in aging mice and Alzheimer's models. In a Parkinson's model (alpha-synuclein), klotho improved cognition by about 70% but did nothing for motor deficits.

• Klotho appears to protect brains despite Alzheimer's pathology.

In aggressive J20 amyloid mice, three- to fourfold klotho overexpression extended lifespan and normalized cognition, even though amyloid-beta and tau levels didn't change. Synapses were preserved, in work with Lennart Mucke and Eliezer Masliah. A colleague's analogy is 'a helmet for neurons' against amyloid, tau, alpha-synuclein and aging.

• It works through the GluN2B subunit of NMDA receptors.

Klotho mice looked like the 'Doogie Howser' GluN2B-overexpressing smart mouse. Klotho increased synaptic GluN2B and plasticity, and blocking GluN2B with drugs abolished the cognitive benefit.

• Klotho doesn't cross the blood–brain barrier, so a blood messenger was proposed—and platelets turned up.

Klotho injected into the belly or arm enhances cognition within 4 hours, and the effect lasts weeks. Plasma profiling after injection showed a surprising rise in platelet factors. A persistent postdoc showed klotho mildly activates platelets to release platelet factor 4 (PF4). PF4 crosses into the brain, acts via GluN2B in hippocampal slices, and enhances cognition in young and aging mice. Saul Villeda (young blood) and Tara Walker (exercise) found PF4 independently, and the three groups published together in Nature-family journals on the same day. Yet klotho still worked fully in PF4-knockout mice, so PF4 is 'sufficient but not necessary,' and other messengers are being sought.

• In old monkeys, one low physiological dose improved working memory for weeks; high doses didn't help.

With Unity Biotechnology and Yale (Graham Williams, Stacy Castner), 18 aged rhesus macaques did a largely blinded spatial delayed-response task: remembering which covered well held a treat. One subcutaneous low dose (within natural range) improved performance within 4 hours, lasting 14–21 days and in some cases tested to 28. Gains were largest on the harder, many-well version. Doses 10–20 times higher neither harmed nor helped, unlike in mice, where even far higher doses worked. Dubal concludes humans likely have a therapeutic window. She calls the study a 'burn your ships' risk she was willing to take.

• In humans, the KL-VS variant links higher klotho to better cognition and blunts APOE4 risk.

About 1 in 4–5 people carry one copy, with about 15–20% higher levels (for example, about 950 vs 800 pg/mL). Dubal and Jennifer Yokoyama found carriers scored better cognitively, by about as much as APOE4 carriers score worse. Michael Belloy and Michael Greicius analysed 22 cohorts and over 20,000 people: APOE4 carriers with KL-VS had near-normal Alzheimer's risk, less MCI-to-Alzheimer's conversion and less amyloid. Dubal says, from personal communication, protection also held for APOE4 homozygotes. Carriers also show less stroke and cardiovascular risk, but a worse prognosis in BRCA1-positive breast cancer. Rare KL-VS homozygotes have about 30% lower klotho and shorter lives.

EXAMPLES

• NHANES mortality signal

In about 10,000 US adults (mean age 56), serum klotho below about 666 pg/mL was associated with roughly 30% higher 5-year mortality, mainly from cancer and cardiovascular disease, and this replicated in another cohort. Attia stresses this is association, not proven causation.

• Mouse dosing

Even about 0.2–1 µg/kg, versus a usual 10 µg/kg, enhanced mouse cognition. Very high doses worked too, with no obvious problems in behaviour or basic blood work.

• Fasting caveat

A 24-hour fast raised klotho and BDNF in mouse brains. Attia warns a mouse fast that long is extreme and doesn't mean skipping breakfast equals a workout.

• A mentor's advice

As a resident, UCSF's neurology chair Stephen Hauser told her to do things 'big and important, not incremental,' because they take the same time.

OTHER RELEVANT

- **Testing is not yet practical**

  There's no standardized clinical klotho assay. Researchers draw samples in the morning while fasting. Attia says KL-VS status is hard to extract from consumer genetic tests.

- **Klotho as kidney marker**

  Klotho falls early in chronic kidney disease, so nephrologists are developing it as a more sensitive biomarker than current measures. Mouse studies also report anti-cancer effects.

- **Therapeutic vision**

  Dubal hopes klotho could be combined with anti-amyloid drugs like lecanemab or donanemab, perhaps as monthly or quarterly injections, but human trials are still needed. Attia disclosed he is an investor in Jocasta Neuroscience, which is developing klotho.

- **Exercise remains the accessible lever**

  Dubal emphasizes that regular exercise's roughly 30% increase in klotho exceeds the genetic KL-VS boost.

302 - Confronting a metabolic epidemic: how to prevent, diagnose, & manage liver disease

Guest: Julia Wattacheril
Date: 2024-05-20 · Duration: 2:37:08
URL: https://www.youtube.com/watch?v=ZiJ2th4rKKA

KEYPOINTS

• The liver is the one vital organ with no temporary external support.

Lungs have ventilators, hearts have balloon pumps and assist devices, kidneys have dialysis. For the liver, devices like the MARS machine exist but nothing really bridges acute failure. Wattacheril, a transplant hepatologist who directs Columbia's MASLD program, notes the 3.5 lb organ performs over 300 functions: macronutrient metabolism and glucose regulation, clotting proteins, immune functions, detoxification of drugs and toxins, bile acids, and lipoprotein production and clearance. Attia recalls a story from his training of baboons once used as temporary external livers.

• MASLD is the new name for NAFLD, with clearer subcategories.

The old name defined the disease by what it wasn't, and patients who never drank were labelled alcoholics. The umbrella is now steatotic liver disease. It includes MASLD (metabolic dysfunction), MetALD (metabolic dysfunction plus moderate alcohol), alcohol-related disease, monogenic forms, drug-associated fat and cryptogenic cases. Steatosis means fat in at least 5% of hepatocytes. MASLD affects an estimated 25–35% of people, conservatively, and disproportionately children.

• A normal ultrasound doesn't rule out fatty liver.

Standard ultrasound usually misses fat below about 30%. Vibration-controlled transient elastography (FibroScan) gives two numbers at the bedside: a CAP 'fat score' and a stiffness 'scar score' (vibrations travel differently through a 'sponge' than a 'brick'). It isn't technically feasible in about 8–10% of her patients. MRI-PDFF quantifies fat and iron precisely and is used in research. A lean person (BMI 22) with a CAP around 400 and no insulin resistance suggests a rarer export problem, such as a genetic lipid disorder.

• AST and ALT are injury markers, not 'function' tests, and lab limits have drifted up.

These enzymes leak when stressed hepatocytes burst. True function is albumin, clotting and glucose handling. Older thresholds were about 19 for women and 30 for men; labs now flag in the 40s–50s because the population has changed. For patients already diagnosed and in treatment, she's pleased below about 30, still uses about 40 as a workup threshold, and becomes concerned at persistent 1.5–2 times the upper limit for about six months. Discussing Attia's AST 34 and ALT 21, she asks about lifting within 24 hours, CK, alcohol timing and medications such as ezetimibe, and suggests retesting after rest days without alcohol.

• Alcohol and metabolic fat injure the liver in similar ways and often coexist.

Alcohol dehydrogenase converts ethanol to acetaldehyde. When capacity is overwhelmed, redox balance shifts, peroxidation occurs, and immune cells are recruited. Biopsies often can't distinguish alcohol from metabolic injury. A standard drink is 1.5 oz liquor, 5 oz wine or 12 oz beer (about 14 g of alcohol), and the CDC's 'moderate' is 2 a day for men and 1 for women. She asks about weekly quantity, binge patterns and context. She uses phosphatidylethanol (PEth), which reflects about 1–2 weeks of drinking, because self-report and shame often diverge. For most women who drink, she says breast cancer risk exceeds liver risk.

• Fibrosis stages progress slowly, and even early cirrhosis can reverse.

NASH (now MASH) means fat plus inflammation plus 'ballooned' pre-death hepatocytes. Fibrosis runs from stage 1 ('chicken wire' around the central vein in adults) to stage 3 (bridging) and stage 4 (cirrhosis, with nodules). Each stage takes about 5–7 years in MASLD, based mostly on European-ancestry data. Hepatitis C cures showed some early cirrhosis regresses. Cirrhosis is 'not a death sentence' but triggers cancer screening every six months.

• For early MASLD, the bigger near-term risks are diabetes, heart disease and cancer.

She often tells patients: your scar score is normal, your fat score is very high, and it can normalize in six weeks to six months, but unchanged you'll likely develop diabetes. Patients tend to hear that as empowering. Hepatocellular carcinoma risk in cirrhosis is about 3–5% a year. It's highest in hemochromatosis, then hepatitis C plus alcohol. Hepatitis B is the outlier, causing cancer even without advanced fibrosis. Her group is studying whether stage 3 MASLD needs earlier screening.

• Lifestyle remains first-line treatment, with specific emphasis on muscle.

Many patients say 'I don't eat that much fat,' but she says the main issue is glucose handling and refined carbohydrates. Many of her female patients with lean fatty liver have low muscle, so she prescribes combined resistance and aerobic exercise or, for sedentary people, a walking prescription. She refers detailed, culturally appropriate nutrition planning to dietitians. On fructose, she says studies that separate it from weight loss and insulin resistance show little net difference, so she recommends avoiding processed foods rather than isolating one sugar.

• Drugs: GLP-1s for appropriate patients, and resmetirom is the first liver-directed success.

For patients with a BMI of about 28–40, stage 2 disease and maximized lifestyle changes, she brings in GLP-1 agonists, with frank talks about muscle loss and weight regain after stopping. She raises bariatric surgery at stage 3 or early cirrhosis. The thyroid-hormone receptor agonist resmetirom showed phase 3 efficacy in a population about 90% of European ancestry. Vitamin E (from the PIVENS trial) helps steatosis but carries concerns about cardiovascular risk, prostate cancer and dose-dependent mortality.

EXAMPLES

• Coffee

Up to about three cups a day of black coffee is linked to benefit across fatty liver, hepatitis C fibrosis and even liver cancer, and is in European and American guidelines. Caffeine alone doesn't reproduce the effect. Attia drinks French press on the untested theory that more of the bean is better.

• Statins and ezetimibe

Small enzyme rises are usually accepted for cardiovascular benefit. She can count on one hand biopsy-proven injury from

lipid drugs. Attia's practice switches agents when enzymes rise.

- **Children differ**
  Pediatric fatty liver centres on the portal areas, often raising GGT and alkaline phosphatase, with higher AST and ALT than adults.
- **Hidden hepatitis C**
  Many cases are found through screening and traced to 1970s–80s drug use, shared intranasal cocaine straws, pre-screening transfusions or dental work abroad.

OTHER RELEVANT

- **When to biopsy**
  She biopsies to exclude autoimmune disease (about 18–20% of MASLD patients have positive autoantibodies), for trials, before major surgery, and to settle conflicting non-invasive tests.
- **Refer outliers**
  Lean patients with high ALT and moderate stiffness by 35 need a specialist for genetic testing, for example for lysosomal acid lipase deficiency.
- **Acetaminophen**
  Under 10% of transplants at her centre are for acute liver failure, and only some of those involve acetaminophen.
- **Screening**
  Screening isn't yet recommended, but a FIB-4 calculation plus FibroScan suits men over 50 and people with insulin resistance. About 30% of her patients refer themselves.

300-Special episode: Peter on exercise, fasting, nutrition, stem cells, geroprotective drugs, & more

Date: 2024-05-06 · Duration: 1:48:22
URL: https://www.youtube.com/watch?v=Io5xV9rtbm4

KEYPOINTS

• Peter sorts claims into five evidence tiers: proven, promising, fuzzy, noise and nonsense.

For the 300th episode, Nick Stenson put listener-submitted topics, drawn from a few thousand Instagram comments, to Peter for ranking. In biology nothing is truly proven, so 'proven' means the chance it's untrue is so small it would be foolish not to act. 'Promising' has strong data with a missing piece, such as human or randomized trial evidence. 'Fuzzy' has inconsistent or contradictory data. 'Noise' has data too thin to judge, perhaps with an appealing mechanism. 'Nonsense' has been studied and found to be bunk. Peter stresses that rankings move as evidence changes.

• Rapamycin: promising, not proven.

Rapamycin was discovered in Easter Island soil bacteria in the 1960s and championed by Suren Sehgal. The FDA approved it for organ transplantation in 1999. In 2009 the Interventions Testing Program (ITP) showed it extended life in male and female genetically diverse mice, even when started late in life, which no other drug had done. It also works in yeast, worms and flies. What's missing is human evidence that intermittent dosing, which short trials suggest can enhance rather than suppress immunity, actually extends life. Peter has taken it for about six years, yet fewer than 10% of his patients do, and he calls handing it out 'like Tic Tacs' irresponsible.

• Metformin: downgraded from promising to fuzzy.

Bannister et al. (2014, UK data) found diabetics on metformin had about 15% lower all-cause mortality than non-diabetics, despite worse glucose control. Peter argues this was likely driven by informative censoring, since patients were dropped when their medication changed, which selected for the healthiest. Keyes et al. (2022), using Danish data that included twins discordant for diabetes, found metformin users still had 33–80% higher mortality. Metformin also failed in the ITP except when combined with rapamycin. The TAME trial may eventually test it in humans.

• NAD and its precursors: noise. Resveratrol: nonsense.

NAD declines with age and is needed by sirtuins, but whether the decline is causal is unknown. The best human data are tiny: a four-month ALS study of nicotinamide riboside (NR) plus pterostilbene showing slowed functional decline, a 20-person Parkinson's study confounded by levodopa timing, and a small MCI study with no cognitive benefit. Peter takes no NR, NMN or infusions. Resveratrol's 2006 mouse benefit came in mice fed 60% coconut oil whose fatty livers collapsed their lungs. The rigorous ITP test at 300 ppm in food, versus under 2 ppm in wine, showed nothing, a result proponents signed off on at the time.

• VO2 max, muscle mass and strength are as close to proven as it gets.

Peter ranks them alongside quitting smoking and controlling blood pressure. Fitness predicts lifespan better than cholesterol, blood pressure, glucose or even smoking, partly because 'you can't cram for the test': a top-2–3% VO2 max or strong grip reflects years of work. He tells patients chasing supplements that they're 'picking up pennies in front of a steam train.' Even if exercise were lifespan-neutral, he says, its quality-of-life benefits would make it worth it.

• Long-term fasting: fuzzy, and Peter stopped his own protocol.

Caloric restriction, like rapamycin, extends life across model organisms. But the duration, depth and frequency that might work in humans are untested, and he admits his old routine of 7–10 days of water-only fasting each quarter plus 3-day fasts in other months was 'made up.' Fasting crashed his thyroid and androgen markers, and over about three years he lost roughly 16–20 lb of muscle he couldn't regain. In about 2021 he stopped, partly also to avoid fasting in front of his kids. He still uses time-restricted eating for calorie control.

• Energy balance: between promising and proven.

A study funded by an organization Peter once ran found that equal-calorie diets with very different macronutrients don't meaningfully change energy expenditure. Thermic effects and appetite differ by food, but someone switching from 3,000 balanced calories to 3,000 keto calories who rapidly loses weight is, he believes, moving more or eating less than they realize. Changing your mind with new data is what separates a scientist from an advocate.

• 'Red meat causes cancer' is nonsense in Peter's ranking, though diet patterns matter.

In a European cohort of nearly half a million people, the heaviest red and processed meat eaters (about 160 g/day) versus near-zero eaters (about 20 g/day) had colorectal cancer risks of about 1.7% versus 1.33%. That's about 0.4 percentage points, or treating roughly 250 people to prevent one case, even assuming causation. Peter blames food-frequency questionnaires and healthy-user bias, and suspects low fiber and vegetable intake drive much of the risk. He considers the weak hazard ratios incompatible with Bradford Hill causality, unlike smoking.

EXAMPLES

• Blood flow restriction (BFR): promising.

Partially restricting venous return with a cuff during light, high-rep lifting produces clearly larger strength and size gains than the same work without a cuff. Jeremy Loenneke's meta-analysis showed this, and each limb can serve as its own control. BFR hasn't been compared head-to-head with heavy lifting. Peter used it after shoulder surgery, uses it for finishers, and has post-op knee patients do bodyweight leg extensions with a cuff.

• Stem cells for osteoarthritis: between noise and fuzzy.

Dog studies are mixed, cell types and protocols vary, and the FDA doesn't authorize them, making the field 'the Wild West.' Still, Peter would try an injection for a borderline rotator-cuff tear before surgery.

• 'Sugar is poison' is the wrong question.

As with Tylenol or alcohol, the dose makes the poison. In a nine-month calorie-controlled mouse study discussed with Rick Johnson, fructose didn't change body weight. Liquid sugar does drive overeating. As a teen training six hours a day, Peter drank two liters of orange juice as a snack at about 4% body fat.

- **Sugar substitutes.**
  Cancer scares came from rats fed the equivalent of about 800 diet sodas a day (saccharin) or about 20 (aspartame). Saccharin, aspartame and sucralose look mildly negative metabolically. Stevia, erythritol, xylitol and allulose look better. Peter chews xylitol gum for tooth enamel.

OTHER RELEVANT

- **Master the basics before supplements.**
  Build VO2 max, muscle mass and strength first. Geroprotective pills don't substitute for them.
- **Swap diet soda for water, not regular soda.**
  Peter's advice to people struggling with weight or glucose who drink a lot of artificially sweetened drinks.
- **Fatty liver.**
  Weight loss improves it regardless of diet. Peter still advises such patients to avoid alcohol and limit fructose to modest amounts of fruit, while admitting the trial evidence is incomplete.
- **Use a three-question nutrition triage.**
  Are you over- or under-nourished? Adequately muscled? Metabolically healthy? The answers guide how you eat and train.

Special episode with Dax Shepard: F1 and the 30th anniversary of Ayrton Senna’s death

Guest: Dax Shepard
Date: 2024-04-29 · Duration: 2:41:39
URL: https://www.youtube.com/watch?v=9YUF9q6VThE

KEYPOINTS

• Senna's greatness shows in qualifying more than in championships.
In this special episode, Dax Shepard, who calls himself 'a three out of ten' on Senna, interviews Attia about his obsession. Attia notes that Senna died in his 161st race, fewer than most current drivers have already started, yet took 65 pole positions. That ratio is unmatched. He won three titles, and Attia argues a fourth was taken from him. He also had the best car in only four of his ten seasons.

• Monaco 1988 is Attia's favourite Senna story.
In his first year at McLaren, driving the MP4/4 (which won 15 of 16 races), Senna out-qualified teammate and reigning champion Alain Prost by about 1.4 seconds (Attia cites 1.47). The decisive lap wasn't filmed because he was already on pole. In the race he led Prost by about 56 seconds, then lost concentration, crashed, and disappeared to his Monaco apartment for hours. His housekeeper had been told to say he wasn't home.

• Rain was where he stood out most.
As an F1 rookie in a 'garbage truck' Toleman at Monaco in 1984, he was closing on Prost in a downpour when officials stopped the race a lap early. He won his first race in heavy rain in Portugal in 1985. Angelo Parilla, whose DAP karting team Senna drove for, said Senna was even better in karts, and in the rain he'd urge officials to just give Senna the trophy.

• His driving technique broke the usual rules.
Rather than rolling smoothly onto the throttle ('smooth is fast'), telemetry showed Senna stabbing it on and off and then going to full. People assumed it kept the turbo spooled and predicted he'd struggle in naturally aspirated cars, but he kept doing it and didn't. He'd run within inches of the Monaco walls one-handed, with no power steering and a clutch. His feedback to engineers was so precise he once came in while injured to check whether a stand-in's feedback could be trusted.

• The 1994 Imola weekend was a series of warnings that should have stopped the race.
On Friday Rubens Barrichello, whom Senna mentored, crashed heavily but survived. On Saturday Roland Ratzenberger was killed, F1's first death in 12 years. Attia says Italian law would have ended the event if a driver was declared dead at the track, so he was flown to hospital. Senna was reprimanded for driving to the crash site. His trainer Josef Leberer told Attia he'd never seen Senna angrier. Senna agreed with Niki Lauda to revive the drivers' safety association and admitted he didn't want to race, but said the people of Brazil needed it. Sid Watkins reportedly urged him to retire and go fishing.

• His Williams FW16 was nearly undrivable after active suspension was banned.
Senna moved to the dominant team only for the ban to wreck its handling. Teammate Damon Hill told Attia it felt like 'a knife's edge' every lap and he stayed well below the limit. Senna still took pole in the first two races but scored zero points while Michael Schumacher won both in a Benetton Senna suspected of illegal traction control. Senna's steering column had been extended about 6 inches and narrowed to fit how he liked to sit.

• Attia doesn't believe the steering column caused the crash.
He thinks Senna took the bumpy racing line through Tamburello on cold tyres (possibly with a slow puncture), bottomed out and lost rear downforce. The car oversteered, Senna corrected it, the car suddenly gripped again and went straight off, and he braked hard into the wall at about 150 mph. Attia owns Senna's steering wheel from qualifying and says on-board footage shows him correcting before leaving the track, with no sign of a free-spinning wheel. Adrian Newey's book and Hill share this view. Italian courts nonetheless found Newey and Patrick Head liable, but the statute of limitations had expired. A suspension rod pierced Senna's helmet.

• His legacy goes far beyond racing records.
Attia compares May 1, 1994, for Brazilians to JFK or 9/11. Senna was nearly as revered in Japan through Honda. Unknown to most during his life, he gave quietly to education. His sister Viviane founded the Senna foundation, which Attia says has given over half a billion dollars. His death transformed F1 safety, and Tamburello is now a chicane. Attia named his youngest son after him.

EXAMPLES

• Shepard's view of risk
Given a choice between living like Senna to 34 or a quiet life to 105, Shepard would choose Senna. On the track, his worries and goals disappear, which he compares to a meditation retreat. Still, he once stopped racing after holding his sick baby daughter and a fatal crash in his series.

• How racing psychology compounds
After one tyre lockup, Attia began braking 50 feet early, costing about 0.8 seconds a lap, and kept spinning. He says no other activity punishes mistakes so geometrically.

• Car vs driver
Attia estimates the split was about 50/50 in the 1980s and about 75–80/20 today, so Max Verstappen couldn't win in a back-marker except in the rain. Shepard notes that unreliability once made races less predictable.

• Senna's rivalry with Prost
Prost, nicknamed 'the Professor,' would settle for third and the points. Senna wanted only to win and would risk a crash while leading. Prost later used a contract clause to block Senna from joining him at Williams in 1993.

OTHER RELEVANT

• Tyres limit everything

Hundreds of millions in engineering still reach the road through four tyre contact patches. Verstappen's edge over Charles Leclerc is making tyres last, not single-lap pace.

• Greatest-of-all-time debates

Attia ranks Senna first and Schumacher second, with Verstappen rising. He compares Senna to Barry Sanders: greatness that statistics don't capture. Senna himself named Terry Fullerton from karting and Fangio in F1.

• The 2021 season

Both consider it the best recent season, a better driver beating a better car, and say calling Abu Dhabi the sport's greatest injustice reflects a shallow knowledge of F1 history.

• The 'what if'

Attia thinks Senna would likely have won 1994–97 at Williams and might have entered Brazilian politics. His grave in São Paulo is a simple plaque.

299 Optimizing muscle protein synthesis: protein quality and quantity, & the key role of training

Guest: Luc van Loon
Date: 2024-04-22 · Duration: 2:38:39
URL: https://www.youtube.com/watch?v=AVOKWvYJM-c

KEYPOINTS

- **Muscle stays responsive to training and protein at any age.**
  Van Loon, a professor at Maastricht University in the Netherlands who has spent around 30 years and about €30 million in research funding on muscle and protein, says you don't need to start at 40 to have good muscle at 80—muscle remains responsive at 70 and even past 100, though starting earlier is better.
- **Stable isotope tracers reveal what happens to the food we eat.**
  Carbon-13 has an extra neutron and is stable. Feeding labeled carbohydrate shows its oxidation via exhaled 13CO2; labeled amino acids such as phenylalanine show incorporation into muscle. His lab even produced 'intrinsically labeled' milk and meat by infusing tracers into cows—one experiment cost more than €50,000 in tracer.
- **Exogenous carbohydrate oxidation tops out around 60–70 g per hour from glucose.**
  Glucose alone is oxidized at about 1–1.1 g/min; adding fructose, which uses a different transporter, can push it to 1.3–1.4 g/min in high-output athletes. Glycogen storage is roughly 100–200 g in the liver and 300–350 g or more in muscle, though trained athletes can store more.
- **Your body recycles far more protein than you eat.**
  You synthesize about 300 g of protein daily but eat perhaps 70–100 g, so roughly 230 g of amino acids are recycled from your own tissues each day. Muscle proteins are fully turned over in about 50–100 days—'in 50 to 100 days you have a new arm'.
- **The '20 grams per meal' figure comes from whey studies—and may underestimate needs.**
  Studies found 40 g of whey didn't stimulate muscle protein synthesis more than 20 g over about four hours, so 20 g became the standard on packages. Body size matters (more for 120 kg, less for 50 kg), and with mixed whole-food meals, 30–40 g per meal may be more appropriate.
- **A 100 g protein dose showed the 'ceiling' isn't real over longer periods.**
  In his study comparing 0, 25 and 100 g of intrinsically labeled protein (mostly casein—milk is about 80% casein, 20% whey), the 100 g dose produced a larger and much longer anabolic response over 12 hours, and oxidation of excess protein had been overestimated. Digestion of a full meal takes 2–3 hours, versus peak amino acids within 30–75 minutes from a shake.
- **Typical intake is modest; targets for muscle gain are higher.**
  Healthy Americans eat about 1.1–1.3 g/kg/day; Peter suggests 1.6 g/kg or more for building muscle. Spreading it—20 g at breakfast, lunch, dinner and an evening snack—reaches about 80 g for a typical person.
- **Presleep protein uses the overnight fast.**
  Dinner at 5–6 p.m. and breakfast at 8–9 a.m. leaves about 15 hours without food, a period of muscle loss risk—'that's stupid'. Protein ingested before sleep, even delivered via nasogastric tube at 2 a.m. in early studies, is digested and incorporated overnight. Evening exercise plus 40–60 g of protein boosted overnight synthesis.
- **Disuse rapidly destroys muscle, and hospital nutrition makes it worse.**
  Immobilizing a leg loses about 220 g of muscle in a week, with declines in oxidative capacity. Healthy elective-surgery patients ate only about 0.5 g/kg during four hospital days—a third of guidelines (ASPEN suggests 1.2–1.5)—and lost about 1.4 kg. Of people over 65 with hip fracture, 15–30% die within a year, and about half of survivors never regain prior function.
- **Older muscle shows anabolic resistance.**
  Michael Rennie's group coined 'anabolic resistance' around 2005; van Loon's lab took nearly 10 years to confirm it. Older adults need more protein per meal and resistance exercise to get the same response, though cross-sectional young-versus-old comparisons limit conclusions.
- **Glycogen recovery and endurance fueling have been rethought.**
  Van Loon notes that with adequate carbohydrate, glycogen can be fully restored after exercise, unlike the old beliefs Peter grew up with as an endurance athlete. For ultra-long events, aiming for over 1 g per minute for 20 hours would be punishing on the gut, so practical intake is lower. Endurance cyclists perform hundreds of thousands of low-force repetitions at 80–100 rpm, none as hard as a heavy lift—different stimuli with different protein needs.

EXAMPLES

- **Peter's glucose during exercise**
  Peter recalls a test where his glucose started around 80 mg/dL and never went above 100 during hours of exercise while consuming carbohydrate, and insulin stayed under about 11—showing insulin-independent glucose uptake by working muscle.
- **Time-restricted eating pitfalls**
  Peter describes a 2–7 p.m. eating window (19-hour fast) that makes reaching 1.6–1.8 g/kg nearly impossible; van Loon suggests 25 g whey shakes at 8 and 11 a.m., then meals at 2 and 7 p.m.
- **Ten grams of essential amino acids**
  About 10 g of EAAs equals roughly 20 g of protein—consistent with dose-response studies.
- **Exercise insulin sensitivity**
  Effects of a session on insulin sensitivity last up to about 48 hours, which is why diabetics are advised to spread 150+ minutes across the week; van Loon considers that a minimum.

OTHER RELEVANT

- **Eat 30–40 g of protein per meal from whole foods.**
  Distribute across 3–4 occasions, including a presleep serving. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prioritize protein and movement during illness or hospitalization.**
  Even a few days of bed rest with low intake costs significant muscle. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Start training at any age.**
  Muscle remains responsive into very old age; resistance training plus protein counters anabolic resistance.
- **Fuel long endurance efforts with mixed carbs.**
  Glucose-fructose blends allow higher carbohydrate oxidation, though GI tolerance limits very long events.
- **Don't fear 'excess' protein at one meal.**
  Van Loon's 100 g study suggests a large protein meal isn't simply wasted; the body extends the anabolic response. Still, for practicality he favors distributing protein, and his team calls a single 100 g dose an unrealistic amount for most people.

298 The impact of emotional health on longevity, self-audit strategies, & improving well-being

Guest: Paul Conti
Date: 2024-04-15 · Duration: 2:33:57
URL: https://www.youtube.com/watch?v=obW0NDzEO88

KEYPOINTS

• Emotional health is the one part of healthspan that doesn't have to decline

Peter splits healthspan into cognitive, physical and emotional health. You can slow the decline of the first two, but you can't reverse it. Emotional health can actually improve with age. Conti says it usually declines, partly because society treats aging as a loss. Improving it takes intention: staying curious, learning, keeping an expansive mindset and caring for the body.

• There are no biomarkers for emotional health, so you assess it by looking inward

Strength or processing speed can be measured. Emotional health can't, so Conti uses questions instead. How do you feel when you wake up? Are you low-grade afraid or 'on the back foot'? What do you say to yourself when you're alone? What phrases repeat? Is there a 'shadow voice' that is ashamed, regretful or oppressive?

• Three drives: assertion, pleasure and the neglected generative drive

Psychiatry has long recognized an assertion (aggression) drive and a pleasure drive. Conti adds a generative drive, the urge to create, explore and grow beyond yourself. He says it, not war (contra Trotsky), is the 'locomotive of history'. When the three are in balance, gratitude and humility follow, along with physical and cognitive self-care.

• Achievement is not the measure of the generative drive

Two people running three companies can look identical from outside. One is engaged, has good relationships and wakes up feeling worthwhile. The other is driven by shame, fear or past deprivation, with a huge assertion drive, little pleasure and a weak generative drive. Conti says outside data without context is misleading.

• Neglected physical health is a strong sign of emotional trouble

Peter asks how well drinking, smoking, overeating or not exercising predict emotional problems. Conti says the predictive value is 'very, very high': it doesn't feel good to know you're unhealthy. The reasons people give ('no time', 'too stressed') 'aren't good reasons.' What matters is curiosity linking the two: noticing the sign is useless if it goes no further.

• Self-care runs on a continuum, and over-management is the hardest to spot

Peter describes three patterns. Some people neglect everything. Some, like Peter with emotional eating ('elbow deep in the Pringles'), are mostly fine with stress-driven lapses. Others over-optimize and 'eat, exercise, sleep like a robot.' Conti uses Freud's id/ego/superego model: when the managing superego takes over, people internalize a persecutor. Perfection is 'the enemy of everything that's not misery.'

• Harsh self-talk is common, invisible and harmful

Peter says a brutal 'Bobby Knight' inner voice ran for about 45 of his 47 years before he recognized it. Conti says such voices get a 'bye' because they feel normal and seem to drive achievement. He links critical self-talk to lost motivation and confidence. He also says it may raise inflammatory markers and illness risk, an association he states without citing specific data.

• Change is slow, then sudden, and repetition rewires both ways

Conti's analogy: say a random word 1,000 times and it's with you later today; say it 5,000 times and it's there tomorrow. Thought patterns work the same way, so undoing years of them takes sustained, brave work against the fear of losing your 'edge.'

• Slowing anger is necessary but not sufficient

Conti describes a cascade: affect (aroused without choice) becomes feeling (related to self), then emotion (related to others or the world: 'it's your fault... I'm cursed'). Pausing helps, but the lasting gain comes from understanding why you're angry. With balanced drives, gratitude and humility cool the reaction.

• Drop comparison framings, even 'be grateful' ones

Peter feels torn: he knows Dust Bowl life (The Worst Hard Time) was far harder, yet he still gets angry at a four-hour flight delay. Conti says to throw that framing out rather than adjust it. You can't know you wouldn't have been happier then, just as Conti's shepherd ancestors may have been. Comparing guarantees shame. He calls these mental constructs 'funhouse mirrors' and says simplicity is the rule of good mental health.

• Not knowing what comes after death can be a source of hope

Peter envies people who believe in an afterlife. Conti notes that older people near death mostly fear loss of control, not death. He says uncertainty about what comes next activates his generative drive rather than despair, and urges glorifying living well over merely not dying.

EXAMPLES

• The recording exercise

When Peter left PCs, his therapist Katie asked him to record, after every mistake, what he'd say to his best friend, and send it to her. The early recordings felt strained, 'like learning a new language.' It took about three months (roughly 100 days of work) to change. Later, when a glass bottle of Nivea aftershave shattered, his only thought was to avoid the glass, instead of 'a three-minute internal lashing.'

• The 40-minute urge gap

Therapist Andy White asks smokers to set a 40-minute alarm whenever they have an urge, then smoke when it rings, separating urge from behavior. Peter adapted it to anger: wait an hour before sending the nasty email or making the call. He says he manages this about half the time and calls his anger only about 50% improved: 'the 400-to-350-lb guy.'

• The silent commute

An underachieving client who loved music didn't listen to any on a long drive to an unnecessary, farther-away job. Through

questioning, Conti found the drive was time to berate himself uninterrupted. Once that stopped, the client's performance rose dramatically.

• Rich and poor, equally unhappy

For a period about seven or eight years earlier, Conti saw very high achievers for about a week at a time. He alternated that with a unit treating uninsured, often indigent patients with addiction problems. He 'could find no difference in overall happiness.' One man living behind a bush was happier than most of the wealthy patients.

OTHER RELEVANT

• Choosing a therapist: does 1 + 1 equal more than 2?

Rapport is necessary but not sufficient. The test is whether something new emerges between you, which Conti traces to Frankl and existential therapy. A clear 'no' can come in the first one to three sessions (for example, no eye contact). Otherwise allow five to seven sessions, because progress isn't linear. Look for a 'holding environment' where you can disclose shame without the therapist recoiling.

• Auditing an existing therapy

If years of weekly sessions leave you unchanged, ask what you're paying for. Is it sympathy while you vent, or help understanding yourself and changing? Therapy shouldn't always be comfortable. Conti has seen his own therapist for about 13 years and says it involves crying as well as fun. The therapist has an obligation to be working toward change.

• Approaches for four common types

Workaholic: ask what they're avoiding. Optimizer: ask what anxiety perfecting something already good enough is soothing. Anxious 'future-tripper': ask what the fear is about. Denier: Peter Grover's sign asks 'How's that working for you?' Lawrence Havens sat beside patients to look at the world together. With deniers, say once how it looks to you, plant a seed ('remember this when it starts feeling different'), then stop before you drive them away.

296 Foot health: preventing common injuries, enhancing strength and mobility, & picking footwear

Guest: Courtney Conley
Date: 2024-04-01 · Duration: 2:34:06
URL: https://www.youtube.com/watch?v=htF_GapzU_c

KEYPOINTS

• The foot is a sensory and mechanical foundation that rehab tends to ignore.

Conley is a chiropractor and foot and gait specialist who came to feet through years of ballet pain and early work in orthotic labs. The foot has 26 bones and 33 joints in three sections (rearfoot, midfoot, forefoot), plus dense receptors that feed the balance system. Quoting Jay Dicharry, she says 'you can't build a jet engine on a paper airplane.' Clinicians train core, glutes and hips but rarely the foot, our first contact with the ground. Attia compares the feet to a race car's tyres.

• The heel is built to absorb shock, while the forefoot carries the biggest loads.

The calcaneus has a spongy core inside a thin cortical shell. Its fat pad has two chambers and, she says, absorbs shock about twice as well as Sorbothane. The forefoot takes about 8 times body weight at push-off in walking. The Achilles takes about 4 times body weight in walking and roughly double that in running, and the inner arch up to 11 times in running. She says the tissues can handle it, but 'if you don't use it you will lose it.'

• Repeated mild ankle sprains are more harmful than they seem.

The talus has no muscle attachments, only ligaments. When the lateral ligaments loosen, the talus can shift and cause inner-ankle pain often misdiagnosed as posterior tibialis dysfunction. Ligaments heal; the bigger issue is stretched or torn superficial peroneal nerves and lost sensory input. One of her patients 'couldn't feel anything' by his last sprains.

• Where a stress fracture occurs tells you how to treat it.

Compression fractures (heel, fifth metatarsal) come from heavy, rigid landings and need cushioning. Tension fractures (navicular, metatarsals, sesamoids) come from failing to control pronation, so after a boot they need strength rehab. Otherwise the healed bone sits in a weaker foot. Bunions are a midfoot–forefoot instability worsened by narrow shoes (shortened adductor, lengthened abductor). She warns many foot surgeries fail and says 'you don't come out of the womb with a bunion.'

• Plantar fasciitis usually signals a weak foot.

The plantar fascia attaches into the deep transverse metatarsal ligament. When the forefoot splays it creates a 'windlass'-like stability signal before push-off, which narrow shoes block. Flexor digitorum brevis shares load with the fascia, and its weakness predicts plantar fasciitis. Orthotics help acutely but, she says, research supports about two weeks to a year, and they need an exit strategy. For chronic plantar fasciosis she relies on loading and strength rather than rest, including shockwave to the medial gastrocnemius. Tendons heal through mechanotransduction: load signals the cells to remodel.

• She uses specific strength and mobility benchmarks.

On a toe dynamometer the big toe should press about 10% of body weight and toes 2–5 about 7–8%, without lifting the heel or clawing. In a straight-body wall lean, your toes should let you lean at least 4.5 inches. A single-leg seated calf raise (soleus) should handle about 1.5 times body weight. Attia managed about 1.3 and says almost everyone fails. Ankle dorsiflexion needs about 10° to walk, but she wants about 35°. The big toe needs 40–45° to walk and 65° to sprint.

• Toe weakness is the single biggest predictor of falls in older adults, she says.

She cites Karen Mickle's research. Toe strength declines about 35% between 50 and 80. Foot receptors need 20% more pressure by 50 and are about 75% less sensitive by 85. Exercise improves circulation and nerve branching and has improved sensation even in neuropathy. Her fall checks: toe strength, dorsiflexion and inversion/eversion range, single-leg balance (abductor hallucis), and hip control (glute max at heel strike, glute med in mid-stance). She'd screen children's feet the way schools check for scoliosis.

• Limited ankle dorsiflexion causes problems up the chain.

The three compensations are early heel rise (more forefoot load), knee hyperextension, and bending forward at the hips (low back pain). If someone can deep-squat while holding a rack, the limit is neurological, not tissue, so they need stability rather than 30 years of calf stretching. Attia notes people under anaesthesia can be stretched far further than awake. Conley says no posture is 'bad' if you can control it and get out of it, and pronation is the first shock absorber.

• Footwear rules: wide toe box, zero drop, and be careful with cushioning.

Test the toe box by standing on the shoe's removed insert: if your forefoot spills over, the shoe is too narrow. A wide toe box differs from a wide shoe, and some brands simply add stretchy uppers. Any heel drop is 'a high heel' in her world. More stack height speeds you through pronation. In one study by Sarah Ridge, simply wearing minimal shoes strengthened most foot muscles about as well as an exercise programme. Super shoes (about a 4% advantage) must be 'earned' with hamstring and calf strength.

EXAMPLES

• Barefoot kids

In an Indian study of about 2,300 children aged 4–13, roughly 3% of those who didn't wear shoes had flat feet versus about 9% of shoe wearers, and closed-toe shoes were worse than sandals. The arch develops in early childhood (the sustentaculum tali ossifies by about age 7).

• Hallux limitus vs rigidus

Weak peroneus longus fails to anchor the first metatarsal, so the big toe jams and its top becomes inflamed. Many patients progress to rigid arthritis if the toe is splinted with carbon plates instead of trained.

• Isometrics as 'pain meds'

After Attia jammed his little toe, she had him do gentle isometrics immediately to reduce the brain's protective inhibition. He still uses five minutes of them when sore.

• Attia's Achilles

Heavy rucking brought months of Achilles pain. Switching to a shoe with an 8 mm drop helped. Conley approves if he keeps up ankle mobility and calf strength.

OTHER RELEVANT

- **Toe spacers**
  Start with 5 minutes barefoot at home. It took Conley about six months on her weaker foot to wear them all day. She avoided recommended bunion surgery this way.
- **Achilles reassurance**
  Achilles tendinopathy can last years but rupture is unlikely. Pain up to about 5/10 is still a green light to train. Insertional cases need end-range calf work and no deep heel drops.
- **Running**
  Overstriding is the enemy, more than heel striking. Moving to a midfoot strike shifts load from knee, hip and back to the foot and calf, so build capacity first.
- **Fashion shoes**
  Stilettos and hockey skates are fine if you 'do the work before and after' in minimal shoes.

295 Roadway death and injury: why everyone should care and what you can do to reduce risk

Guest: Mark Rosekind
Date: 2024-03-25 · Duration: 2:40:55
URL: https://www.youtube.com/watch?v=75LkR4p3Sj4

KEYPOINTS

- **Roadway deaths are a daily catastrophe: 42,915 Americans in 2021, about 118 a day.**
  Rosekind—a sleep and fatigue scientist who later served on the NTSB and as NHTSA administrator—insists on precise numbers because each is a person who can't be brought back. Globally, about 1.4 million people die on roads each year, roughly 3,700 a day. His own father died at 30, when Rosekind was three and a half; his badge and Purple Heart hang in a shadow box behind him.
- **Rates have fallen more than 90% in a century, but progress has stalled.**
  Deaths per 100 million vehicle miles were about 18.5 in 1923 and are now around 1.5, thanks to seat belts, airbags, crumple zones and better roads. But absolute numbers have barely budged in recent decades, and the decline stopped around the arrival of mobile phones 20–25 years ago.
- **Three behaviors drive a huge share: alcohol, speed and distraction.**
  Alcohol impairment has accounted for about 30% of deaths (some estimates over a third) for about 20 years—the percentage hasn't moved even as absolute numbers fell. Speeding contributes roughly 20–25%. Distraction is harder to measure but significant.
- **Five seconds on your phone at 55 mph covers a football field.**
  Phone use can degrade performance comparably to a 0.08 blood alcohol level. Rosekind suggests technology could prevent cars starting above a certain BAC—perhaps 0.05—saving perhaps 40–50 lives a day, if society accepted the inconvenience.
- **Teens and older drivers are most at risk.**
  Drivers aged 16–17 are inexperienced and less risk-aware; drivers 65–70+ face declining perception and reaction. Peter notes road injury is disproportionately a killer of the young, unlike heart disease, cancer and Alzheimer's.
- **About 94% of crashes involve human choice or error.**
  A 2015 NHTSA analysis found the last event before a crash was human-related 94% of the time; Rosekind calls it 'human choice or error'. He prefers 'crash' to 'accident', a term that spread in 1920s–30s workplaces implying inevitability. Human factors account for 70–80% of incidents in many fields, echoing the 'To Err Is Human' report on about 100,000 annual medical-error deaths.
- **Fatigue impairs like alcohol.**
  From sleep research, Rosekind cites roughly 50% reductions in decision-making, 30% in memory and big increases in lapses with sleep loss. People rate themselves 'fine' while objective measures show impairment. For an average man, 0.08 might be two to three beers.
- **Vehicle technology has saved tens of thousands of lives but spreads slowly.**
  Fourteen federal safety technologies (seat belts, airbags, electronic stability control) saved an estimated 613,501 lives over about 50 years. But with 280–300 million vehicles on U.S. roads, new technology takes 10–12 years to penetrate the fleet; a 1967 Corvette is still legal to drive.
- **A voluntary agreement made automatic emergency braking nearly universal years faster.**
  Because regulations take 10–12 years, Rosekind's NHTSA got 20 manufacturers—covering 95–99% of new vehicles—to commit to standard automatic emergency braking by 2022.
- **Crash investigation should learn from aviation and F1.**
  The NTSB runs a 24/7 operations center, and Rosekind warns against speculation in the first 24–48 hours—final reports rarely match early guesses. Peter notes after Ayrton Senna's death at Imola on May 1, 1994, Max Mosley's push for safety meant only one F1 death in 30 years; similar analysis isn't done for most of the 42,000 road deaths.
- **Pedestrians and cyclists are increasingly vulnerable.**
  About 7,500 pedestrians die per year; 64–67% of those deaths occur outside intersections. Rosekind advises walking on sidewalks or facing traffic, maximizing visibility and avoiding distraction.
- **Fault matters less than prevention.**
  Peter asks how many of the people who died were at fault; Rosekind says the data aren't categorized that way, but the point is that defensive choices save your life regardless of blame. Even if a share of pedestrian deaths involve the pedestrian's error, safer roads, slower speeds and alert drivers reduce the toll. He frames road safety as a public-health problem comparable to the diseases Peter usually discusses—just concentrated among the young.

EXAMPLES

- **Peter's near-miss on a bike**
  Around 2010–11, heading out for intervals on Palomar, Peter describes a driver on her phone drifting on a steep hill; on another ride on a 50 mph road he had to slam on his brakes when a car turned in front of him.
- **A crash not his fault**
  Peter recalls a serious crash where the other driver ran a red light while he drove the 50 mph limit—showing defensive habits matter even when you're right.
- **PTSD after crashes**
  Among survivors, 25–33% develop PTSD within 30 days or longer—a hidden cost beyond deaths.
- **Car seats**
  Rosekind cites estimates that roughly 60–70% of car seats are installed incorrectly; certified technicians can check them.

- **Mothers Against Drunk Driving**
  MADD in the late 1970s–80s changed social norms and pushed the 0.08 limit state by state.

OTHER RELEVANT

- **Never drive impaired—by alcohol, fatigue or your phone.**
  Put the phone away entirely; treat drowsiness like drinking. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Choose cars with modern safety features.**
  Automatic emergency braking and stability control save lives; older cars lack them.
- **Coach teen drivers intensively.**
  Their crash risk is highest; supervised practice and clear rules matter.
- **As a pedestrian or cyclist, be visible and assume drivers don't see you.**
  Most pedestrian deaths happen mid-block, often at night. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Drive at or below the limit, especially on fast roads.**
  Speed contributes to about a quarter of deaths and magnifies the consequences of every error; on 50 mph roads, turning cars and cyclists leave little margin.
- **Don't trust your own sense of impairment.**
  Whether from alcohol or sleep loss, people consistently rate themselves fine while objective performance drops. Plan alternatives—rideshares, naps, a designated driver—before you need them.

294 Peak athletic performance: How to measure it and how to train for it

Guest: Olav Aleksander Bu
Date: 2024-03-18 · Duration: 2:47:04
URL: https://www.youtube.com/watch?v=FOhb_D-5cgw

KEYPOINTS

• VO2 max is a powerful longevity metric because it integrates every system.

Olav Aleksander Bu is a Norwegian engineer turned exercise physiologist and coach. His athletes include triathletes Kristian Blummenfelt and Gustav Iden, who have won Olympic, World Championship and Ironman titles. He calls VO2 max 'the holy grail' for quantifying longevity. A great heart isn't enough: lungs, muscles, the nervous system and more must all work for you to reach a high VO2 max. Peter argues everyone, athlete or not, should know their number and how it ranks for their age and sex.

• Think of the body as an engine: oxygen in, power out, velocity as the final test.

Rather than getting lost in metabolic pathways, Olav often treats physiology as a black box. Oxygen consumption measures fuel burned, power meters measure work, and distance per time is the ultimate outcome. If an intervention improves these, keep doing it. Elite athletes convert energy more efficiently, roughly 20% into propulsion and 80% into heat, so the same distance costs them less oxygen. The further a metric sits from velocity (power, then ventilation), the noisier it becomes.

• How a lab VO2 max test works, and why portable analyzers now rival the lab.

On a treadmill or bike, a turbine or mixing chamber measures airflow while a sample line measures oxygen and CO2. Room air is about 20.9% oxygen, and about a quarter of the oxygen you inhale gets used. From the difference in concentrations and the volume of air breathed, the system calculates oxygen uptake. Olav's team works with the portable VO2 Master. In side-by-side testing on his athletes, who use about 6–7 L/min, it differs from lab equipment by only about 50 mL, which surprised Peter. Lab precision comes at the cost of less realistic conditions, such as cooling and how athletes move.

• Absolute versus relative numbers, and why 60-minute power beats short tests.

Relative VO2 or watts per kg predicts hilly racing, such as the Tour de France, where power at threshold per kg historically lined up the podium. On flat courses, absolute output matters more. Blummenfelt is about 175 cm and 80 kg, built for propulsion, not looks. Olav warns that estimating 'functional threshold power' from 8–10-minute tests is misleading, because much of that energy comes from glycolysis rather than aerobic metabolism. A true 60-minute effort can't be faked, and comparing 5-minute with 60-minute power reveals sprinter versus time-trialist profiles.

• At the elite level, energy supply becomes the limiter.

Olav's rule of thumb is about 20 joules per mL of oxygen. At 6 L/min, Peter calculates about 30 kcal per minute, or roughly 1,800 kcal per hour, far beyond what the gut can absorb. Peter cites the Weir equation as the fuller version. This is why specialization matters: Blummenfelt and Iden tested near 90 mL/kg/min for Olympic racing, but to set Ironman records the team deliberately let VO2 max fall below 80. That 'detuned the engine' toward sustainable multi-hour power, since athletes can't eat enough to train both.

• To raise VO2 max, accumulate as much work as possible near VO2 max.

Olav reframes VO2 max training around total oxygen consumed per session, or kilojoules of work at high output, rather than a fixed interval pattern. Peter's old routine was 6–10 efforts of 5 minutes on and 5 minutes off, accumulating 30–50 minutes. Olav suggests experimenting with interval lengths to pack in the most high-output work, using heart rate near maximum as a sign you're close to VO2 max. Peter has tried everything from 30 seconds on and off to 8 minutes on and off at a 1:1 work-to-rest ratio.

• Low-intensity training isn't junk if it's mindful.

Olav argues every session should be 'high quality.' Easy riding leaves the mental capacity to feel and refine position and movement, which hard efforts don't. Peter recalls training as a cyclist at a relaxed 200 W while hunting for the narrowest shoulder and knee position, and believes most of an approximately 5% gain came from reduced frontal area. Specialist cyclists and swimmers build this feel more than triathletes, who tend to solve problems by brute force, with swimming showing the biggest gap.

• Lactate markers: LT1, LT2 and maximal lactate steady state.

Peter defines his zone 2, about three hours a week, as the highest power at which lactate stays under 2 mmol, roughly an RPE of 6–7. On a step test, Olav describes a flat section, then a linear rise (LT1, near maximal fat oxidation), then a near-vertical climb (LT2, close to maximal lactate steady state, or MLSS). True MLSS requires 20–30-minute efforts with lactate sampled about every five minutes. Contrary to common belief, it doesn't correspond to an RER (respiratory exchange ratio) of 1 and occurs at lower RER in longer events. For Ironman athletes, LT1 sits near 80% of VO2 max. Their fat oxidation exceeds 1 g/min even on high-carb diets.

EXAMPLES

• Hold your breath, watch your heart rate.

Peter's experiment: ride at constant power and change your breathing. Slower breathing raises CO2, lowers pH and spikes heart rate with no change in power. Olav notes that even sipping from a bottle or swallowing creates a small oxygen debt that shows up in VO2 data.

• The swimming flume.

Olav's team tested swimmers in a full-cross-section water tunnel, roughly 3 m wide and 1.5 m deep, that works like a wind tunnel. It lets athletes swim naturally in place with no turbulence.

• Doping-era wattage.

Peter notes that in the EPO era, top Tour riders reportedly held markedly higher watts per kilogram for an hour than today's riders are believed to. Such data are now closely guarded, and comparisons are rough.

• Cadence and wasted power.

Higher cadence raises gross power (useful plus wasted) more than net propulsive power, which is why oxygen use climbs. At very low cadence, you eventually run out of muscle fibers to recruit.

OTHER RELEVANT

- **Get your VO2 max tested.**
  Lab testing is ideal, and good portable analyzers are now accurate enough for most people.
- **Joy beats perfection for longevity training.**
  Olav's advice for non-athletes is to make exercise enjoyable and sustainable. Riding at 1 mmol lactate that you'll keep doing for years beats 2 mmol you'll abandon.
- **Judge interventions by outcomes.**
  Track power, oxygen cost and speed over time, and keep what improves them.
- **Don't fight over terminology.**
  If a coach and athlete share a working language for training zones, Olav says that matters more than textbook definitions.

292 Rucking: benefits, gear, FAQs, and the journey from Special Forces to founding GORUCK

Guest: Jason McCarthy
Date: 2024-03-04 · Duration: 2:47:48
URL: https://www.youtube.com/watch?v=yaEwGqXE2Vo

KEYPOINTS

• 9/11 redirected McCarthy from a conventional career to Special Forces.
McCarthy graduated from Emory in May 2001; four months later 9/11 filled him with sadness, anger and rage. Visiting New York in October 2001, he could still smell it. After working in Florida feeling far from the fight, he enlisted in October 2003 on a Special Forces contract, even as soldiers were dying in Iraq.

• Earning a Green Beret took about two and a half years.
He earned his Green Beret in May 2006, joined 10th Special Forces Group and deployed to Iraq in 2007 during 'a really nasty time', leaving the Army in late 2008 at the end of his initial contract.

• Selection centers on rucking under brutal loads.
Training included rucking for 18+ hours with about 125 pounds after jumping into a North Carolina airstrip from around 800–1,000 feet. During selection candidates weigh their own rucks; the dumb put in 55 pounds, the smart about 47. Peter asks whether veterans now in their 40s and 50s could do it again; McCarthy, who was about 24 then, isn't sure.

• GORUCK began as a bag nobody wanted.
In the summer of 2010, between business-school years, he drove his Ford Expedition with his dog to all 48 contiguous states in about two months, pitching the GR1 rucksack (website price $295, roughly $100 in direct costs, $147.50 wholesale) to small men's stores with about 2,000 in inventory. Nobody walked into a store wanting to ruck in 2010; the tour was painful.

• Events made the product: the GORUCK Challenge.
Obstacle races like Tough Mudder drew 10,000 people a weekend in 2010. McCarthy launched a team event priced at $147.50—later you kept the ruck—lasting 10–12 hours, often overnight from 10 p.m. Friday. GORUCK has since run about 10,000 events, peaking at 1,000–1,200 a year before the pandemic; the 2010–11 Afghanistan surge put Special Forces culture in the media.

• Standard event weight: 30 pounds for 150+ lb participants, 20 for lighter.
He eventually told participants to bring their own bricks. Teams must carry casualties and shared loads—if a teammate drops, 'his 30 plus their 30' is the team's problem, building cohesion.

• Rucking is an accessible on-ramp for non-athletes.
McCarthy's advice: don't wait to buy gear—grab any backpack, put in 10–20 pounds, and walk. People capable of 10,000 steps can add weight. Start with 20–30 pounds for a couple of miles; 30–45 if fit. Military basic training used about 45 pounds—less than 25% of a 200 lb soldier.

• Footwear is the most common failure point.
Nearly all experienced ruckers would name footwear: when it goes wrong it's excruciating. Peter, with hypermobile feet, had many foot problems with his 50–60 pound daily ruck. Most people at 20–30 pounds will see little beyond shin splints if unprepared or Achilles irritation.

• Heavy rucking blends cardio and strength, and changes character with load.
Peter's favorite hard workout is an 80–100 pound ruck; shuffling a mile with 100 pounds took him about 9:30, while a competitive runner did 6:30. Heart rate swings from zone 1 to zone 4 rather than staying steady. At 100 pounds it shifts toward pure strength; 60 pounds feels completely different.

• Commemorative ultra-rucks connect fitness with history.
GORUCK runs events marking WWII anniversaries, like a 75 km (about 50 mile) ruck from Utah Beach for the 75th D-Day anniversary, and 80 km and marathon events. McCarthy recalls walking through a German cemetery seeing graves of 16–18-year-olds.

• Rucksacks versus weight vests: posture and breathing differ.
Peter used a weight vest to train for hunting trips; McCarthy explains that vests are vital for soldiers and police who must fight in them ('train like you fight'), but for general training a well-fitted rucksack is better. A vest compresses the chest and belly, and as fatigue builds people hunch to create room to breathe. McCarthy cites Kelly Starrett's idea that you have to own your breath to own a position; a ruck sitting high on the shoulders lets you stand tall and breathe. He credits a debate involving Andrew Huberman with prompting deeper analysis with writer Michael Easter.

• Simplicity is part of the appeal.
McCarthy likes that rucking removes the pressure of bench and deadlift numbers—just put weight on and walk, alone or with others. Military food during training was MREs packing a couple thousand calories; 'hunger is the best sauce', and some of his best meals were MREs.

EXAMPLES

• Peter's training for an 80 km event
To finish 80 km in under 20 hours with only 25 pounds, Peter trains with 50–60 pounds almost all the time, aiming to ruck a marathon in 10 hours.

• Pride before the fall
Peter admits going into an event too proud, thinking he'd rucked for years—only for 20 pounds plus water to become 25+ and the distance humbling him.

• Stuff sacks over plates
Peter's daily 20–30 pound load often uses a stuff sack instead of a plate so a dumbbell isn't jabbing him on long walks;

heavier plates are more likely to be confiscated at airports.

- **Spare rucks at home**
  Peter and his wife have three packs to rotate, so guests can join walks.

OTHER RELEVANT

- **Start with what you have.**
  Any backpack and 10–20 pounds is enough to begin; add weight gradually.
- **Invest in footwear and foot care first.**
  Blisters and foot problems end more rucks than fitness does. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Use rucking for zone 2 and strength.**
  Light loads build aerobic base; heavy loads become strength-endurance sessions. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Train heavier than your event weight.**
  If an event requires 25 pounds, training with 50–60 makes race day easier.

291 Role of testosterone in men & women, performance-enhancing drugs, sustainable fat loss, & more

Guest: Derek (More Plates More Dates)
Date: 2024-02-26 · Duration: 2:48:56
URL: https://www.youtube.com/watch?v=-wkQA_oxOwA

KEYPOINTS

• Testosterone therapy for women is often dosed far too high.
Derek, the fitness and hormone commentator behind More Plates More Dates, and Peter discuss practitioners promoting cookie-cutter targets of 200–300 ng/dL total testosterone for women—levels in the male range. One woman, through a compounding error, took 10 times her dose for a month, effectively a male physiologic dose. Peter has never seen a woman in her 30s naturally in that range.

• Restore a woman's own physiology, not a population number.
Premenopausal women typically run perhaps 10–20+ ng/dL (units confuse the issue—some labs report picograms). Peter might target 80–100 ng/dL, roughly 70th–80th percentile, but notes that for a woman who naturally lived lower, even 80 may be supraphysiologic—nobody measured her at 30.

• DHEA can raise testosterone in women on oral contraceptives.
Women's androgens derive substantially from adrenal production; Derek cites papers where DHEA supplementation (25–50 mg daily) roughly quadrupled total testosterone (about 15 to 60 ng/dL) in women on the pill, which suppresses ovarian output. Even castrated men can make 30–40 ng/dL from their adrenals.

• Progesterone dosing should be individualized.
Many women can't tolerate a full 200 mg progesterone dose but feel great at 50–100 mg; the goal is finding each woman's dose while protecting the uterus from unopposed estrogen.

• Assay choice changes your numbers dramatically.
On the same blood, an immunoassay read testosterone 502 while LC-MS/MS read 381; estradiol was 41.3 by immunoassay versus 18.3 by LC-MS—more than double. Look for 'LC-MS/MS' on the report. Timing matters too: measuring three days after a TRT injection misses the peak and trough.

• For low-normal testosterone, address basics before TRT.
For a symptomatic man around 300–381 ng/dL, sleep, body fat, vitamin D and other factors can move levels 100+ ng/dL. Clomiphene and hCG can raise endogenous production—hCG might take 381 to around 1,200—and Derek expects much more clomiphene use, though bodybuilders' post-cycle regimens of 100 mg/day are absurdly high.

• FDA's Category 2 peptide list restricted compounding of popular peptides.
About 30 peptides, including BPC-157 and CJC-1295, were placed on a list the FDA said lacked sufficient safety data for compounding. Derek thinks some never should have been sold but is sad about others; he wants real trials, such as 8–12 weeks of BPC-157 in post-operative orthopedic patients.

• Myostatin inhibition is promising but expensive and modest.
A company claims follistatin gene therapy at about $25,000 per shot. In aged mice, near-complete myostatin knockdown (over 99% of mRNA) increased muscle mass about 25%. Phase 2 sarcopenia trials could matter if people over 60 gain 5–10 pounds of muscle.

• Bodybuilding prep shows how far careful dieting can go—and its hormonal cost.
Derek recommends starting with about a 300-calorie deficit and 'milking' it, with a split like 40% protein, 40% carbs, 20% fat. A natural sub-200 lb competitor may be below 2,000 calories on stage; a 260 lb pro might eat 2,500–2,600. Crash dieting from 2,800 to near nothing backfires.

• Extended fasting crushes hormones.
Peter describes how 7–10 days of water fasting dropped his testosterone from 500–600 to 100–200 ng/dL, TSH from 2 to 4–6, free T3 from about 3 to 1.5, and reverse T3 from 12 to 32.

• Supraphysiologic testosterone builds muscle even without training.
In Bhasin's classic studies, 600 mg/week (about 6x physiologic) produced the most lean mass with training—but the untrained testosterone group gained more lean mass than the training placebo group.

• Androgens like DHT shape development, so exposure timing matters.
Derek notes DHT is best known for hair loss but is central to how masculine a person becomes during development, with critical windows of exposure. Even adult women exposing themselves to androgens can push their physiology in a masculine direction—one reason supraphysiologic dosing in women can cause irreversible changes such as voice deepening.

EXAMPLES

• High-protein 'ice cream'
Derek describes a homemade blend of about 25 g whey plus 25 g casein that yields roughly 60 g of protein for about 300 calories and takes 10–20 minutes to eat.

• Cutting calories painlessly
Peter notes that dropping cooking oils and a few habits could easily remove 500–600 calories; unless you're Bryan Johnson, you probably don't want 25% of calories from oil.

• Injected carnitine
People inject L-carnitine because oral bioavailability is only about 10–15%; Derek questions whether supraphysiologic doses help those with adequate dietary intake.

• Overpriced supplements
They mock a $600 genetic test when whole-genome sequencing costs about $300, and a supplement costing $4 to make

sold at $130.

- **Wild game as lean protein**

  Peter argues hunting is practical advice: one cow elk—tags for females are often over the counter—can feed a family for more than a year, and wild game may be among the healthiest meats since the animals live unstressed. He believes rifle hunting is more humane than bow hunting because a good shot within 300–400 yards kills instantly, and it doesn't take long to become a good shot.

OTHER RELEVANT

- **Ask for LC-MS/MS hormone testing.**

  Immunoassays can overstate estradiol and testosterone, leading to bad decisions. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Women: be wary of male-range testosterone targets.**

  Aim for restoring your own physiology with a clinician who titrates carefully. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Diet with modest deficits.**

  Start around 300 calories below maintenance with high protein; aggressive cuts damage hormones and muscle.

- **Fix sleep, body fat and vitamin D before TRT.**

  These can raise testosterone meaningfully for borderline-low men. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Treat expensive 'optimization' tech skeptically.**

  From $140,000 red-light beds to pricey genetic interpretation, they suggest asking what evidence exists before paying—basics like protein, training and sleep deliver most of the benefit.

290 Liquid biopsies for early cancer detection, the role of epigenetics in aging, and the more

Guest: Dr. Alex Aravanis
Date: 2024-02-19 · Duration: 2:21:31
URL: https://www.youtube.com/watch?v=9RaQyvI-Rgg

KEYPOINTS

• Genome sequencing costs have fallen faster than Moore's Law.

Alex Aravanis, Peter's medical school classmate, is an electrical engineer turned MD-PhD. He later became Illumina's chief technology officer and co-founded GRAIL. Sequencing one more genome right after the Human Genome Project would have cost a few hundred million dollars. By about 2012 it was in the low tens of thousands, and today it's a couple hundred dollars. The leap came from sequencing-by-synthesis chemistry developed by Cambridge chemist Shankar Balasubramanian and brought to Illumina through its acquisition of Solexa. Billions of DNA fragments are attached to a glass slide and read one base at a time, all in parallel.

• Tumors constantly shed DNA into the blood, which makes liquid biopsies possible.

Cell-free DNA was first seen in blood in the 1940s, and in the 1970s researchers noticed cancer patients had much more of it. Tumors grow chaotically, so their cells die at high rates and release DNA. Fragments are about 160 base pairs long because DNA wound twice around a nucleosome is protected from enzymes. Alex describes three uses: choosing targeted therapy without risky biopsies (lung biopsies can cause a collapsed lung), monitoring for residual disease after treatment, and screening people with no known cancer.

• Prenatal tests accidentally proved blood DNA could reveal hidden cancers.

Dennis Lo, and Stanford's Steve Quake, developed blood tests that detect fetal trisomies from placental DNA. Alex says these cut amniocentesis by about 80% in the US. At Verinata, an Illumina company, Meredith Halks-Miller and Daria Chudova noticed rare results with chaotic abnormalities across many chromosomes, which isn't compatible with a viable fetus. The mothers turned out to have undiagnosed invasive cancers. All of the roughly 10 women flagged, described in a 2015 JAMA paper, had cancer. That was no false positives, though most cancers in that population were surely missed.

• The key challenge for cancer screening is specificity, not sensitivity.

Alex notes that in 50 years nobody had built a broad blood test for cancer, and PSA's high false-positive rate cost it its USPSTF A or B grade. Proteins and metabolites rise in benign conditions too, giving false-positive rates of 5–10%. Population screening needs about 1% or less. GRAIL's CCGA study took nearly three years and hundreds of millions of dollars, using about 15,000 samples split into blinded training and test sets. It compared mutations, chromosomal changes, cell-free RNA and DNA methylation.

• Methylation, the 'dark horse,' won decisively.

Methylation adds a methyl group to cytosines at about 28 million CpG sites and controls which genes a cell uses. Alex calls it 'the software of the genome.' It's read by chemically converting unmethylated cytosines (bisulfite sequencing). Methylation detected the most cancers, reached a false-positive rate under 1%, and uniquely predicted tissue of origin. Adding other signals didn't help, because they weren't independent. His analogy: once you spot Ford's blue oval, also looking for 'F-150' adds nothing. Two tubes (about 10 mL) of blood suffice, since background biology, not blood volume, limits screening sensitivity.

• In PATHFINDER, about 40% of positive Galleri results turned out to be cancer.

In this interventional study of about 6,500 people at average or slightly elevated risk, with cancer prevalence just under 1%, about 40% of 'cancer signal detected' results were confirmed as cancer. By comparison, about 4–5% of abnormal mammograms lead to a cancer diagnosis. Specificity was above 99%, and the test caught about half of the cancers that emerged. Added to guideline screening, it roughly doubled the number of cancers found, mostly types with no existing screen. Alex notes that about 70% of cancer deaths come from unscreened cancers. The test predicts a top-two site of origin about 90% of the time, using a methylation atlas of healthy cell types built with Yuval Dor in Jerusalem.

• It's a functional test: it preferentially finds the dangerous cancers.

Sensitivity varies widely by type. Peter's review found roughly 20% detection of early-stage hormone-positive breast cancer versus about 75% for triple-negative. To shed detectable DNA, a tumor needs enough mass, cell turnover and blood access, traits linked to aggressiveness. In CCGA survival curves, people whose cancers the test missed did very well, while detected cancers carried substantial mortality. Low sensitivity for indolent prostate or hormone-positive breast cancer may therefore partly avoid overdiagnosis.

• Does earlier detection save lives? The two make their case, and NHS data are coming.

Peter states his bias that it does, noting that breast and colorectal cancers treated with the same adjuvant therapy fare far better when localized. Alex cites five-year survival of 70–80% for localized solid tumors versus under 20% for stage 4, and asks what surgeon would decline to treat a stage 1 pancreatic cancer found this way. The NHS is testing Galleri in about 140,000 people, using a reduction in stage 4 diagnoses as an earlier endpoint than mortality. Peter adds that single-cancer trials are rarely powered to show changes in all-cause mortality.

EXAMPLES

• 'Kiss-and-run' synapses.

In Richard Tsien's lab, Alex's PhD work helped explain how neuron terminals with only about 30 vesicles fire hundreds of times in seconds: vesicles briefly fuse, release transmitter and reseal.

• The airport metal detector.

Peter's analogy for the tradeoff. Turning sensitivity up stops everyone with a metal zipper. A 40% positive predictive value is excellent when the detector usually beeps thousands of times without catching anyone. GRAIL's algorithm has a similar dial.

• The insulin promoter.

Only pancreatic beta cells leave the insulin gene's promoter unmethylated. Every other cell type methylates it heavily, the kind of signal that lets the test infer tissue of origin.

- **Partial reprogramming.**
  Yamanaka factors can revert cells to stem cells but risk tumors. Juan Carlos Izpisua Belmonte's mouse work stopping partway reported improvements in eyesight and cognition. Alex hopes direct epigenetic editing could give more control.

OTHER RELEVANT

- **Discuss false positives before testing.**
  Peter tells patients up front that a positive may be false and will require follow-up imaging. Some reasonably decline.
- **Methylation may be the 'hallmark of hallmarks' of aging.**
  Smoking, exercise and obesity leave distinct patterns. The open question is whether restoring youthful patterns would restore youthful function.
- **Aged immune cells carry methylation signatures.**
  Exhausted T cells show distinct, largely shared changes that could become rejuvenation targets.
- **Disclosures.**
  Alex owns Illumina shares and now runs an epigenetics company in which Peter is an investor and adviser.

288 The impact of gratitude, serving others, embracing mortality, and living intentionally

Guest: Walter Green
Date: 2024-02-05 · Duration: 1:39:38
URL: https://www.youtube.com/watch?v=5yQ-p-mypFk

KEYPOINTS

• Walter Green sees his life as three 29-year stages

Walter is about to turn 85. He describes the first 28–29 years as finding himself, the next 29 as making himself, and the last 29 as giving back. He says he has spent the last 30 years in mentoring and philanthropy rather than business.

• A childhood of loss taught him that life can be short and that relationships matter

His father put about $4,000 of savings into an Adirondacks dude ranch, and a flood that wiped out the bridge bankrupted the family. They moved into a two-bedroom flat in the Bronx with grandparents who didn't speak English, and Walter lived in 16 different cities growing up. His mother got breast cancer when he was nine. His father died of a heart attack at 53, two months after Walter left for the University of Michigan, and an uncle also died at 53. He later calls this deprivation an advantage.

• A breakdown at 22 was born of empathy, and he kept it secret for 40 years

Two months into selling rags in Pittsburgh, he was praised and told the older man training him would be let go once Walter learned the job. He couldn't get out of bed and was hospitalized for two to three months, followed by two years of therapy. He didn't talk about it for 40 years because of the stigma around mental hospitals. He says he was terrified of failing, failed, and survived.

• The fear of dying at 53 shaped how fast he lived

He became president of an executive conference-centre company at 32, with 400 employees. Over the next 25 years he became its major shareholder, growing it to 10 centres running about 6,000 conferences a year for 150,000 executives. He never had a long-term view of his life because he assumed he would die at 53 like his father. So he became 'really good at deciding what I don't do'.

• Thinking in reverse: define success before you start

In his 30s, a course with Fred Jervis at the Center for Constructive Change taught him to start every important interaction, including personal ones, by asking: 'If this is really successful, what will have happened by the end?' He applies it to meetings, health targets and his life plan. For over 40 years he has written out an ideal next few years; the horizon has shrunk from five years to one. Saying no gets easier because anything that doesn't serve the outcome is easy to drop.

• His tributes began at his 50th birthday

He invited his five closest friends, their spouses and his family, 17 people, to New York for the opening weekend of Phantom of the Opera. At the reception he paid tribute to each friend in front of everyone, explaining specifically how each had enriched his life. He says a tribute in front of a group is far more powerful than a private one.

• At 70 he spent 11 months thanking 44 people in person

Tim Russert's death in his early 50s, and the crowds at the funeral he never got to see, combined with turning 70 to prompt a gratitude journey. Walter visited 44 people in Kenya, Mexico, Canada and across the US, combining trips where he could. He insists that most listeners have at least one such person, and that one is enough to start.

• Each meeting followed the same four 'bases'

First, how they met. Second, the experiences they shared. Third, the main one: reading from a prepared legal pad exactly why that person mattered, with specifics rather than a general 'I love you'. Fourth, asking each person for one piece of a 'mosaic' of who Walter is. He recorded every conversation. Because appreciation is hard to take in during the moment, he later mailed each person a framed photo, a 120-word letter and a CD of the conversation.

• Deep friendship rests on authenticity, empathy and compassion

Asked why he is the first or second person his peers turn to with a problem, Walter credits authenticity, empathy and compassion, which he believes everyone has but not everyone uses. He has spent about 800 sessions, roughly 4,000 hours, in groups of 10–12 company presidents, some lasting 37 years. Not all 44 people were close friends: one was a blind man in New Hampshire who taught him how to think.

• We save our best words for funerals, and the dying want to hear them first

Walter cites a hospice nurse who said that for months before death her patients' central belief was that they don't matter to anyone, and that her own ideal death would include hearing that she mattered. Peter points out how absurd it is to let people die believing that, then praise them at their funerals. Walter blames custom and a lack of models.

EXAMPLES

• Say It Now went global

After the book, a Hay House editorial director heard his story and a contract followed three days later. That led to the Say It Now movement. Its teaching materials are now in about 38,000 classrooms in 75 countries, mostly grades 5–12, and a kindergarten teacher in Ontario has used them too. His goal was a million expressions of gratitude by his 85th birthday, and they passed 1.4 million.

• Finishing strong after a recent medical scare

He reverse-planned the end of his life with key results and says he achieved them within a year. He moved his wife into a lifestyle community she could settle into, wound down complex investments, and left a 15-step financial checklist. He also says he is 'current' with every relationship and mentee, many of whom attended his TEDx talk.

• Bargaining in Corsica

In his 60s, while on a cruise, he needed emergency surgery at a clinic in Corsica that he says saved his life. He promised to be of service if given more time.

- **A ritual for peace**
  In his office, Walter has portraits of the 44 people from his journey next to photos of his mentees. He plays a favourite violin concerto and goes through them one by one, about 60 lives, remembering what each gave him.

OTHER RELEVANT

- **Start expressing gratitude now**
  Walter's point: if you wait until your 60s or 80s, it's really tough. Pick one person, write down specifically what they gave you, and tell them while they can hear it.
- **Use the reverse question before important conversations**
  Before a meeting, a visit or even a hard talk with a friend, define what would make the time well spent, such as 'I want to help lighten his load'. Then let that shape what you say yes and no to.
- **Make tributes specific and, where possible, public**
  General affection fades. Specific stories of impact, said in front of others or written down so the person can reread them, land more deeply.
- **Put your affairs in order as an act of care**
  Writing a clear financial checklist and planning your spouse's living situation spares loved ones chaos. Walter has kept his estate in order for 35 years.

287 Lower back pain: causes, treatment, and prevention of lower back injuries and pain

Guest: Stuart McGill
Date: 2024-01-29 · Duration: 2:45:19
URL: https://www.youtube.com/watch?v=Z1_sb1auiV8

KEYPOINTS

• McGill says Attia's history fits a classic disc pattern.

Attia had disabling episodes every three years (at 21, 24 and 27), each triggered by bending (rowing, a steep climb, bending to lock a bike) and lasting about two weeks. The last became burning foot pain and required surgery for a roughly 5 cm free fragment from L5–S1. McGill, a professor emeritus at Waterloo, identified a posterior, left-biased open-fissure disc bulge that could be 'vacuumed' back in between episodes. He predicts Attia's facet joints at that level have since thickened, causing the occasional grumbling ache of the 'unstable phase' that Kirkaldy-Willis described.

• The spine is a flexible rod that must stiffen to carry load.

Discs allow motion and act as a mechanical stop at end range, which keeps the torso slender. Discs are layered collagen around a pressurized gel. Repeated load plus motion delaminates the layers from the inside out until the last layer gives way. The gel has never been exposed to the immune system, which sets off a fierce inflammatory reaction. Healthy discs have no nerves or blood vessels because high pressure prevents ingrowth; damage lets both grow in, so 'the body grows more hardware to feel pain.'

• L4–L5 and L5–S1 fail most because thicker structures tolerate bending poorly.

Strain, not force, drives damage. Like a thick stick versus a willow branch, the thick lower discs bear compression well but bending badly. Bigger skeletons have more lobed discs that concentrate stress when twisted, which is why world-record sit-up holders aren't powerlifters. Gymnasts' open facet joints allow twisting but make them prone to pars stress fractures (spondylolysis).

• Don't combine powerlifting and yoga adaptations.

Deadlifters stiffen their discs and tend to bulge posteriorly when flexing under load. Very flexible yoga spines bulge anteriorly when bending backward. Each should train hip and shoulder mobility for its own goal, and yogis should avoid very heavy loads. According to McGill, surgeons mostly replace the hips of 50-year-old women with 30 years of yoga and men around 50 who've deadlifted all their lives, not moderates.

• 'Chronic' back pain is usually repeated acute irritation, and 'non-specific' pain doesn't exist.

Most of his 'chronic' patients are re-triggering a specific mechanism throughout the day. Stop the trigger and the pain stops. He reserves 'chronic' for pain with changed central sensitivity and no clear mechanical trigger. He spends three hours per assessment provoking the pain to find its mechanism. No insurance billing code covers this, which he sees as the system's core failure.

• The McGill Big Three build stiffness in the core so the hips and shoulders can deliver power.

They are the modified curl-up (hands under the low back, head and shoulders hovering), the side plank and the bird dog. All spare the spine; the side plank loads only half the musculature. They're done as 10-second holds in a 'Russian descending pyramid.' One session increases torso stiffness for about 20 minutes or longer, so pain patients do short sessions mid-morning and mid-afternoon. Isometric training increased punch force in MMA athletes. But they aren't for everyone: already stiff people need mobility instead.

• Most people told they need surgery can avoid it with 'virtual surgery.'

At his university clinic every patient was followed for two years. Of those told they needed surgery, 95% reported avoiding it and being glad. The plan copies post-surgical rest and gradual return (day one: up only to use the bathroom), then desensitizes the pain mechanism and retrains mobility, stability and movement. He even manages sciatica this way if he can move the pain during assessment, including in NHL, pro tennis and UFC athletes.

• Surgery is warranted in specific cases.

These include red flags, which he says referrals have still let through: aortic aneurysm, pulmonary embolism, metastatic cancer. Also pain patterns that don't fit a spinal mechanism, severe multilevel stenosis needing laminectomy, cervical myelopathy, post-trauma instability, unstable spondylolisthesis compressing nerves that can't be controlled, and some Tarlov cysts. Even with spondylolisthesis he tries intensive stabilization first, and says slippage distance isn't the deciding factor.

• Aim for 'sufficient' strength rather than maximal deadlifts.

Ed Coan took months off after a true personal best. Max lifts cause microfractures under the end plates that take about a week to scaffold, so deadlifting heavy three times a week lets them accumulate. McGill steers older lifters toward goals like getting off the floor with grandchildren at 80. He uses backward uphill walking, sled work and log lifting. He values grip strength over deadlift numbers.

EXAMPLES

• The toilet squat

On stage in Europe, a tearful woman in her 70s was told she'd have to leave her home because she couldn't rise safely from the toilet. He taught her hands on thighs, hip hinge, feet apart and 'pull your hips through.' Within three repetitions she stood easily: 'I don't have to leave my home, do I?' 'Weightlifting 101,' he says.

• The suicidal patient

A man told his pain was 'in his head' gave McGill two weeks. Muscle EMG and motion tracking showed he switched off all his muscles at the top of a twist, which made the spine shift and trap the sciatic nerve. Coaching him to keep muscle tension through the movement stopped the episodes; he had none in 10 years.

• Whiplash on video fluoroscopy

Patients dismissed as pain magnifiers showed a mid-range vertebral 'clunk' matching their pain. Activating the deep neck

flexors (tongue to the roof of the mouth, grimace) stopped the clunk. A static MRI couldn't show it.

• Two gymnasts, same spondylolysis

One rested six months and stabilized; one kept training. McGill says he can predict nearly perfectly who makes the Olympic team.

OTHER RELEVANT

• Let inflammation work

He cites recent studies suggesting skipping anti-inflammatories lets macrophages clear extruded disc material. Lying face-down and breathing can help pull a bulge back in. Attia uses a mild muscle relaxant like baclofen instead of prednisone.

• Clues in daily life

Sharp pain when rolling over in bed, or needing many pillows, suggests micro-instability. A mobile, weak spine can hurt more than a strong, arthritic one; Attia's ugly MRI with big, healthy muscles is the contrast.

• Self-assessment

McGill's book Back Mechanic guides readers through pain triggers and simple tests (slouch, extension, compression, shear, nerve tension). Backfitpro.com lists certified and master clinicians.

• Desk life

He retired early partly because his job had become sitting. A 30-year-old who'd sat 'like a cashew' since 14 showed pain when slumping.

286 Journal club with Andrew Huberman: light exposure on mental health & an immunotherapy for cancer

Guest: Andrew Huberman
Date: 2024-01-22 · Duration: 2:56:43
URL: https://www.youtube.com/watch?v=eU7VneEQayM

KEYPOINTS

• Outdoor light is far brighter than indoor light, and the body clock adds up photons over time

Huberman notes that midday sun is usually over 100,000 lux and can reach 300,000. Even a bright department store is closer to 4,000–6,000 lux. A cloudy day can still be far brighter than indoors even when it doesn't look it. Because the brain's master clock sums photons over time, an overcast 8,000-lux UK winter walk still counts, as long as you aren't wearing sunglasses that filter much of the light.

• Low-angle sunlight at sunrise and sunset is the key circadian signal

Specialized retinal cells compare short-wavelength (blue) with long-wavelength (orange/red) light. That contrast is richest when the sun is low. Huberman suggests about 10 minutes of sunlight in the eyes early in the day and at least 10 in the late afternoon, more on overcast days, and as much safe daytime light as you can get. Looking toward a low sun carries little cataract risk (blink as needed). Sunglasses are fine at midday, but he advises against wearing them for morning light.

• The study: about 86,000 UK Biobank adults wore wrist light sensors

Participants, mostly in their 50s and 60s, wore wrist sensors measuring light from 470 to 650 nm. Researchers split them into quartiles of daytime and nighttime light exposure and compared these with psychiatric diagnoses. Models adjusted step by step for age, sex, ethnicity, photoperiod, employment, physical activity, sleep and more. The two hypotheses: more daytime light means lower psychiatric risk, and more nighttime light means higher risk. Both held up.

• More nighttime light tracked with depression and self-harm

Compared with the lowest quartile, depression odds rose about 20% in the third quartile of nighttime light and about 25% in the fourth. Self-harm was flat across the first three quartiles, then jumped about 30% in the top 25%. PTSD (with nighttime light) and psychosis (inversely, with daytime light) also stood out. Generalized anxiety and bipolar disorder were weaker and noisier.

• How to read an odds ratio

An odds ratio compares the odds of an outcome in two groups: subtract 1 for the percent change, so 1.78 means 78% higher and 2.0 means 100% higher. If the 95% confidence interval doesn't cross 1.0, the result is significant without needing the P value. Peter also checks whether a study is sensibly powered, and stresses clinical relevance, not just statistical significance.

• Reverse causality is the big caveat

Depressed people may stay up late on screens and avoid going outside, so behaviour could drive light exposure rather than the other way round. Peter's example is diet soda: it correlates with obesity probably because people gaining weight switch to it. Huberman, while admitting bias, guesses 65–75% of the effect comes directly from light. Peter, using the Bradford Hill criteria (including the dose-response across quartiles and strong mechanisms), would say about 80/20.

• Cancer evades the immune system even though most solid tumours are visible to it

Lung, breast, prostate, colorectal and pancreatic cancers cause more than half of US cancer deaths. Peter says at least 80% of solid tumours present antigens that the immune system can recognize, yet they survive by hijacking the brakes on T cells. Checkpoint inhibitors remove brakes such as CTLA-4 and PD-1, rather than pressing the accelerator. The scientists who discovered these brakes won the Nobel Prize, which Peter recalls as 2018.

• The ipilimumab phase III trial in metastatic melanoma

Fewer than 700 patients with advanced melanoma who had failed standard therapy and had perhaps 6–12 months to live were randomized 3:1:1. The groups were anti-CTLA-4 plus a gp100 peptide vaccine, anti-CTLA-4 alone, or gp100 alone as the control. More than 70% had metastases in their organs and more than 10% in the brain. Median survival was about 10.0 and 10.1 months on the drug versus 6.4 months on gp100 alone. Peter focuses on the right-hand tail of the survival curve, where a minority of treated patients survived for years.

• Taking the brakes off brings autoimmune side effects

Almost everyone reported some adverse event (about 97–98% in all arms), but immune-related events were about 60% on the drug versus about 30% on the control. Grade 3–4 immune events were 10–15% versus 3%. The gut is hit most often, with colitis serious enough to need IV fluids, and skin effects such as vitiligo also occur. These events are often reversed with corticosteroids, sometimes after stopping the drug.

• Why melanoma responds, and why Peter calls immunotherapy the best hope

Most cancers carry roughly 40–50 mutations. Melanoma and kidney cancer carry hundreds, which gives T cells more targets ('shots on goal'). Peter argues that overall survival for metastatic solid tumours has barely moved since the 1970s apart from immunotherapy. He imagines a future of banking young T cells around age 30 to expand later, since T cells taken from inside tumours tend to be too exhausted to multiply a thousandfold.

EXAMPLES

• A friend with Lynch syndrome and pancreatic cancer

The friend had stage 3 colon cancer around 40. About five years later, around 2013–14, he developed inoperable pancreatic cancer with an expected survival of about six months. His mismatch-repair defect meant his tumour carried many mutations, so he joined a checkpoint-inhibitor trial. He had a complete regression and is cancer-free 10 years later, though his immune system destroyed his pancreas and he now injects insulin.

• Oncology's low bar

Peter criticizes drugs that extend median survival by weeks and cost $50,000–100,000 per treatment. He cites a pancreatic cancer drug that added about nine days for about $40,000, which helps explain public distrust of pharmaceutical companies.

• Indoor light at night adds up

A phone or tablet can deliver hundreds of lux close to the eyes, while candlelight is roughly 50–200 lux. Huberman's advice is to dim and lower light sources at night, and he cautions against draping fabric over lamps because of the fire risk.

- **Sunscreen, clarified**

  Peter says he is not anti-sunscreen. He avoids certain chemical sunscreens that may disrupt hormones, but nobody disputes physical-barrier sunscreens, and avoiding sunburn matters for preventing melanoma.

OTHER RELEVANT

- **Front-load daylight and protect darkness**

  Go outside early and again in the late afternoon (longer when it's cloudy), skip sunglasses for morning light, and keep nighttime light dim and low.

- **Read the dose-response, not just the headline**

  When judging an observational study, look for a gradient across quartiles, a plausible mechanism and consistency with earlier work. The researchers' earlier 400,000-person UK Biobank study linked time outdoors to better mood and sleep.

- **Use trackers briefly for insight**

  Both hosts think sleep and light trackers mostly teach you something within about 30–90 days. After that, the habits matter more than the data.

284 Overcoming addictive behaviors, elevating wellbeing, & thriving in an era of excess

Guest: Michael Easter
Date: 2024-01-08 · Duration: 2:06:11
URL: https://www.youtube.com/watch?v=gN2mySEkXbg

KEYPOINTS

• Scarcity Brain began with pandemic hoarding.

Journalist Michael Easter, author of The Comfort Crisis, finished that book in March 2020 and watched people hoard canned food, toilet paper and sanitizer. Over the following months, drinking, drug use, shopping and weight gain all rose. That led him to ask how a brain built for scarcity copes with a world of abundance in food, stuff and information, the subject of his book Scarcity Brain.

• Obesity reflects an evolutionary mismatch with a cheap, hyper-palatable default food environment.

Overeating once gave a survival edge, since stored energy carried you through the next lean stretch. Now food is abundant enough that the US throws out about a third of what it produces. Michael says Americans spend about 8% of income on food, versus over 40% in the past, and Mexican women once spent about five hours a day grinding corn for tortillas. Peter's 'default food environment' is palatable, calorie-dense, non-perishable and cheap. He doesn't see it as nefarious, but 'healthy' was never one of the design criteria. About 40-plus percent of Americans are obese.

• The Tsimane eat 'every fad diet's forbidden foods' but almost no ultra-processed food, and have remarkably healthy hearts.

Michael traveled to Bolivia after reading a 2018 paper on this Amazonian forager-horticulturalist group. From La Paz it took a 12-hour drive and a six-hour boat trip up an Amazon tributary. The Tsimane eat white rice, plantains, sweet potatoes, corn, fish, small wild chickens and tapir, with few vegetables. Everything is a single ingredient, usually unsalted and fire-baked. CT heart scans brought out by researchers showed hearts that looked about 30 years younger. People who avoid accidents (snakebites are a real risk) often live into their 70s. The nearby Mosetén, who buy processed food and fry with oil, appear to have more heart disease.

• Kevin Hall's ultra-processed food study: about 500 extra calories a day.

Kevin Hall at the NIH, an empiricist skeptical that processing mattered beyond calories, ran a metabolic-ward study. Volunteers ate as much as they wanted for two weeks each of ultra-processed and minimally processed diets matched for nutrients such as carbs and salt. On ultra-processed food they ate about 500 more calories a day and gained weight. On minimally processed food they spontaneously lost weight. One explanation is eating speed. A food-industry contact told Michael snacks need 'three Vs': value, variety (many intense flavors) and velocity (fast to eat). He says snacking barely existed as a habit before about 1970.

• Michael's one-ingredient diet experiment made him lose weight without trying.

For a month at home he ate only single-ingredient foods, combined as he liked: oatmeal and eggs, air-fried plantains and fish, sweet potatoes, green beans, elk he had hunted, and fruit for snacks. Whole aisles at Costco were off-limits. He dropped weight so quickly from about 180 lb that he had to force-feed 'mountains' of plantains to stay near 175, eating 50–70% carbs. Social meals forced compromises. He suggests it as an experiment to find foods that fill you up, then eat that way 80–90% of the time. Michael says about 60–70% of the American diet is ultra-processed.

• The 'scarcity loop' is three parts: opportunity, unpredictable rewards and quick repeatability.

Common casino myths (no clocks, songs only in the key of C, no right angles, pumped-in oxygen) didn't hold up. Michael found the real explanation at a Las Vegas research casino funded by 73 gambling and tech companies. Slot machines offer a chance at something of value, unpredictable payouts from nothing to $20,000, and instant replay: players average 16 games a minute, faster than we blink. Modern machines return about 85 cents per dollar, with frequent small wins. The same loop drives social media likes, dating apps, Robinhood's fee-free trades and spin-the-wheel discount ads, which he says raised conversion sevenfold.

• Addiction isn't purely a moral failing or purely a brain disease.

Michael describes the 'moral failing' and 'brain disease' models. A counterexample: about 20–25% of US soldiers in Vietnam regularly used heroin. Under Nixon's Operation Golden Flow they had to pass a urine test to go home, and nearly all did. Back home, about 95% stayed clean, and those who relapsed tended to have used drugs before the war. Michael also reports from Baghdad, where war trauma, few other outlets and a flood of the stimulant captagon from Syria fueled a new drug epidemic, much as factory closures preceded the US opioid crisis. Drinking at 15 or younger carries a coin-flip chance of alcoholism, versus about 10% when starting at 21 or older.

• Happiness comes from enjoyment, satisfaction and purpose, which often require struggle.

Peter favors Arthur Brooks's 'macronutrients' of happiness: enjoyment, which is deeper and more shared than pleasure; satisfaction, which is fleeting and highest after struggle; and purpose. Michael spent a week at a Benedictine monastery in New Mexico. The monks rise around 3 a.m., eat little, keep silence, are celibate and do about four hours of labor daily ('pray and work'). Researcher Alex Bishop has found them happier than average Americans. Michael's takeaways: hard-won rewards satisfy more, and serving something beyond yourself matters. Peter admits the routine would drive him mad.

EXAMPLES

• Stuff.

A couple of centuries ago a person owned about three outfits. Today the average is about 104, and people regularly wear only about 10% of them. Homes hold an estimated 10,000–40,000 items. Michael's four reasons we buy: tools, status ('no one buys a Rolex to tell time'), belonging and boredom, which one-click shopping and eerily accurate Instagram ads exploit.

• Boredom as a signal.

Boredom evolved to say your current activity's return has worn thin. Hunters would switch to fishing or gathering. Now we reach for a phone. Both men practice going out without their phones, and Peter calls rucking a 'no-phone zone.'

- **The penny press.**
  Michael traces negativity-driven media to an early newspaper publisher who sold papers at a loss for one cent, made money on ads, and grew readership by covering murder and mayhem.
- **Peter's own wiring.**
  Slot machines and getting drunk hold no appeal for him, but food is a lifelong struggle. Neither man sees these differences as moral. Michael, who is sober, thinks early exposure during vulnerable years sets the pattern.

OTHER RELEVANT

- **Change your environment to subtract a habit.**
  Peter's rule: when quitting something, reshape what's in your pantry and around you, rather than relying on willpower.
- **Favor foods that are ingredients rather than foods that have ingredients.**
  They're slower to eat and harder to overeat. Nobody eats 1,000 calories of broccoli.
- **Add friction to the loop.**
  Michael's rule that the faster a behavior can be repeated, the more likely it is to be repeated suggests the reverse: slowing it down weakens the cycle.
- **Seek voluntary hardship and purpose.**
  Uncomfortable challenges and service beyond yourself counter the pull of easy, endless rewards.

283 Gut health & the microbiome: improving and maintaining the microbiome, probiotics, & more

Guest: Colleen Cutcliffe, PhD
Date: 2023-12-18 · Duration: 2:48:48
URL: https://www.youtube.com/watch?v=th3UwC10EZU

KEYPOINTS

• The microbiome is seeded at birth, peaks early in life and loses diversity with age.

Colleen Cutcliffe is a biochemist who worked in pharma and DNA sequencing before co-founding the microbiome company Pendulum. She defines the microbiome as all the bacteria, viruses, fungi and yeasts living in and on us. The womb is nearly sterile. Initial seeding comes largely from passage through the birth canal, then breast milk, food and environment expand diversity. Diversity peaks around the years 'when you could eat whatever you wanted,' then declines with age. She considers the '10-to-1' ratio of microbes to human cells questionable. Their importance lies in what they produce, not their numbers.

• There aren't really 'good' and 'bad' bugs. Context decides.

Bacteria are independent organisms that can divide every 10–15 minutes, so they evolve fast. That speed drives antibiotic resistance, but it also lets your gut community adapt to what you feed it. After a week of eating abroad your microbiome can look very different. Many healthy people carry Clostridioides difficile at low levels without harm. Peter compares this to calling cholesterol 'good' or 'bad.' The Human Microbiome Project, a one-time snapshot of more than 10,000 people, showed people differ hugely at the strain level, with more overlap in function.

• Butyrate from fermented fiber is one of the most important things gut microbes make.

In the oxygen-free distal colon, bacteria ferment fiber we can't digest into short-chain fatty acids, ultimately butyrate. Colon cells are the only cells that use butyrate as their main fuel, and low butyrate is associated with poor colon health, including colon cancer. Butyrate also triggers receptors on gut L cells that release GLP-1. Colleen says recommendations are roughly 20–30 g of fiber a day, far above what most Americans eat. Peter notes his daily green drink supplies vitamins and polyphenols but not meaningful fiber.

• C. diff shows the power of restoring a gut ecosystem.

Antibiotics act like 'a nuclear bomb' on the microbiome. If a resistant C. diff strain survives, it multiplies unchecked and can become fatal. More antibiotics cure it only about 70% of the time, by Colleen's figure. Fecal microbiota transplant (FMT) re-establishes competition and succeeds about 99% of the time. Colonoscopic delivery works better than capsules, likely because freeze-drying loses diversity. She says the FDA once tried to halt FMT but reversed course after an outcry from patients and doctors. The risks: unknown pathogens, and donors' metabolic traits may transfer, including case reports of new obesity after transplant.

• FMT is a 'messy drug.' The goal is to isolate the strains that matter.

Transplants from lean to obese mice, or human microbiomes into mice, reliably shift body weight, and FMT has been tried in type 2 diabetes. But a single donor's stool changes with travel, diet and antibiotics, so dosing can't be standardized. Pendulum's premise was to identify specific beneficial strains and manufacture them reproducibly. Akkermansia is a strict anaerobe that a single oxygen exposure can kill. Contract manufacturers kept sending back dead batches, so the company built its own roughly $10 million plant.

• Many probiotics barely deliver live organisms.

Most products contain Lactobacillus and Bifidobacterium, which tolerate some oxygen and are easy to grow. Manufacturing involves growing cultures in large vats, centrifuging, then freeze-drying, which kills a large share: for hardy common strains Colleen estimates about 50–80% survive, and early on her company sometimes lost 90%. Cheap capsules may dissolve in stomach acid, while enteric-coated or time-release capsules reach the gut. She argues CFU counts can overstate live, active cells, so Pendulum reports 'active fraction units' (AFU) counted by flow cytometry. Its products should stay refrigerated.

• Akkermansia drives GLP-1 release in three ways.

Akkermansia muciniphila, linked to bariatric surgery work by Lee Kaplan at MGH, has a surface protein (Amuc_1100) that signals L cells via TLR2. It secretes a protein called P9 that stimulates L cells, and it makes propionate, which Clostridium butyricum and related strains convert to butyrate, activating receptors that trigger GLP-1. It also maintains the gut's protective mucus layer. Unlike injected semaglutide, this would produce meal-timed, physiological GLP-1 pulses, so Peter and Colleen agree it wouldn't produce drug-level weight loss.

• The company's 76-person pilot trial found modest glucose benefits, with clear caveats.

Colleen describes a double-blind, placebo-controlled pilot in people with type 2 diabetes, with three arms. Over 90 days, a five-strain formula including Akkermansia lowered A1C by about 0.6 points versus placebo and reduced glucose spikes on an oral glucose tolerance test by 34%. A subset without Akkermansia didn't reach statistical significance. Diet wasn't logged. After a 30-day washout, about 15–20% kept Akkermansia levels. Colleen is the company's CEO. The product costs about $165 a month, a lower-dose version $49. Further data are mostly customer reports, an unblinded cravings pilot, and about a dozen investigator-led trials using donated product.

EXAMPLES

• The hyena researcher.

An antibiotic hunter convinced of hyenas' antibiotic-rich mouths refused antibiotics after being bitten, signed waivers, and reportedly never got infected.

• Diet soda swaps.

Peter has seen some patients' weight and metabolism improve after replacing six daily Diet Cokes with soda water, while his wife thrives on one every other day. Colleen calls evidence on sweeteners and the microbiome conflicting and proposes crossover trials.

• Akkermansia predicting diet response.

In a study of a high-fiber diet that Colleen cites, people starting with more Akkermansia improved more in BMI, waist-to-hip

ratio, A1C and weight. The finding is correlational.

- **Estrogen recycling.**
  Some gut microbes remove the tag marking estrogen for excretion, potentially raising circulating levels. Colleen calls microbiome-menopause research very early.

OTHER RELEVANT

- **Eat much more fiber.**
  Vegetables, fruits and well-delivered fiber supplements feed butyrate-producing strains.
- **Treat antibiotics as a major disruption.**
  Use them when needed, but recognize they can wipe out the gut ecosystem.
- **Scrutinize probiotic claims.**
  Look for human trial data, live-cell delivery and appropriate capsules. Very few supplements are tested.
- **Weigh the source.**
  Much of the product discussion comes from the company's own founder and its small pilot study. Larger independent trials are still pending.

281 Longevity drugs, aging biomarkers, and updated findings from the Interventions Testing Program

Guest: Richard Miller
Date: 2023-12-04 · Duration: 2:31:20
URL: https://www.youtube.com/watch?v=sZ-krUa6VH0

KEYPOINTS

• The ITP is a small, rigorous program for testing longevity drugs in mice.

Miller, who directs aging research at the University of Michigan, describes the NIA-funded Interventions Testing Program. It runs at three sites: Michigan, UT San Antonio (Randy Strong) and the Jackson Laboratory. Each gets about $1 million a year in direct costs, roughly $4.5 million in total. Anyone can nominate a compound; there were 28 nominations in a record year, and about six are chosen annually. About 100 drugs have been tested in 20 years. Miller says the budget is not too small.

• Genetically diverse mice are essential; the standard inbred B6 mouse misleads.

About 97% of aged-mouse requests are for one inbred strain, C57BL/6. Every B6 mouse is identical and inbred, many are deaf by a year old, and drug effects often don't carry over to other strains. Miller compares it to testing a cancer drug on identical triplets. The ITP uses UM-HET3 mice, which share four grandparent strains, so the population is reproducible but every animal is different. About 12,000 DNA samples from mice with known lifespans have also allowed lifespan genes to be mapped.

• Study design is pre-specified and statistically conservative.

The primary endpoint is overall death risk, roughly equivalent to median lifespan. For maximum lifespan they use the Wang–Allison test: what share of the mice still alive at the pooled 90th percentile were treated? Each year has 300 male and 300 female controls and 150 of each sex per drug. That gives 80% power to detect about a 12% effect even if one site failed. Michigan males consistently live 5–10% longer than at other sites, for unknown reasons, so results are analysed site by site and then pooled. Drug levels in food and tissue are confirmed first. Rapamycin needed encapsulation because stomach acid destroyed about 90% of it.

• Four drugs give more than a 10% lifespan gain, compared with about 3% for curing cancer.

Work by Jay Olshansky and Bruce Carnes (1990) estimated that eliminating cancer or heart attacks after 50 would raise human median lifespan less than 3%. The ITP's winners are rapamycin, acarbose, 17; ÖW7G adiol and canagliflozin. Rapamycin plus acarbose gave a 29% increase in males, the largest yet and the first gain from a combination. Rapamycin consistently benefits females more, possibly because their blood levels are about three times higher. Canagliflozin works only in males, and in aging females blood levels reach about 10 times those of young males, likely toxic.

• Starting late still works.

Rapamycin started at 20 months (roughly a 55–60-year-old human) extended lifespan as much as starting young, in both sexes. 17; ÖW7G adiol and canagliflozin work in middle-aged males. Acarbose works about half as well when started late. Mice given acarbose or 17; ÖW7G adiol in middle age also had better grip strength and rotarod performance. Rapamycin, originally nominated by Dave Sharp based on mTOR genetics in worms and flies, also boosted vaccine responses in old mice.

• 17; ÖW7G& F–öÂ —2 Ö ÆRÖöæÀy puzzle.

It's a stereoisomer that barely binds classic estrogen receptors. The original idea was to give males estrogen's benefits without feminization. But males ended up outliving females, and females gain nothing. Treated males produced over 20-fold more estriol, but only if not castrated. In unpublished data, 16-hydroxyestriol seems to work in males at least as well, but it's the first drug found to shorten female lifespan.

• 'Aging rate indicators' act like a speedometer rather than an odometer.

Miller doesn't think we have good biomarkers of biological age. Instead, his lab found 13 traits that shift the same way in 10 slow-aging mouse models (four mutants, calorie restriction, four drugs and a PTEN overexpressor), even in young adults. Examples include more UCP1 in all three fat depots, fewer inflammatory M1 and more M2 macrophages in fat, higher BDNF and doublecortin in the brain, more of the muscle protein FNDC5 and blood irisin, and higher GPLD1 (an exercise-linked factor tied to cognition). For the male-only drugs, these changes appear only in males. Ames dwarf mice given growth hormone for just six weeks as babies lost both their long life and these traits permanently.

• RNA levels predict protein changes poorly.

Gary Churchill's Jackson Lab work found only about 30% of age-related protein changes matched mRNA changes. GPLD1 is regulated by cap-independent translation, not transcription. Selective protein breakdown (chaperone-mediated autophagy) also shapes the proteome. Miller says transcript-only studies are 'not only incomplete but mostly wrong.'

• Notable failures: resveratrol, metformin, nicotinamide riboside and fisetin.

The NIA director required them to test resveratrol, and it failed at doses David Sinclair recommended. Miller says the positive study used mice on a 60% coconut-oil diet, and experts' suggested doses spanned a million-fold range. Metformin failed, and others confirmed it. NR failed alone but will be tried in combination, and Miller keeps an open mind about NAD. Fisetin, suggested by Jim Kirkland and Paul Robbins, didn't extend life and didn't reduce p16, p21 or ;"Öv Â Ö kers in blinded tissue analyses.

EXAMPLES

• Over-the-counter winners

In a paper under review, the seasickness drug meclizine (found by screening for mTOR inhibitors) and astaxanthin (what makes farmed salmon pink) each extended male lifespan by about 10%. Neither changed maximum lifespan. They're the first ITP winners you can buy without a prescription; higher doses are being tested.

• Captopril

The blood-pressure drug gave a small lifespan gain, which surprised Miller since mice don't die of hypertension. It's being retested at a higher dose.

• Senescence skepticism

In the original ;"Öv Â 6¶–â 7GVG•, the highest score was about 1 positive cell in 10,000, in a woman in her 90s. Miller argues 'senescent cell' lumps distinct cell types together, like asking whether you 'believe in stress.'

• Euthanasia method

Rapid CO2 makes mice unconscious in 5 seconds. The newer gradual method takes about 7 minutes, doubles glucose and floods the body with adrenaline, which would distort measurements.

OTHER RELEVANT

• Sex differences in drug metabolism

Liver drug-metabolizing enzymes differ greatly by sex in mice and humans, yet human dosing rarely accounts for it. Attia calls this a missed opportunity.

• Bridging to humans

Miller is testing aging rate indicators in muscle and fat biopsies from people in their 70s in a UCSF study, and searching for blood metabolites that mirror tissue levels.

• Cognition next

A new Michigan neuroscientist will test whether lifespan drugs also preserve memory.

• Tissue sharing

Frozen tissues from 22-month-old mice have gone to outside labs, though NIA is moving to slower, once-a-year allocation. Philanthropists could fund additional ITP work through the universities.

280 Cultivating happiness, emotional self-management, and more | Arthur Brooks Ph.D.

Guest: Arthur Brooks, PhD
Date: 2023-11-27 · Duration: 2:06:04
URL: https://www.youtube.com/watch?v=X1GNc70-584

KEYPOINTS

• Feelings are evidence of happiness, not happiness itself.

Harvard professor Arthur Brooks, discussing his book Build the Life You Want, says happy feelings relate to happiness the way the smell of turkey relates to Thanksgiving dinner. Emotions are limbic-system signals carrying information. If you mistake them for happiness, last night's sleep or a morning argument end up running your life. Happiness and unhappiness aren't opposite ends of one scale and can coexist. The average person spends about 40% of their time with predominantly positive feelings and about 16–17% with predominantly negative ones, which evolution makes louder because they kept us alive.

• Six basic emotions: four negative, two positive.

Fear and anger run through the amygdala. Arthur says the stress response to a car about to hit you takes about 74 milliseconds, and only seconds later does your prefrontal cortex ask whether flipping off the driver fit your values. Disgust, centered in the insular cortex, protects against pathogens, and demagogues exploit it by making opponents seem like cockroaches. Sadness, the mental pain of separation, registers in the dorsal anterior cingulate cortex, the same region that handles the 'I hate this' part of physical pain. Grief is unremediated sadness. The two widely agreed positive emotions are joy, often after struggle, and interest.

• Know your emotional profile, and look for complementarity in partners.

Using the PANAS positive/negative affect scales, people fall roughly into quarters. 'Cheerleaders' run high positive and low negative. 'Mad scientists' run high on both (Arthur is about 95th percentile positive and 90th negative). 'Poets' run low positive and high negative. 'Judges' run low on both and are unflappable. Twin studies suggest about 44–52% of baseline well-being is heritable, which Arthur sees as useful knowledge to manage, not destiny. In relationships, he urges a baseline of compatibility plus complementarity: introvert with extrovert, mad scientist with judge. Two mad scientists can 'be an accelerant to each other.'

• Happiness has three 'macronutrients': enjoyment, satisfaction and meaning.

Enjoyment is pleasure plus people plus memory. Arthur warns that pleasure-seeking alone, supercharged by technology into fentanyl, slot machines or pornography, makes us miserable: 'if something gives you pleasure and you're doing it alone, you're usually doing it wrong.' Peter connects this to alcohol data, where any benefit seems tied to Mediterranean-style drinking with food and company, not the molecule. Arthur says people who eat candy one to three times a month live about a year longer than total abstainers, while eating it daily is another matter. His wife smokes twice a year with her sister. He, a former smoker, won't touch it.

• Satisfaction fades fast by design: satisfaction equals haves divided by wants.

Satisfaction is joy after struggle, which is why cheating on an exam brings none. Evolution hides how short it lasts: for admission to Harvard Business School, studies show a few weeks. The joy of a bonus peaks when you hear about it, not when it hits your paycheck, and moving to California brings 'a few months' of happiness while 'the taxes are forever.' This hedonic treadmill drives a 'more' strategy. Arthur's alternative is to want less. He cites the Buddhist view that dukkha means dissatisfaction caused by attachment, and the Dalai Lama's line about wanting what you have.

• Meaning has three parts, tested by two questions.

Arthur calls meaning the 'protein' of happiness, the macronutrient you can't do without. It combines coherence (things happen for a reason), purpose (a heading, like a navigator's rhumb line) and significance (it would matter if you were gone). His diagnostic questions are 'Why are you alive?' and 'For what would you be willing to die today?' Failing them begins the search. His son, a Marine scout sniper, answers 'God made me to serve' and 'faith, family, fellow Marines, country.' Peter, who leans agnostic, finds peace with mortality by accepting his insignificance. Arthur cites research on awe and 'getting small.'

• Metacognition moves emotions from the limbic system to your 'CEO.'

Dogs and toddlers are limbic. 'Use your words' teaches kids to process emotions in the prefrontal cortex, which is also why chosen discomfort like Peter's 42°F cold plunge 'hurts so good.' Arthur's tools: write down the five things bothering you to turn diffuse anxiety into bounded problems; ration news to 15–30 minutes a day rather than avoiding it; and keep a failure and disappointment journal. In it, he writes each setback, adds after 30 days what he learned, and after six months something good that came from it. 'There's no good or bad emotions, there's only information.'

• US happiness has declined for 50 years, with periodic 'storms.'

Using General Social Survey data back to the 1970s, and dismissing cross-country rankings because cultures define happiness differently, Arthur describes a slow decline punctuated by sharp drops, including around 2008. Historically about twice as many Americans said they were 'very happy' as 'not happy.' That has now flipped for the first time. His message: treat your happiness like a CEO running a startup, deciding by what's right rather than what feels good. Happiness is a direction, not a destination.

EXAMPLES

• The reverse bucket list.

Every birthday Arthur lists his worldly attachments and crosses them out. Last year he crossed out about half his political opinions, inspired by Thich Nhat Hanh's teaching that opinions are a great source of misery: 'I need fewer opinions because I need more friends.'

• Sculpture, not painting.

By your mid-40s a striver's canvas is full. Arthur suggests seeing your life as a sculpture you chip away at rather than a painting you keep adding to.

• Optimism versus hope.

Optimism predicts things will be OK. Hope says something can be done and I can do it. Hope, not optimism, is tied to

happiness, and its opposite is despair.

- **Dragging the gas pump.**
  Lost in thought, Arthur drove off with the hose still in his tank, an illustration of William James's 'I self' (observing the world) versus 'me self' (being observed). Social media pushes us toward the latter.

OTHER RELEVANT

- **Share pleasures to turn them into enjoyment.**
  Pair indulgences with people and memories, and keep them occasional.
- **Run a twice-yearly happiness review.**
  Arthur scores his enjoyment, satisfaction and meaning in a weighted spreadsheet, avoiding days of unusual highs or lows.
- **Expect a 'second adolescence' around 50.**
  The Hindu stage of vanaprastha ('retiring to the forest') suggests shifting toward transcendent priorities in midlife.
- **Faith and science can coexist for some.**
  Arthur, a religious scientist, sees no conflict. Peter suspects believers may find death easier to process.

278 Breast cancer: how to catch, treat, and survive breast cancer | Harold Burstein, M.D., Ph.D.

Guest: Harold Burstein
Date: 2023-11-06 · Duration: 2:17:14
URL: https://www.youtube.com/watch?v=IdKIF28C1xg

KEYPOINTS

• Breast cancer is common, but most women are now cured

Harold Burstein, a Dana-Farber breast oncologist, gives a US lifetime risk of about 1 in 8 (12–13%). There are roughly 250,000–300,000 invasive cases a year (he first says about 275,000), plus another 50,000–60,000 cases of DCIS, and about 38,000 deaths. Assuming a steady state, about 80–85% of women are cured, while 15–18% remain at risk of recurrence and death. Outcomes depend on both stage and subtype.

• Three subtypes drive treatment

Estrogen-receptor-positive, HER2-negative tumours make up 70–75% or more. They are the type most often found on mammograms, peak around age 65 and, size for size, usually have the best prognosis. Triple-negative cancers (ER, PR and HER2 negative) are about 10–15%, skew younger and are more aggressive. HER2-positive tumours were once very aggressive but now have some of the best treatment results.

• Most risk factors move individual risk only a little

Early first period, late menopause, hormone therapy, fewer pregnancies and less breastfeeding all extend estrogen exposure and may raise risk 25–30%. Burstein says that only moves an individual from about 12% to about 15%. Postmenopausal women with denser breast tissue are at slightly higher risk, and not just because density hides tumours. He calls obesity a relatively weak risk factor, and smoking is not a major one.

• DCIS is a precancer, like a colon polyp

Ductal carcinoma in situ is cells building up inside a duct without invading the surrounding tissue. Seventy years ago it showed up as a lump, but today it is found on mammograms. In about 15–20% of excisions, a small invasive cancer turns up, so the diagnosis is upgraded. In the NSABP B-17 trial, about 25–30% of women treated with lumpectomy alone had a recurrence or new breast cancer within 10 years, and radiation cut that roughly in half. B-24 added tamoxifen. Burstein thinks the baseline risk for today's mammogram-detected DCIS is much lower.

• Radiation after DCIS is a trade-off in risk

For healthy women up to about 65–70, radiation after lumpectomy is standard. It lowers the risk in that breast to something like 1–2% with three to four weeks of treatment. Recurrence risk without radiation ranges from about 5–10% for low-risk lesions to 20–25% for higher-risk ones. Ongoing trials ask which low-risk women can safely skip it.

• LCIS signals higher risk rather than being a precursor that must be removed

Lobular carcinoma in situ and atypical hyperplasia raise the risk of future cancer by roughly 0.5–1% a year and warrant monitoring. In the NSABP P1 prevention trial, which enrolled many women with LCIS, tamoxifen cut breast cancer diagnoses from about 13 to 5–6 per 1,000 women per year. However, it did not improve survival, partly because it prevents the most treatable tumours.

• Stage, nodes and biology together predict cure

Burstein's ballpark 10-year cancer-free survival figures are about 90% or more for stage 1, 75–80% for stage 2 and 65–75% for stage 3. Peter cites 90–95% for tumours of 2 cm or smaller without lymph-node involvement. Risk rises steadily with size, with each additional lymph node, and with tumour grade, Ki-67 and receptor status.

• Genomic tests now spare many women chemotherapy

In 1999 the NCI said essentially every woman with a 1 cm cancer needed chemotherapy. Today, ER-positive tumours are scored with tests such as the Oncotype DX recurrence score or MammaPrint, which show that most low-scoring patients gain little from chemotherapy. Anti-estrogen therapy is advised for nearly all ER-positive patients, longer for high-risk cases, and oral CDK4/6 inhibitors are now added for very high-risk tumours.

• Screening plus better drugs each account for about half the mortality decline

Breast cancer mortality has fallen by about half over 30–40 years. Burstein credits roughly half of that to early detection and half to effective drug therapy, notably trastuzumab (Herceptin) for HER2-positive disease, with data emerging in 2005. Neoadjuvant therapy, meaning drugs before surgery, is increasingly used for larger tumours, and the tumour's response guides prognosis and later treatment.

• Hereditary mutations explain only about 8–10% of cases

BRCA1 and BRCA2 account for about half of hereditary cases, and PALB2, CHEK2 (also linked to colon cancer) and ATM for most of the rest. Clinical panels now test up to about 100 genes. Burstein doesn't rely on consumer tests like 23andMe for clinical decisions. Carriers may consider preventive mastectomy, ovary removal once childbearing is done (there is no good ovarian screening), or intensive screening: an annual MRI and an annual mammogram, staggered six months apart.

EXAMPLES

• Peter's case for aggressive screening

The same chemotherapy can cure early disease after surgery yet rarely cures metastatic disease. So Peter argues that finding cancers earlier, which shifts more of them to stage 1, must cure more women, despite overdiagnosis and lead-time bias. Burstein agrees. He notes that most screening trials ended in the late 1980s, before modern drugs, which partly reduces the advantage of early detection, though smaller tumours still need fewer or less toxic drugs.

• Hormone therapy after breast cancer

Burstein generally avoids systemic hormone replacement for survivors. Instead he uses non-hormonal treatments for osteoporosis and hot flashes (including a recently approved drug) and is fairly liberal with vaginal estrogen, which is absorbed very little into the body. A few women can't function without hormones, and that becomes an individual conversation with them.

• Male breast cancer

There is about 1 male case for every 200 female cases. Nearly all are ER-positive; triple-negative disease is very rare and HER2-positive uncommon, and treatment principles are the same. BRCA mutations in a family also raise men's prostate cancer risk.

• Where to get treated

Burstein says excellent breast cancer care is available at many centres. He thinks variation in care is greatest outside the top institutions, and that multidisciplinary teams combining surgery, radiation and medical oncology are the real test.

OTHER RELEVANT

• Get any lump checked

A palpable lump calls for an evaluation: a diagnostic mammogram, ultrasound and, if needed, a needle biopsy. Ultrasound and MRI supplement mammograms for high-risk or dense breasts but don't replace them.

• Know your family history and test for a reason

A strong history of breast or ovarian cancer warrants clinical genetic testing and counselling for relatives. A positive result changes screening and prevention options.

• Ask about genomic scores before agreeing to chemotherapy

For ER-positive, HER2-negative cancers, a recurrence-score test can show whether chemotherapy adds meaningful benefit.

277 Food allergies: causes, prevention, and treatment with immunotherapy | Kari Nadeau, M.D., Ph.D

Guest: Kari Nadeau
Date: 2023-10-30 · Duration: 1:46:13
URL: https://www.youtube.com/watch?v=ZxXppnbzFOo

KEYPOINTS

• Food allergy is driven by IgE, a tiny but potent antibody class.
Nadeau, an allergist-immunologist and immunotherapy pioneer, explains that IgE represents about 0.005% of the immunoglobulins in blood—the least concentrated class—yet triggers mast cells and basophils to release histamine and other mediators, causing hives, swelling, vomiting and potentially fatal anaphylaxis. For every IgE molecule, the body can make about 100 IgG molecules, which become important in tolerance.

• Food allergies are common and becoming more persistent.
Her colleague Ruchi Gupta's data show about 1 in 12 U.S. children have a food allergy, and roughly 1 in 30 adults—whether persisting from childhood or newly developed. Nadeau trained when children under five with milk or egg allergies had an 80% chance of outgrowing them; now it's closer to 50%. Peanut, tree nut, shellfish and fish allergies usually persist (about 80%).

• It's largely environmental, not genetic.
Nadeau says roughly 70–80% of food allergy risk isn't genetic. A key insight is the 'dual allergen exposure' idea: allergens encountered through inflamed skin (eczema) tend to sensitize, while those eaten early tend to build tolerance.

• Old avoidance guidelines likely made things worse.
Twenty years ago, well-meaning guidelines—based on as few as about 20 individuals—told pregnant women and families to avoid peanuts and tree nuts and delay introduction. Later, much larger studies showed it's fine to eat peanuts and tree nuts during pregnancy and that early introduction lowers risk.

• Introduce allergenic foods early, alongside breastfeeding.
WHO recommends breastfeeding, and Nadeau says families should also start other foods, including common allergens, around 4–6 months. She doesn't think we'll fully return to prevalence levels of 30 years ago, but prevention can bend the curve.

• Reactions are unpredictable, and cofactors matter.
The same dose can produce worse reactions with repeated exposure, and factors such as exercise, illness or altitude can change severity—one reason allergic people must always carry epinephrine.

• Oral immunotherapy retrains the immune system by giving tiny, increasing doses of the allergen.
The principle dates back about 100 years with environmental allergies. For peanut, therapy starts around 1/200th of a peanut, increasing about 25% every two weeks; once patients reach about 40–60 mg, steps can be skipped. Shots aren't used for foods because foods are too potent in a specific IgE disease.

• Treatment has gotten faster as the immune switch became visible.
Researchers learned by about 3 months the immune response begins shifting, allowing faster dose increases by 6 months, and by a year the immune system has switched—it shouldn't take 10 years. Many patients target 600 mg (protecting against accidental ingestion), a threshold the FDA also uses.

• Time on maintenance determines the chance of cure.
After at least 2 years on dose, about 20% reach the 'cure' category (eating freely after stopping); after 5 years, about 60%. For some allergens, after 5 years of immunotherapy, roughly 25% regain the allergy, 25% have it reduced, and 50% have it resolved for life.

• Modern protocols are very safe.
Because dosing goes 'low and slow', epinephrine is needed during dosing only about 1 in 10,000 times, or 1 in 100,000 in some trials. Combination with biologics like anti-IgE can help.

• PM2.5 air pollution is a major and underappreciated hazard.
PM2.5 particles are 2.5 microns—smaller than a red blood cell—so they penetrate lungs and enter blood. The category contains about 200 chemicals, including volatile organic compounds. Wildfire smoke, even more potent, can circle the globe within four days. Pollution kills an estimated 8–10 million people a year, and she calls it more dangerous than tobacco smoke because it's so prolific.

• Protect yourself indoors and outdoors.
Check AirNow; in the yellow zone, wear a mask, and outdoor workers should wear an N95 when AQI is around 100. She advises patients not to exercise outdoors when AQI exceeds about 50. We spend over 90% of time indoors, so use MERV 13 or higher filters (not MERV 7–8) and watch gas or wood stoves.

EXAMPLES

• The family who assumed
A family assumed their child had outgrown a milk allergy after five years because they were told it would happen, but never tested—an example of why confirmation by an allergist matters.

• EpiPen pricing
Nadeau criticizes charges of $400–600 for epinephrine auto-injectors—no one should pay that for a life-saving drug. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• London's micro-measurements
Studies in London, where street-level PM2.5 is measured, compared people exercising on polluted versus cleaner routes, showing measurable harm.

• A growing field

There are now about 17 companies working on food-allergy treatments, many more than five years ago.

- **Memory cells last a long time**

  Nadeau notes vaccines show the immune system can maintain memory T cells for up to 100 years, which helps explain why allergies can persist and why tolerance, once built, can endure.

OTHER RELEVANT

- **Feed allergens early.**

  Introduce peanut, egg and other common allergens around 4–6 months, ideally guided by a pediatrician if eczema is present.

- **Treat eczema aggressively.**

  Inflamed skin may be a route to sensitization. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Consider oral immunotherapy with an experienced allergist.**

  Expect gradual dosing, a year or more of buildup and years of maintenance. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Monitor air quality.**

  Use AirNow, MERV 13 filters, N95s on bad days, and move workouts indoors above AQI ~50.

- **Don't assume a child outgrew an allergy—test.**

  Persistence rates have risen, so confirm with an allergist (often via supervised food challenge) rather than reintroducing at home.

- **Always carry epinephrine if diagnosed.**

  Reactions can escalate unpredictably with cofactors like exercise or illness; epinephrine is the first-line treatment for anaphylaxis, and antihistamines are not a substitute.

276 Special episode: Peter on longevity, supplements, protein, fasting, apoB, statins, & more

Date: 2023-10-23 · Duration: 1:24:16
URL: https://www.youtube.com/watch?v=em5xwtivnkg

KEYPOINTS

• Peter doubts anyone alive today will reach 120–150.

In this listener-question AMA with Nick Stenson, Peter says he has seen no evidence we can reverse the underlying processes of aging: mitochondrial dysfunction, protein misfolding, DNA damage and repair, or nutrient-sensing breakdown. He calls the gap between the actual science and the hype in media, social media and podcasts enormous, and dismisses aging clocks claiming a 60-year-old is 'really 35.' For a 50-year-old to live another 70 years, a cure for aging would have to arrive within about a dozen years. Assuming today's tools are roughly as good as it gets, he argues, should make you more serious about using them.

• The realistic prize is one to two extra decades and a stronger 'marginal decade.'

Peter believes his approach can add perhaps a decade to two of life. Heart disease is the one horseman he sees a clear path to nearly eliminating, through 'ultra-primary prevention' from your 30s: apoB never above 30–40 mg/dL, not even a year of mild hypertension, and constant metabolic health. Cancer, dementia, sarcopenia and arthritis can't be deferred indefinitely. So he fixates on the last decade of life: still able to ruck carrying 10–20 lb, swim half a mile and get out of the pool unaided, and get up off the floor. He sees rapamycin's mTOR inhibition as the most promising incremental drug, partly because it worked even when started late in life in animals.

• Geroprotective drugs lack biomarkers, so you can't tell if they're working.

With an ACE inhibitor like lisinopril, blood pressure dropping from 135/85 to 115/75 without dizziness tells you the dose is right. Diet, exercise and sleep all have feedback signals. Drugs aimed at aging itself have none, so you can't know if you're taking too little or too much short of side effects. Peter calls diagnostics an 'unsexy,' underfunded but crucial field. His old fasting routine of 7–10 water-only days each quarter plus 3-day fasts monthly probably cost him about 20 lb of muscle over six years, and he still doesn't know whether it did any good.

• His supplement list comes with a warning: don't copy it.

Mornings: Carlson high-EPA fish oil (about 2 g EPA and 1.5 g DHA), dosed to a red-cell omega-3 level of about 12%. Vitamin D, 5,000 IU, which he calls 'picking up a five-dollar bill in front of a tricycle,' since he considers vitamin D trials poorly done. About 1 g of magnesium total from Slow-Mag, magnesium L-threonate (Magtein) and magnesium oxide. Methylfolate and methyl-B12 (Jarrow) to keep homocysteine below 9. B6 cut from 50 mg daily to three times a week because excess can cause neuropathy. A baby aspirin, which he admits is a 'soft call' with weak evidence. Nights: 600 mg ashwagandha (Solgar), 2 g glycine (Thorne) and Magtein. Phosphatidylserine, about 400 mg, for jet lag. Also AG1, in which he discloses he is an investor and adviser, and Pendulum's probiotic, which he's testing on himself after its small 90-day trial showing a 0.6-point A1C drop.

• Lowering apoB to 30–40 mg/dL takes drugs. Exercise doesn't move it.

Diet has two levers. Cutting carbohydrates lowers triglycerides, and with them apoB. Cutting saturated fat leads the liver to add LDL receptors and pull more LDL from the blood. Few people reach Peter's target that way. His own baseline apoB is about 90–100 mg/dL, roughly the 50th percentile. He takes Repatha (a PCSK9 inhibitor) plus Nexlizet. Its bempedoic acid component is a prodrug activated only in the liver, so it blocks cholesterol synthesis there alone. Ezetimibe blocks reabsorption of cholesterol from the gut and is the weakest of the three. He has no side effects on this combination.

• There's rarely a reason for mega-dose statins now.

Statin efficacy flattens quickly: rosuvastatin delivers about 85% of its maximum apoB reduction at 5 mg, though doses go up to 40 mg. Statins have real, measurable side effects: muscle aches, elevated liver enzymes and insulin resistance. When cost rules out newer drugs, Peter suggests trying low-dose pitavastatin or rosuvastatin to find the best-tolerated option. PCSK9 prices have fallen by more than half, and a twice-yearly injection with a different mechanism is adding price pressure.

• Energy balance matters most in diet, and sustainability beats perfection.

Any diet (keto, paleo, Mediterranean, vegan) eaten in excess pushes fat into the liver and viscera. In Peter's clinical experience, people with profound insulin resistance do best cutting carbs to create a deficit. A 7-out-of-10 diet you can keep forever beats a perfect one you'll abandon in three months. Long-lived populations eat very different diets, and Okinawans' advantage fades as they Westernize, which suggests factors like activity, sleep, stress and social ties matter too. Nutrition science is hard because the organism and the intervention are both complex. Long controlled studies, like the Wisconsin and NIA monkey trials, take decades.

• Protein targets depend on muscle mass and life stage.

An over-nourished but well-muscled person in a calorie deficit can relax to about 0.6–0.7 g per lb. An over-nourished, under-muscled person needs to keep protein high to build muscle while losing fat. Peter isn't convinced by data linking high protein to mortality under 50, which he attributes to excess calories, confounding and very low absolute risk. Under 50 is the time to build muscle, because after 50 'you're clawing on for dear life.' He targets 150–180 g a day over about four sittings, partly from venison jerky sticks of about 10 g each. He discloses an investment in Maui Nui.

EXAMPLES

• The risk-reward grid.

Peter rates interventions as picking up a penny or a gold coin, in front of a tricycle or a train. He recalls teenage games of laying coins on train tracks, and a friend's younger brother who was killed playing chicken with a Toronto subway, the extreme of high risk for no reward.

• 'Good' and 'bad' cholesterol.

Cholesterol is one molecule. LDL and HDL are carriers, and lab panels measure LDL-C and HDL-C. LDL is harmful because it carries cholesterol into the artery wall.

• A biggest glucose spike.

Peter's highest CGM reading, about 180 mg/dL, came after dessert at a carb-heavy vegan restaurant in New York. With CGMs he prioritizes average glucose (a proxy for A1C), then variability, then spikes.

- **Testing a readiness app.**
  For six months Peter compared Morpheus's predicted zone 2 heart rate with his perceived exertion and end-of-ride lactate, and found it tracked well.

OTHER RELEVANT

- **Lp(a) therapy may be coming.**
  An antisense drug eliminated Lp(a) in phase 2. Its phase 3 trial in people who have already had cardiac events will determine approval.
- **A cuffless blood pressure monitor.**
  A wrist device approved in Europe gives about 12 readings a day, and Peter hopes the FDA approves it.
- **Why he stopped long fasts.**
  He no longer travels, the fasts were hard to do at home, and their benefit is unproven.
- **He hopes for continuous lactate sensors.**
  They would make zone 2 and VO2 max training far easier to calibrate.

274 - Performance-enhancing drugs and hormones—risks, rewards, & broader implications for the public

Guest: Derek (More Plates More Dates)
Date: 2023-10-09 · Duration: 3:30:34
URL: https://www.youtube.com/watch?v=JNpgqpyzW98

KEYPOINTS

• Derek's own history illustrates how young men drift into steroids.
A skinny 138-pound high-school basketball player, Derek started lifting under peer pressure, later used anabolic steroids and reached 260+ pounds. At peak he estimates a combined weekly dose of about 1,500 mg to 2 g—at 20–21, 'you just think you're invincible'.

• Supraphysiologic doses don't produce proportional results.
Peter notes he's never prescribed more than about 150 mg/week of testosterone cypionate for TRT, so Derek's peak was 10–13 times that—but results were nowhere near 10–13x. At 500 mg+ per week, users often need aromatase inhibitors such as 1 mg anastrozole daily or every other day to control estrogen.

• Underground labs fill the gray market.
A vial is typically 250 mg/mL (versus pharma's 200 mg/mL increments) and costs perhaps $60–70; Chinese-sourced HGH can be about $150 for 100 IU. Quality and dosing accuracy are uncertain.

• Growth hormone secretagogues differ greatly in hunger effects.
Ipamorelin, though a ghrelin-receptor agonist, barely affects appetite, while MK-677 (ibutamoren) can drive people to eat around 2,000 extra calories a day; its half-life is roughly 24–36 hours. GHRP-6 causes acute hunger after injection. CJC-1295 with DAC has an extended half-life; most of these lack FDA approval, and some users push IGF-1 to 500+.

• Drugs dominate elite bodybuilding outcomes.
Derek ranks drugs first, then nutrition, then training—reluctantly putting numbers like 50/40/10. Physiques changed dramatically in the late 1980s–90s; growth hormone and insulin are credited for 20–30 lb lean-mass jumps, with 300 lb competitors eating around 5,000 calories and chugging 100–200 g shakes with hydrolyzed whey before workouts to avoid insulin-induced hypoglycemia.

• The cardiovascular toll is real.
They discuss deaths of young bodybuilders, including one in his 30s who did lots of cardio and ate clean, and Rich Piana, who died in his 40s with a heart reportedly around 660 g. Peter relates lipid harms to apoB and the limited tools of decades past.

• Testosterone declines gradually, not off a cliff.
After about 30–35, total testosterone falls about 1% a year and free testosterone 2–3%, varying with lifestyle—so a 45-year-old shouldn't assume a 20% drop. Some very muscular men feel fine at 450 ng/dL.

• Good TRT starts low and mimics physiology.
A reasonable starting dose is 80–120 mg/week, adjusted in fine increments like 20 mg/week. The old standard of 200 mg every two weeks produced wild peaks and troughs; daily or frequent small doses (e.g., 15 mg injected daily) or nasal Natesto avoid huge spikes to 1,500–2,000 ng/dL. Peter's clinic adjusts doses 100–120 mg/week; 'fitness-industry TRT' starts at 200 minimum.

• Estradiol shouldn't be crushed in men.
A New England Journal study around 2013–14 with 10 groups showed estrogen matters for men's fat mass and sexual function. The old idea of pinning estradiol at 20–30 pg/mL regardless of testosterone dose is outdated. Peter's T is 300–400 ng/dL with estradiol rarely above 25; he notes a higher T would bring useful estradiol too.

• hCG preserves testicular function on TRT.
To maintain intratesticular testosterone while suppressed on exogenous androgens, Derek cites about 375 IU every other day; a common starter dose is 625–750 IU twice weekly, rarely above 2,000 IU twice weekly. hCG's half-life is roughly 24–36 hours, and a study using 4,000 IU examined effects on FSH.

• Hair-loss drugs shift hormones.
Finasteride and dutasteride block conversion to DHT (a 5 mg BPH dose inhibits up to ~70% systemically), raising testosterone and estradiol by about 15–22%. By the time hair loss shows in photos, 20–30%+ may already be lost. Derek doesn't recommend the topical RU58841 given alternatives with human safety data on the horizon.

• Natural testosterone release is steady; weekly 'hammers' aren't physiologic.
Derek points out there's no situation in which healthy testes blast a man once a week with a huge dose of testosterone and its metabolites. Large, infrequent injections create spikes, then troughs with symptoms, and drive more aromatization and hematocrit rise. Smaller, more frequent dosing—or shorter-acting formulations—keeps levels closer to what the body would produce, which is why both favor it.

EXAMPLES

• Lab artifacts
Patients tested by enzyme-based assays came back with estradiol around 100 pg/mL; retested by LC-MS at LabCorp, the same men were at about 31.

• High SHBG
A man with total testosterone of 1,000 ng/dL but SHBG of 100 might have free T of only 8 ng/dL—0.8% free instead of about 2%—so total T alone misleads.

• The tennis-dad question
Peter poses a hypothetical parent wanting growth hormone to push a son from a predicted 5'10" to 6'2" for pro tennis—raising unknown risks of manipulating growth.

- **Cheap hCG**
  Derek mentions hearing of a Texas pharmacy selling 1,500 IU vials of hCG for a couple hundred dollars—cheap by his standards, though pricing varies widely by pharmacy.
- **Llewellyn's pharmacology**
  Peter recalls reading pharmacokinetic curves in an anabolics reference and thinking the then-standard 200 mg every two weeks was 'an awful idea' because of the roller-coaster levels it created.

OTHER RELEVANT

- **If considering TRT, confirm need and start low.**
  Rule out sleep, weight and other causes; use LC-MS testing and frequent small doses.
- **Don't chase estradiol down reflexively.**
  Men need estrogen; treat symptoms and accurate labs, not a number. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Understand gray-market risks.**
  Underground products vary in dose and purity; cardiovascular and hormonal costs can be severe.
- **Use hCG to preserve fertility.**
  If fertility matters, discuss hCG or alternatives before or during TRT. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prefer modest, sustainable changes for body composition.**
  Derek's own approach to losing 10 pounds is to trim about 300 calories or find more satiating foods—not drugs. For most people, nutrition and training adjustments deliver results without the risks discussed.

273 Prostate health: common problems, cancer prevention, screening, treatment, and more

Guest: Ted Schaeffer
Date: 2023-10-02 · Duration: 3:46:39
URL: https://www.youtube.com/watch?v=poTcAm_rknw

KEYPOINTS

• Urinary symptoms are the norm with age, not the exception

Ted Schaeffer, a Northwestern urologist, says 50–60% of men over 50 have lower urinary tract symptoms, rising to 75–80% by 60, and these almost always involve the prostate. A normal prostate is about 20–30 g at 40–50 and grows with age. Size doesn't predict symptoms well: men can have severe symptoms with a 35 g gland.

• Waking at night to urinate is often about fluid handling, not just the prostate

Antidiuretic hormone normally rises in the evening to cut overnight urine production. That rhythm weakens with age, and alcohol inhibits the hormone. Fluid that pools in the legs during the day (look for sock marks in the morning) returns to the circulation when you lie down. Schaeffer says changing when you drink, plus knee-high compression stockings, can often cut nighttime trips from two to one without drugs.

• Medications: alpha blockers first, then 5-alpha-reductase inhibitors for large glands

Modern selective alpha blockers relax smooth muscle in the prostate to widen the urethra, without the steep blood-pressure drops of the first generation. Finasteride (5 mg) or dutasteride (0.5 mg) shrink the prostate by 20–30% over time. Their half-lives are long, so Schaeffer notes that a weekly 5 mg finasteride tablet roughly matches the 1 mg daily hair-loss dose.

• HoLEP has changed surgery for large prostates

TURP, still the gold standard, scrapes out tissue in roughly 1 g chunks. Holmium laser enucleation (HoLEP) shells out the gland along its natural plane. His colleague Amy Krambeck has removed 400 g from a 450 g prostate, about the size of a big grapefruit, and can operate on glands as small as 25–30 g. He estimates only about 10 surgeons in the US work at her level.

• Chronic prostatitis is often not an infection

The four-glass test cultures the first void, bladder urine, prostatic fluid and urine after massage. Bacteria found only in the prostatic fluid point to a true prostate infection. Many men instead have pelvic-floor tightness, which Schaeffer treats with transrectal myofascial release, which he says can change lives. He is wary of repeated 30–60-day antibiotic courses. In bed-bound or dementia patients, he warns that indwelling catheters drive urosepsis.

• Finasteride hides PSA, and that can kill

After about five years on a 5-alpha-reductase inhibitor, PSA falls about 2.5-fold. If patients and doctors don't adjust for this, a rising PSA gets missed. A UCSD study of veterans found markedly higher prostate cancer death rates in men taking these drugs, which Schaeffer attributes to this neglect. He also takes post-finasteride syndrome (lasting sexual and neurological effects) seriously and thinks young men at hair-loss clinics aren't properly warned.

• The deadliest prostate cancers may thrive without testosterone

In about 100,000 tumour gene-expression profiles (the Decipher database now has 140,000+), Schaeffer's group found luminal-like and basal-like cancers. Fewer than 10% of metastatic tumours are luminal. Basal tumours survive without androgens, which makes them most likely to spread and least hurt by androgen deprivation. That is why he is comfortable treating genuinely low testosterone in men diagnosed with or recovering from prostate cancer.

• Know your PSA relative to the median for your age

Median PSA is about 0.5 at 40 and about 1.0 at 50. Being above the median signals a much higher risk over the next 20–30 years and calls for closer follow-up. PSA density (PSA divided by prostate volume) refines this: he gets concerned above about 0.1–0.12 in men under 60 and 0.15 in men over 65–70. A free PSA above 18–20% is reassuring. Screening trials showed PSA cut prostate cancer deaths by 20–25%, yet about 35,000 US men still die each year.

• Use MRI to decide on a biopsy, and go through the skin

PI-RADS 3–5 lesions generally warrant a biopsy unless PSA density is very low (around 0.02). Transrectal biopsies carry about a 1–4% infection rate even with antibiotics. Transperineal biopsies go through the skin with buffered lidocaine and nearly eliminate infection. Schaeffer leads a 16-centre randomized trial comparing the two. A good biopsy takes 12 systematic cores plus targeted samples.

• Gleason 6 can usually be watched; pattern 4 changes the picture

Grade 3+3=6 is the least aggressive type. In the Johns Hopkins active-surveillance cohort started in 1996, about 30–35% of men were upgraded within five years, with roughly 2–3% added per year after that, about one in five overall over 10 years. Gleason 4+3, meaning more than 50% pattern 4, behaves worse than 3+4, and 3+5 behaves like 4+4. About 95–96% of prostate cancers are diagnosed while still localized.

EXAMPLES

• Prostatectomy outcomes at a high-volume centre

Schaeffer quotes a 95–96% chance that surgery succeeds against the cancer. He puts continence at about 66% at one month and 95% at three months. A 65-year-old with good erections before surgery has a 65–75% chance of recovering erections adequate for intercourse (with Cialis) within 24 months, as nerve recovery takes 24–30 months. Men who already needed Cialis before surgery do 10–20% worse.

• Inherited risk

BRCA2 carriers have a lifetime prostate cancer risk of about 60–70%, enough to warrant intensive screening. A USC polygenic study of about 235,000 men found that roughly 250–260 risk variants are enriched in Black men and in men diagnosed young.

• A PSA of 10 at 34

Schaeffer recalls a man from his Hopkins years who had workplace screening only to get a $250 insurance discount and was

found to have a PSA of about 10 at 34, not from infection. The median age at diagnosis is 68, and a diagnosis at around 50 or younger warrants genetic testing.

- **Advanced disease**

  For high-risk or lymph-node-positive disease, surgery debulks the tumour, typically followed by radiation and 6–24 months of androgen deprivation. In newly diagnosed metastatic disease, median survival without treatment is about 2–3 years. Traditional androgen deprivation alone extends this to about 48–50 months, at a real cost to metabolic health and quality of life.

OTHER RELEVANT

- **Get a baseline PSA early**

  The NCCN guideline says every man should have a baseline PSA by 45. Schaeffer sees no reason not to test earlier. Track your PSA against the median for your age and your prostate volume: if it's below 1, retest every 2–4 years; if it's above the median, follow it more closely.

- **If you take finasteride or dutasteride, tell every doctor**

  Roughly double the PSA value (Schaeffer's figure is about 2.5×) and watch the trend, since any rise matters.

- **Before a biopsy, ask for MRI and a transperineal approach**

  These cut unnecessary biopsies and nearly eliminate infection risk.

- **Choose a high-volume surgeon and ask for their numbers**

  Ask about continence and erectile outcomes, and how much nerve-sparing their approach allows.

272 Rapamycin: potential longevity benefits, surge in popularity, unanswered questions, and more

Guest: David Sabatini & Matt Kaeberlein
Date: 2023-09-25 · Duration: 3:01:29
URL: https://www.youtube.com/watch?v=O67pvKxio10

KEYPOINTS

• mTOR connects nutrient availability to whether the body builds up or breaks down.

Sabatini purified mTOR as a student in Solomon Snyder's lab. He describes it as the protein that links nutrients to anabolic versus catabolic states, which is why it touches nearly everything. Rapamycin was found in an Easter Island (Rapa Nui) soil sample collected around 1966–67, and Suren Sehgal championed it. FDA approval for transplant patients didn't come until 1999. Both guests think that transplant history, where the drug was given daily alongside prednisone and other harsh immunosuppressants, gave it an undeserved reputation as a dangerous drug.

• Rapamycin is the most reproducible longevity drug across species.

Kaeberlein found mTOR by accident in an unbiased yeast lifespan screen. Rapamycin, and genetic inhibition of mTOR, extend lifespan in yeast, worms, flies and mice, and appear to improve nearly every healthspan measure tested. His 2007 work with Brian Kennedy and Daniel Promislow showed that genes controlling longevity are often shared between yeast and worms. That's why simple organisms can tell us about aging in mammals.

• How rapamycin works: it's a 'molecular glue,' and it inhibits only part of mTOR's activity.

Rapamycin binds FKBP12 and attaches it to mTOR complex 1 near its active site, like a boulder partly blocking a cave entrance. Some substrates get through and others don't. With prolonged exposure, it also prevents mTOR complex 2 from forming, by binding mTOR before Rictor can join it. Sabatini's postdoc showed this around 2004–2005, and Sabatini didn't believe it at first. Cells need only about 10–15% of complex 2 to keep AKT working. Catalytic (ATP-competitive) inhibitors block both complexes fully. Sabatini says they're highly toxic and can kill a mouse within hours.

• Leucine is sensed by sestrin, at the lysosome.

Tim Peterson's experiments showed mTOR moves onto lysosomes within minutes of adding amino acids, docking on a 'pier' made of about 20 proteins. Earlier work by Joe Avruch had pointed to leucine and arginine as the key signals. Sabatini's lab identified sestrin as the leucine sensor, and its crystal structure shows a small pocket with a lid that fits only leucine. That explains why better-than-leucine mimics have been so hard to make.

• The muscle paradox.

mTOR activation builds muscle, so rapamycin was expected to cause sarcopenia. Instead, rodents treated throughout adulthood kept more muscle into old age, perhaps through reduced inflammation. Kaeberlein notes there's no human data on whether lifespan-type doses blunt resistance-training gains. He also warns that mice are poor models of sarcopenia, so mouse protein-restriction findings may not carry over to people.

• Starting rapamycin in middle age still works.

The 2009 ITP study started treatment at 20 months, about the equivalent of a 60-year-old human, only because the drug couldn't be formulated sooner. Kaeberlein calls it one of the most important studies in the field and says a grant proposing that design would never have been funded. Full dose-response and timing studies have never been done, and his grants for them have been rejected.

• Mannick's everolimus trial changed how the drug is viewed.

In mice, six weeks of rapamycin before vaccination raised flu protection in old animals from about 30% to 100%. In Joan Mannick and Lloyd Klickstein's trial (about 80 per arm), older adults took everolimus for six weeks before a flu shot. Doses of 5 mg weekly and 1 mg daily improved antibody responses, and the 5 mg weekly arm had side effects close to placebo. The guests now call rapamycin an immune modulator rather than an immunosuppressant. A later pivotal trial used RTB101, a non-specific PI3K/mTOR inhibitor, without everolimus. It was stopped early, so it says nothing about rapalogs.

• What people in the off-label survey reported.

Kaeberlein's survey compared about 300 rapamycin users with nearly 200 health-conscious non-users. All data were self-reported. Mouth sores were the only side effect more common in users, at about 15%. Abdominal cramps, depression and anxiety were less common. Most users took 6 mg once weekly, with a smaller cluster at 3 mg and some up to 20 mg. People who took it continuously through COVID reported milder illness and less long COVID, though the numbers were small.

• Why it may work: autophagy, inflammation, or the 'general contractor' effect.

Sabatini would pick autophagy, via TFEB and lysosome production. He adds that you can't fix an old house with just a plumber; mTOR matters because it touches everything. In worms, the benefit runs mostly through autophagy; in yeast, through protein translation. Kaeberlein increasingly credits reduced sterile inflammation for the organ-level benefits in mammals. Attia points out there's no good clinical biomarker of autophagy.

EXAMPLES

• Dog Aging Project trial

The TRIAD trial is enrolling 580 healthy dogs aged 7+ and weighing 40–110 lb, on 0.15 mg/kg weekly or placebo for three years. It's powered to detect a 9% lifespan change, with results expected around 2026. Sabatini says he'll take rapamycin if it's positive. Kaeberlein worries the dose may be too low; ITP mice got roughly the human equivalent of 0.1 mg/kg per day.

• Attia's patients

Attia describes two high-risk patients on 5–8 mg weekly whose blood amyloid (C2N) scores improved. He stresses that's anecdotal and may not reflect the brain. Kaeberlein notes that inhibiting mTOR in the liver rescued a mouse brain disease, so effects outside the brain may matter.

• Mouth-sore fix

Sabatini wonders why no one uses FK506 or inert FKBP-binding mouthwashes to occupy the binding sites in the mouth.

Kaeberlein would rather test rapamycin mouthwash for gum disease.

- **Lab accident**
  Sabatini has never taken rapamycin, apart from inhaling the powder while purifying mTOR without gloves.

OTHER RELEVANT

- **Avoid compounded rapamycin**
  Without an enteric coating, stomach acid can leave bioavailability near zero. Branded or generic sirolimus costs about $5/mg. Some users take grapefruit juice to raise blood levels.
- **Ovaries vs. sperm**
  Short courses restored fertility in older female mice but impair sperm production in males. A Columbia trial is testing it in women with premature ovarian failure.
- **Brain penetration**
  In Sabatini's experience, brain inhibition needed repeated doses; once-weekly doses probably don't reach the brain much.
- **Marmoset data**
  Adam Salmon's ongoing primate study hints at a survival benefit, though in captivity.

270 Journal club with Andrew Huberman: metformin, power of belief, & how to read scientific papers

Guest: Andrew Huberman, PhD
Date: 2023-09-11 · Duration: 2:11:13
URL: https://www.youtube.com/watch?v=boyTPdYJArs

KEYPOINTS

• Metformin weakly blocks the cell's power plant, and its main job in diabetes is to rein in the liver's glucose output.

In this journal-club format, Peter explains that metformin, a generic drug used for 40–50+ years, first in Europe, partially inhibits complex I of the mitochondrial electron transport chain. Cyanide, by contrast, shuts down a later step completely. Why this helps diabetics is debated. What's clear is that it lowers hepatic glucose output. A healthy person has only about 5 g of glucose in circulation. Consistently carrying one extra teaspoon of it is roughly the difference between normal metabolism and type 2 diabetes. Insulin resistance starts mostly in muscle, which stores 75–80% of glucose. Insulin signaling moves glucose transporters to the cell surface, and fat building up inside muscle cells disrupts that signal, work Peter credits largely to Gerald Shulman at Yale.

• A 2014 study made metformin look like an anti-aging drug, but Peter later found a key flaw.

Bannister and colleagues compared UK patients with type 2 diabetes on metformin alone with matched non-diabetic controls. Crude death rates were 14.4 versus 15.2 per 1,000 person-years, and modeling showed a 15% relative reduction in all-cause mortality over a median 2.8 years. Diabetes normally shortens life by about six years, so this was striking. Around 2018 Peter noticed 'informative censoring': patients who stopped metformin, were lost to follow-up, or progressed to stronger drugs were dropped. His analogy is a smoking study that stops counting smokers who die.

• A larger 2022 Danish study using twins found the opposite.

Keys and colleagues sampled about half a million people from Danish registries. They compared 7,842 metformin users with diabetes against matched non-diabetics, and 976 same-sex twin pairs discordant for diabetes. Crude mortality was about 24.9 versus 16.9 per 1,000 person-years in the singletons, and about 24.7 versus 12.9 in the twins. Hazard ratios ran from 1.48 unadjusted to about 1.32–1.33 after adjusting for medications, marital status and education. In the twins they ran from 2.15 to about 1.7–1.8. Censoring like Bannister's only nudged these down, to 1.39 and 1.97. It never produced a benefit.

• What the Danish result does and doesn't show.

Peter says it shows metformin doesn't erase the extra mortality of diabetes. It doesn't prove metformin is useless: those patients might have fared even worse on nothing. The groups' medication use couldn't be matched (lipid-lowering drugs 45.6% versus 15.4%, for example). Only a randomized trial like TAME (Targeting Aging with Metformin) can settle it. In the rigorous mouse Interventions Testing Program, metformin failed while rapamycin, 17-alpha estradiol (in males), acarbose and the SGLT2 inhibitor canagliflozin extended life. Peter still prescribes metformin for insulin resistance but doesn't see it as a longevity tool for insulin-sensitive people who exercise.

• Peter quit metformin after seeing his resting lactate.

He started at a full 2 g a day in May 2011 without titrating up, and was so nauseous at the Berkshire Hathaway meeting he couldn't eat ice cream. In 2018, finger-prick testing for zone 2 training showed a fasted resting lactate of about 1.6 mmol/L. Healthy is below 1, roughly 0.3–0.6. That fits a mild mitochondrial toxin pushing glucose toward lactate. He also suspects metformin blunts gains in muscle size and strength. The only glucose-lowering drug he takes now is an SGLT2 inhibitor, based on mechanistic data, the mouse results and human trials including heart failure in non-diabetics.

• Statistical tools you need to read papers.

Rates per 1,000 person-years normalize for follow-up time. A 95% confidence interval that excludes no effect signals significance. Kaplan-Meier survival curves only go down or stay flat, but they can cross. A hazard ratio minus one gives the relative change: 1.48 means 48% higher risk and 0.85 means 15% lower. Power matters: a null result only rules out effects the study was sized to detect. Overlapping error bars don't automatically mean no difference. Epidemiology makes up for not randomizing with huge samples and long follow-up. A randomized trial like the Women's Health Initiative can cost a billion dollars.

• Huberman's paper: being told a bigger dose produced a bigger brain response.

In a not-yet-peer-reviewed preprint from Xiaosi Gu's lab at Mount Sinai (first author Ofer Perl), experienced smokers who had abstained vaped the same low-nicotine pen, confirmed by blood levels, while told it was low, medium or high strength. Their perceived effect matched what they were told. Thalamic activation in regions rich in nicotinic receptors scaled with belief, significantly between the low and high groups, during a market-prediction task in the fMRI scanner. Signaling from the thalamus to the ventromedial prefrontal cortex rose significantly at each step. Reward-pathway activity didn't change. Huberman calls it the first study of dose-dependent belief effects, while noting it lacked a zero-nicotine arm and had movement artifact from coughing smokers.

• Belief effects aren't the same as placebo.

Placebo is binary: you think you got the drug or you didn't. Belief effects scale with the information people get. Huberman cites Alia Crum's work. People taught that stress enhances performance did about as much better as those taught it impairs performance did worse, very roughly 10–30% each way. A shake labeled high-calorie suppressed the hunger hormone ghrelin more than the identical shake labeled light. Hotel workers told their work was exercise lost more weight without measurably moving more. Telling patients that side effects mean a drug is working lessened how bad the side effects felt.

EXAMPLES

• Huberman's berberine trick.

On Tim Ferriss's Slow-Carb Diet, he took berberine (about a couple hundred mg, by memory) before cheat days and felt fine after huge carb loads. Taken without carbs, it gave him headaches he attributes to low blood sugar.

• Acarbose's surprise.

Acarbose was nominated to the mouse longevity program as a calorie-restriction mimic. Treated mice lived longer without weighing less, possibly because of lower glucose and insulin.

- **How Huberman reads papers.**
  From his UC San Diego course: write down the general and specific question, the approach, the findings (figure titles help) and the conclusions. Then ask whether the conclusions are actually supported. Peter adds that the supplementary material often holds key numbers.
- **Why vegetarians look healthier.**
  Peter uses meat-eater comparisons to show residual confounding. Choosing not to eat meat usually comes with other health-minded choices that are hard to measure.

OTHER RELEVANT

- **Calorie restriction and fasting for longevity.**
  Peter says there's no evidence short fasts extend life. His past heavy fasting cost him muscle without a clear benefit.
- **Aging biomarkers.**
  Without biomarkers, nobody can tell whether rapamycin, metformin or fasting is working. Peter wants more funding there than anywhere else.
- **Men need estrogen too.**
  Both hosts say men shouldn't crush estrogen, which matters for libido, brain function and bone.
- **Possible uses of belief effects.**
  Huberman speculates, without evidence yet, about tapering nicotine or ADHD medication while patients believe the dose is unchanged.

269 - Good vs. bad science: how to read and understand scientific studies

Date: 2023-09-04 · Duration: 2:02:03
URL: https://www.youtube.com/watch?v=Vnzodlb8rzE

KEYPOINTS

• A good study is planned in detail before anyone is enrolled.

Peter and Bob Kaplan walk through the steps. Start with a hypothesis framed as a null hypothesis: coffee does not change eye color. Design the experiment, ideally randomized and blinded. Use a power analysis to set the number of subjects. Get ethics (IRB) approval, name primary and secondary outcomes, write a statistical plan, pre-register, and secure funding. Treat the hypothesis as 'innocent until proven guilty' and try hard to falsify it.

• Study types range from anecdote to experiment, and Peter disputes the standard evidence pyramid.

Case reports and case series generate hypotheses. Peter's own early case report described a melanoma patient whose dangerously high calcium came from a tumor-made parathyroid-hormone-related hormone, not bone metastases. Cohort studies can look backward or forward but are only observational. Non-randomized trials carry selection bias, and randomized controlled trials are the gold standard. Meta-analyses pool studies, weighting each by its precision. Peter rejects the usual pyramid that ranks a meta-analysis above a well-done randomized trial.

• Drug trials move through four phases.

Phase 1 tests safety in fewer than about 100 people, often patients with advanced cancer who have run out of options, raising doses step by step in small cohorts. Phase 2 adds efficacy in tens to a few hundred people, often open-label and compared against the disease's natural course. Phase 3 is typically ten times larger: thousands of people, randomized and blinded where possible, measured against placebo or standard care. It's the main basis for approval. Phase 4 follows approval, for example testing semaglutide for obesity after it was approved for diabetes, which can reveal side effects in new populations.

• Observational studies are dogged by healthy-user bias, recall bias and confounding.

The WHO's reading of red and processed meat studies found about a 20–30% higher associated risk. But people who avoid meat also tend to smoke less, exercise more and follow medical advice more closely. The same logic explains studies claiming diet soda is more fattening than regular soda: people who are becoming metabolically ill get told to switch. Hot chocolate 'causes' ski accidents only because cold climates drive both. Peter would scrap food frequency questionnaires, which ask people to recall a year of eating, often once at baseline, and which validation studies show correlate poorly with food logs. Recall works better for unforgettable events like pregnancies.

• Randomized trials have their own traps.

Performance bias, a relative of the Hawthorne effect, arises when one arm gets more attention, coaching or contact; Peter calls it the most common bias in lifestyle trials. Taking many looks at the data inflates false positives. Ten coin flips almost guarantee at least one heads, so a Bonferroni correction divides the p-value threshold by the number of looks. In PREDIMED, a review of thousands of trials by John Carlisle flagged odd randomization. It turned out entire clinics had been assigned to one diet. The results held on reanalysis, but a cloud remains. Also check blinding (psychedelic trials are nearly impossible to blind), whether the subjects were all men, funding, conflicts of interest and whether the effect matters clinically.

• Power determines whether a null result means anything.

The p-value threshold (alpha, usually 0.05) caps false positives. Power is 1 minus the false-negative rate, typically 80–90%. Using a classic table, Peter shows that detecting a rise from 25% to 35% success needs about 358 people per arm at 80% power, or 459 at 90%. A 25% versus 75% gap needs about 18–23, and 25% versus 30% needs roughly 1,300–1,700. Underpowered studies miss real effects. Overpowered ones, common in data-mining studies, make trivial effects 'significant,' like a drug that lowers systolic pressure by 1 mmHg.

• Always ask about absolute risk, not just relative risk.

The Women's Health Initiative's widely reported 25% rise in breast cancer on hormone therapy was 4 versus 5 cases per 1,000 women: an absolute increase of 0.1%. Peter calls that a ceiling on the true risk, given what he sees as the study's many flaws. Number needed to treat is 1 divided by the absolute risk reduction. Cutting events from 5 to 4 per 1,000 is a 20% relative reduction but means treating 1,000 people to prevent one event. Clinicians like to see an NNT under 100.

• Hazard ratios and confidence intervals are easy to read once you practice.

A hazard ratio minus 1 gives the relative change: 0.82 means 18% lower risk and 2.2 means 120% higher. A 95% confidence interval that crosses 1 isn't significant. Bob cites statistician Andrew Gelman, who prefers 'uncertainty interval.' A hazard ratio of 1.4 with an interval of 1.1–17 deserves little confidence. Trials stop early for three reasons. Torcetrapib was stopped for safety after 82 deaths versus 51 on Lipitor alone. PREDIMED was stopped for benefit. Look AHEAD was stopped for futility, at a hazard ratio of 0.95 with an interval of 0.83–1.09.

EXAMPLES

• Where Peter heard the torcetrapib news.

He remembers walking up Kearny Street in San Francisco in late 2006, at McKinsey, stunned. He'd expected the drug, which raised HDL cholesterol, paired with Lipitor to be a home run.

• The Minnesota Coronary Experiment went unpublished for years.

Replacing saturated fat with polyunsaturated fat in a residential care population lowered cholesterol but not cardiovascular deaths. The results weren't published until 1989. The lead investigator, Ivan Frantz, reportedly said the study didn't turn out as hoped.

• Peter's order for reading a paper.

Abstract (go or no-go), introduction only if the topic is unfamiliar, then methods, figures and legends, the results text, and finally the discussion, after forming his own view.

• The Rosenberg lab rule.

After an experiment, draft the figures and legends first. Once they're right, 'the paper writes itself.'

OTHER RELEVANT

- **Countering publication bias.**
  Pre-registration on ClinicalTrials.gov and registered reports from the Center for Open Science, in which journals accept the protocol before results exist.
- **Journal impact factor.**
  Citations divided by articles. About half of roughly 13,000 journals score under 2. In 2019 the New England Journal of Medicine scored about 75 and The Lancet about 60.
- **Crossover designs.**
  Subjects serve as their own controls, in A-B and B-A orders, if washout periods allow.
- **Reading science is a skill.**
  It takes repetition. Much health reporting skips these checks.

268 Genetics: testing, therapy, editing, association with disease risk, autism, and more

Guest: Wendy Chung, MD, PhD
Date: 2023-08-28 · Duration: 2:35:33
URL: https://www.youtube.com/watch?v=qSbanRiMg1o

KEYPOINTS

• PKU is the model for newborn screening: catch it early and a disabling disease becomes manageable.

Wendy Chung, a clinical and molecular geneticist who is leaving Columbia to chair pediatrics at Boston Children's Hospital, started her career on phenylketonuria. It's a recessive disease: both parents are carriers and the child can't clear phenylalanine. Untreated, toxic byproducts damage the brain. A carefully titrated low-phenylalanine diet started in infancy prevents intellectual disability, and it's needed for life, especially during pregnancy. Through research she has found teenagers who were missed at birth and now have irreversible damage. Screening has moved from bacterial growth tests on heel-prick blood spots in the 1960s to tandem mass spectrometry. Her program adds DNA as a second, independent check, since neither the genetic sequence nor a single blood level perfectly predicts who needs treatment.

• Gene discovery went from years to hours, and still only about a third of genes are linked to disease.

Chung's first cloned gene took eight years. Her most recent took hours. The cost of a genome fell from about $1 billion around 2000 to about $1,000 today. Humans turned out to have about 20,000 genes, not the predicted 100,000; complexity comes from each gene making many versions of its protein. Roughly 7,000 genes now have a known disease association. A standard genome reads short fragments of about 100 bases and maps them onto a reference. Some regions are never placed, and most clinical interpretation still focuses on coding regions. For a healthy middle-aged person the result is usually 'we don't see much here,' since they've already survived the most devastating variants.

• Mutations build up over a lifetime, including in sperm and eggs.

Peter learned from family sequencing that he is mosaic for a variant one of his children inherited in full. Chung explains that new mutations arise with each cell division. In sperm they accumulate roughly linearly with paternal age, and some 'selfish' sperm mutations even help those cells divide. Maternal age raises chromosome errors such as Down syndrome more sharply from the mid-30s, because the machinery that separates chromosomes in eggs must work for decades after it starts in fetal life.

• About 20% of cancer has a genetic component, and blood tests read what you were born with.

Chung estimates that about 5% of cancers come from powerful single genes with very high lifetime risk, another roughly 5% from moderate-risk genes that raise risk two- to threefold, and perhaps about 10% from polygenic risk scores summing hundreds to thousands of variants. Polygenic scores aren't yet used routinely in clinics. Cheek swabs and blood show inherited risk, not changes inside a breast. Liquid biopsies that look for tumor DNA in blood are, in her view, not ready for population screening; they're mainly useful for monitoring recurrence or high-risk people.

• Consumer DNA tests are 'recreational' and can mislabel samples.

23andMe-style tests read selected single-letter variants (SNPs) to report ancestry and traits like earwax type or lactose intolerance. They don't read your whole genome and aren't built to answer medical questions, though they do report APOE status. Peter has seen several APOE results that didn't match later clinical sequencing. Chung notes mix-ups as simple as a flipped sample plate. Before anything irreversible, such as a mastectomy or a big insurance purchase, confirm with a clinical test.

• The GUARDIAN study screens newborns' genomes for about 250 treatable conditions.

It began in New York City in September 2022 after her spinal muscular atrophy screening program, started in 2016. SMA had been the leading genetic cause of death under age 2. Screening found babies before symptoms, while the treatment window was still open. GUARDIAN had screened just over 3,000 babies at recording and aims for at least 100,000. It costs about $1,000 per baby including interpretation and counseling, with a goal of about $100. Many conditions found don't need gene therapy at all: Wilson disease, which can end in liver transplant, is treated with inexpensive zinc that crowds out copper.

• Gene therapy delivery is still the hard part.

Jesse Gelsinger died around 2000 at Penn in a trial for ornithine transcarbamylase deficiency, after an overwhelming immune and liver reaction to the adenovirus used to carry the gene. Vector reactions have caused other deaths since. Doses are tricky: too high provokes immunity, too low wastes what may be the only chance, since the body then neutralizes a repeat dose. Few gene therapies are approved (SMA is the standout) and they cost about $1–3 million. The CRISPR-Cas9 system's weak point is that it cuts both DNA strands, risking edits in the wrong places. Prime editing nicks only one strand, which gives more accurate repairs. Tay-Sachs needs a missing enzyme added back to the brain, where even 20–50% of normal may be enough. Fragile X needs an oversized DNA repeat edited down.

• Autism is highly heritable but spread across many genes.

Its heritability is about 0.8–0.9, compared with roughly 0.5–0.6 for bipolar disorder and schizophrenia, about 0.3 for major depression and about 0.5 for obesity. No single gene accounts for more than 1% of cases, and new mutations not inherited from either parent aren't counted in heritability. Prevalence is about 2%, a rise that reflects changing diagnostic criteria, better recognition (especially in underserved groups) and access to services. Chung runs the large SPARK autism study, which found a teenager whose autism stemmed from undiagnosed PKU. Most of what's known comes from people under 20, and some subtypes may be degenerative in adulthood.

EXAMPLES

• Peter's PCSK9 mea culpa.

He remembers reading Helen Hobbs's papers on people with overactive and underactive PCSK9 about 15 years ago and predicting the idea wouldn't pan out. The drug class proved him wrong.

• The aspartame warning label.

People with PKU follow a tightly controlled diet. Labels matter most for pregnant women, whose fetus can be harmed without any warning symptoms.

• Weighing the price tag.

Peter contrasts about $1 million in chemotherapy for a year of life at the end of life with a $1 million infant gene therapy that could give 80–90 years.

- **The CRISPR babies case.**
  The edit of CCR5 to prevent HIV in IVF babies was a poor choice of use case, since sperm washing already prevents transmission. The scientific community rallied against germline editing.

OTHER RELEVANT

- **Lp(a) and FH.**
  High Lp(a) affects roughly 1 in 10 people. FH, defined by LDL cholesterol above 190 mg/dL, involves thousands of genes, so gene therapies would more likely mimic drugs, for example by switching off PCSK9.
- **Genetic cardiomyopathies.**
  They affect about 1 in 500 people. Early animal data for genetic therapies look promising, though Chung is wary of tinkering with the heart.
- **Where the line sits.**
  Current consensus is to treat the body, not edit the germline. Enhancements are 'a trigger word for we shouldn't go there.'
- **Chung's 2040 forecast.**
  She expects diagnosis to become trivial with cheap sequencing and AI. Therapies will take longer to reach people.

267 The latest in cancer therapeutics, diagnostics, and early detection | Keith Flaherty, M.D.

Guest: Keith Flaherty
Date: 2023-08-21 · Duration: 2:05:39
URL: https://www.youtube.com/watch?v=hBrTtKmcg3k

KEYPOINTS

• Cancer's share of deaths peaks in midlife

By age band, cancer causes about 6% of deaths at 25–34, 13% at 35–44, 23% at 45–54, 30% at 55–64 and 31% at 65–74. The share then falls only because heart disease and neurodegeneration take over. Cancer ranks among the top three causes of death in every decade from the mid-20s and is number one in parts of midlife. Five cancers (lung, breast, prostate, colorectal, pancreatic) account for just over half of US cancer deaths.

• Hormone-driven cancers appear when the hormones are low

Peter points out that men have their highest testosterone and DHT in their 20s to 40s, yet prostate cancer appears when levels have fallen. Breast cancer likewise doesn't peak at peak estrogen. Low-androgen prostate cancers tend to be worse, as a New England Journal paper showed about 15 years ago. Keith Flaherty's takeaway is that the biology runs deeper than 'hormone in, cancer out'.

• Obesity is the second-biggest environmental cause of cancer after smoking

About 25–27 cancers have a tight link to obesity. Peter suspects the driver is not fat itself but insulin, probably IGF-1, and the inflammation that comes with it. These effects take years to kick in, so rising obesity rates today predict more cancer later.

• Survival with metastatic solid tumours barely moved for 30 years, and has only recently started to

Ten-year survival with distant spread was essentially 0% in 1970 and about the same in 2000. The only exceptions were the 10–15% of kidney cancer and melanoma patients who responded to high-dose interleukin-2. Flaherty thinks 15% is now a conservative estimate for durable survival, moving toward 20%. He notes that 52 FDA approvals since then cover only 19 unique mechanisms, and roughly half the gain comes from the PD-1 drug Keytruda.

• PD-1 does the heavy lifting in immunotherapy

Tumours display PD-L1, 'the foot that presses on the brake' of T cells. Blocking PD-1 gives roughly 10% of all cancer patients long-term, roughly 10-year-type benefit, by Flaherty's math. Adding CTLA-4 blockade helps about a fifth of tumour types but contributes only around 1% in addressable patients on top of that.

• Most epithelial tumours are visible to the immune system

Steve Rosenberg's finding that roughly 80% of epithelial tumours carry novel neoantigens means the immune system could, in principle, take most cancer deaths off the table. Spontaneous regressions are rare but real: Rosenberg's career began after seeing a patient who had been sent home to die with metastatic gastric cancer return 10 years later, needing his gallbladder out and cancer-free.

• Cell therapies work but are hard to scale

CD19 CAR-T is the poster child: every B cell carries CD19, so lymphomas arising from B cells can be targeted. Most solid tumours lack such a clean target, so researchers are engineering cells that require two markers. TIL therapy requires surgically removing tumour, for example a wedge of lung, then growing its lymphocytes to about 10 y cells and reinfusing them with interleukin-2. That is costly and bespoke, and it often fails against the tumour's defences.

• Tumours build a 'force field' that has to come down first

Flaherty uses a Star Wars analogy: you have to take out the shield generator before attacking the Death Star. Cancers recruit suppressive immune cells and fibroblasts (notably in pancreatic cancer) and alter their own metabolism. Lasting cures will need combinations matched to each patient, not one cocktail. Peter asks what it would take, over five years, to double long-term survival with these therapies from about 20% to 40%, a number he says he is making up for illustration.

• The same drugs cure microscopic disease but not visible metastases

Stage 3 colon cancer treated with surgery and chemotherapy gives about 60–70% five-year survival. Add liver metastases and give the same drugs, and five-year survival falls to somewhere between none and a few percent, with none alive at 10 years. Flaherty's explanation is clonal: drugs kill the dominant 99% of cells, but the remaining 1% contains about 10 subclones, one of which already carries resistance. Larger tumours hold more of them. Hence his view that early detection is the problem that 'wins the game'.

• Liquid biopsies are reasonable now and will get much better

Blood tests such as Grail's (ordered by a physician) detect tumour DNA and suggest the tissue of origin. Flaherty considers testing reasonable for early adopters who can tolerate uncertain results. Peter uses Grail selectively. Methods in development are 10–100× more sensitive from the same 10–20 mL blood draw, and repeated testing over 6–18 months may be needed to locate a cancer after a positive result.

EXAMPLES

• A friend with Lynch syndrome

Peter retells the case: stage 3 colon cancer at about 40, then advanced pancreatic cancer around 2012–13 with a 6–12-month prognosis. Because Lynch syndrome tumours carry many mutations, he received anti-PD-1 therapy and went into complete remission, but now needs insulin because his immune system destroyed his pancreas.

• Screening's limited reach

Colonoscopy and mammography cut deaths from those cancers by roughly 25–30%. Peter also notes that by using 4Kscore and multiparametric MRI before biopsies, none of his patients has had an unnecessary prostate biopsy in 10 years.

• P53

P53 is mutated in about 50% of cancers, with hundreds of variants, which is one reason mutation panels for blood tests need to be broad.

- **Expert access is a lottery**
  Peter can phone Flaherty about an unusual case; most patients can't. Flaherty argues AI decision support built on outcome data could handle the 95% of typical cases and leave experts free for the edge cases.

OTHER RELEVANT

- **Prioritize early detection**
  The same therapies are far more powerful against small numbers of cells. Combine standard screening with risk-appropriate extras.
- **If you use a blood-based cancer test, have a plan for a positive result**
  Do it through a physician who can manage serial testing and imaging, not as a standalone purchase.
- **Reduce the modifiable drivers**
  Don't smoke, and address obesity, high insulin and inflammation; their effects on cancer risk build over many years.

265 - Time, productivity, and purpose: insights from Four Thousand Weeks | Oliver Burkeman

Guest: Oliver Burkeman
Date: 2023-08-07 · Duration: 2:08:51
URL: https://www.youtube.com/watch?v=B0PaNe5sb4g

KEYPOINTS

• Chasing productivity is often an attempt to avoid the emotional fact that we're finite.

Burkeman, author of Four Thousand Weeks, tried about 100 productivity systems. He kept feeling just 'a month or two' away from effortless control, then starting again with a new app or notebook. He realised the systems never gave him the emotional peace he was after, so the problem was the question he was asking. He quotes Richard Bach: we teach what we most need to learn. He says he still struggles with all of it.

• Treating time as a resource to master is a fairly modern idea, and it makes us feel at odds with time.

Philosophers have always grappled with death. But viewing time as something separate from you, to be handled efficiently, spread mainly around the industrial era. Burkeman argues that much of the stress around time comes from this view. Our most meaningful moments tend to be the ones where it falls away. He links the urge to David Brooks's 'insecure overachievers,' whose sense of worth depends on output.

• Efficiency brings in more work.

In any system with effectively unlimited demands, processing faster just attracts more. Answer email quickly and people reply to your replies, and you get a reputation that brings more email. Burkeman says he misread David Allen's Getting Things Done, which is about staying calm with too much to do, as a way to stop having too much to do.

• The 'big rocks in the jar' story is rigged.

The professor brought only as many big rocks as would fit. In real life there are always more things that truly matter than you have time for. The real skill is choosing which important things to neglect. Elizabeth Gilbert puts it this way: the true art of saying no is saying no to things you do want to do. In the (probably misattributed) Buffett story, you list 25 goals and then avoid numbers 6 to 25, the middling priorities, at all costs.

• Time is a network good, valuable mainly when shared.

Unlike money, time is more like phones: valuable because others have them too. The Soviet Union tried a staggered five-day week with colour-coded groups so factories never stopped. It meant friends and even spouses rarely shared days off, and someone wrote to Pravda that a holiday spent alone in a café isn't a holiday. Burkeman says modern flexible schedules do something similar, which is why three friends struggle to meet for a beer. Choirs, sports and families all depend on shared time.

• Seeing that the task is impossible, not just hard, is freeing.

In 2014, on a Brooklyn park bench, Burkeman was trying to schedule an impossible week. He realised it simply couldn't be done, and felt relief. Moving from 'really hard' to 'impossible' ends the self-blame. He suggests the same applies to longevity: living forever is impossible, but you can still improve your odds and the quality of your life.

• Meaning doesn't have to be cosmic.

Burkeman draws on philosopher Iddo Landau. The nihilist thinks he's facing facts but is holding onto impossibly godlike standards for meaning. You don't call a dog useless because it can't drive. Helping a friend through a crisis, parenting and being a good neighbour are real meaning on a human scale. Attia describes swinging from wanting a surgical-manual 'legacy' in residency to feeling nothing matters, and lands on mattering to his family and friends.

• Living for the future postpones life.

Burkeman quotes Keynes on the 'purposive' man who loves not his cat but its kittens, and their kittens, forever. Projecting meaning forward gives a false sense of immortality. Attia admits he spends enjoyable days thinking about the next one. Burkeman suggests 'atelic' activities (philosopher Kieran Setiya's term), such as hiking, done for their own sake.

EXAMPLES

• Three practical tools

'Pay yourself first': do some of your most important work at the start of the day, before clearing other tasks. Limit work in progress: keep an open list and a closed list of five, adding a new item only when one is finished. Watch for middling priorities. Attia kept a 'no journal' of things he wanted to do but turned down, and reviewed it with an accountability partner.

• Three hours with one painting

Harvard's Jennifer Roberts has students look at one artwork for three hours. Burkeman did it with a Dürer. Once the discomfort passed, he saw objects he'd missed for the first 45 minutes. Reading is similar: what feels like 'not liking reading' is often discomfort at slowing down.

• Stopping on a roll

Researcher Robert Boice found the most productive academic writers wrote modestly every day and stopped on schedule, even when going well. Attia now leaves 'matches in the matchbox' at the end of workouts.

• Northern Lights

Burkeman tried so hard to be present that he ended up thinking they looked like an old PC screensaver.

OTHER RELEVANT

• Act on generosity immediately

Meditation teacher Joseph Goldstein acts on a generous impulse right away. Burkeman warns that plans to become 'someone who sends three notes a week' can get in the way of sending one now.

• Being a researcher in relationships

Approach people with curiosity about how things will go, not a fixed idea of how they should. The conversation keeps the

claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Gratitude for experience itself**

  A grieving man in traffic thought about what his friend would give to be stuck there. Zen teacher Joko Beck: what makes it unbearable is the belief it can be cured.

- **Attia's desert-island test**

  Most patients say they wouldn't be happy living forever with everything except other people. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

264 Hip, knee, ankle, and foot: common injuries, prevention, and treatment options

Guest: Adam Cohen
Date: 2023-07-31 · Duration: 2:18:40
URL: https://www.youtube.com/watch?v=ovyCBmINXRE

KEYPOINTS

• Hip problems in younger adults often trace back to how the hip formed.
Cohen, a Manhattan orthopedic surgeon specializing in sports medicine, explains that hip dysplasia in infants can be corrected if caught early. In adults under 50, abnormal hip shape contributes to labral tears and early arthritis; in his practice, far more women than men under 50 have had hip issues.

• Femoral-neck stress fractures are high-risk and must not be missed.
He separates stress fractures into high- and low-risk by the consequence of mistreatment. A tension-side femoral-neck stress fracture that becomes complete can lead to a hip replacement—devastating for someone in their 20s–40s. A 28-year-old runner with new hip pain needs imaging, not reassurance.

• Hip replacement has become remarkably successful.
Once a debilitating operation 30 years ago, it is now often outpatient, with satisfaction rates around 90–95% and low complications—which is why Cohen weighs cortisone and other temporizing measures against simply replacing a worn-out hip.

• Hip fractures in older adults are deadly, and the numbers haven't improved.
For people 65+ who fracture a hip, one-year mortality is about 15–30% depending on the study—roughly 20–30% for decades despite faster surgery—and about half of survivors lose a level of function, such as moving from no aid to a cane. Strength around the hips and bone health are the prevention.

• PRP evidence is mixed: decent for tennis elbow, weak for hip arthritis.
Platelet-rich plasma contains 800–1,000 plasma proteins; preparations vary, so 'dose' is undefined. Tier 1–2 evidence supports PRP for tennis elbow, but it doesn't seem to work well in hip arthritis. Saline injections also help some patients in trials, underscoring placebo effects.

• Stem cell marketing is largely inaccurate.
A study by NYU colleagues of about 1,000 websites promoting stem cell therapy found 94% made inaccurate statements, such as guaranteed new cartilage. Cohen advises skepticism toward '100% guaranteed' claims.

• An ACL tear raises arthritis risk whether or not it's reconstructed.
About 50% of people with an ACL tear develop significant knee arthritis within 15–20 years, and surgery doesn't seem to change that. One analysis suggested treating about 90 people to save one ACL. Any mechanical trauma to a joint raises arthritis risk; a shoulder dislocation makes shoulder arthritis 10–20 times more likely.

• Graft choice depends on age.
Reconstruction often uses the central third of the patellar tendon (about 10 mm of a ~30 mm tendon, with bone plugs from kneecap and tibia). Under about age 34, allograft (donor) tissue has unnecessarily high re-rupture rates; for a hiker in their 40s, allograft is reasonable.

• Knee replacement satisfaction lags behind hips.
About 85% of knee-replacement patients are satisfied—meaning 15% aren't. Recovery is nonlinear: about 80% of improvement comes by six months, with continued gains up to a year. Cohen sees patients about 10 days after surgery; many walk without a cane.

• Tendon degeneration is part of aging.
You may not be able to do everything you did at 20–30 because tendon degeneration is a biological process affecting everyone; cortisone can harm tendons, and Cohen has seen problems after a single dose.

• Save the meniscus when you can; sham-surgery studies don't apply to everyone.
The meniscus spreads force across the knee, so losing it accelerates arthritis—especially in knock-kneed or bow-legged people who already overload one compartment. Peripheral tears with good blood supply can be sewn back; bucket-handle tears can flip into the joint. Cohen says the sham-surgery trials showing no benefit studied degenerative tears in arthritic knees; a young person with a repairable tear and no arthritis should strongly consider fixing it.

• Arthritis often 'flips' from silent to painful after a minor event.
Cartilage wears away slowly as a low burn; then a stumble, a twist while lifting or a small further meniscus tear tips the joint into a painful, inflamed state. That's why patients often blame a trivial event for long-developing disease.

EXAMPLES

• Cohen's son's hips
His infant son was diagnosed with hip dysplasia and wore a brace 23 hours and 45 minutes a day—hell on his wife—but nine months later his hips were fine.

• Living without an ACL
Cohen tore his ACL and meniscus at 14 in the 1980s, rehabbed instead of reconstructing, lived actively from 15 to 30 with only occasional swelling, and had surgery after his fellowship—a bucket-handle meniscus tear included.

• The cyclist with a femoral-neck fracture
A 40-year-old crashed on the West Side Highway and broke his femoral neck; when a resident told him he had a 30% chance of dying that year, Cohen had to explain those statistics apply to frail older patients.

• A marathon on a new knee
A patient around 50 ran a marathon after total knee replacement, knowing the risks. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Good mechanics matter more than load for joints.**
  Cohen describes an athlete squatting enormous loads safely with perfect mechanics. Running itself isn't inherently bad for knees; mechanics, strength and prior injury matter more.

OTHER RELEVANT

- **Investigate new deep hip or groin pain in active people.**
  Stress fractures can be catastrophic if missed. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Strengthen hips and bones to prevent fractures.**
  Given 20–30% one-year mortality after hip fracture, strength, balance and bone density are priorities.
- **Be skeptical of biologic injections.**
  Ask what evidence supports PRP or stem cells for your specific condition; avoid guarantees.
- **Vet your surgeon.**
  Ask how often their patients get infections, need reoperation or still have pain a year out.
- **Young with a meniscus tear? Ask about repair.**
  If you don't have arthritis, preserving the meniscus may protect the knee for decades; don't assume 'surgery doesn't help' studies of older, arthritic knees apply to you.

263 Concussions and head trauma: symptoms, treatment, and recovery | Micky Collins, Ph.D.

Guest: Micky Collins
Date: 2023-07-24 · Duration: 1:29:47
URL: https://www.youtube.com/watch?v=CBqBNCHOe2Q

KEYPOINTS

• A concussion is an energy crisis at the cellular level, not a structural injury.

Collins explains that when the brain shifts inside the skull, neuron membranes stretch. Potassium leaks out of the cell, raising demand for glucose so ATP can pump it back. At the same moment calcium floods in, causing vasoconstriction and reduced cerebral blood flow. Demand rises just as supply falls, a metabolic mismatch. The cells don't die; they run less efficiently. Standard imaging shows no structural change, and he says no reliable biomarker exists yet or is likely soon.

• There are six types of concussion, and treatment depends on which system is failing.

Collins lists cognitive fatigue, vestibular (the central brain pathways, not the inner ear), ocular (the eyes working as a team), migraine, anxiety/mood and, less often, cervical (neck). Patients can have one or all six. In his clinic's data the most common profile is anxiety, then migraine, vestibular, ocular and cognitive fatigue. His job, he says, is to find which system is 'decompensated' and target it.

• On-field dizziness predicts a slow recovery better than loss of consciousness.

Collins challenged Attia to name the strongest on-field predictor of long recovery. Attia guessed loss of consciousness, which was wrong. Dizziness was about six times more predictive of a recovery lasting a month or more, and fogginess ('feeling one step behind') came second. He notes that athletes who lose consciousness are always pulled from play, while dizzy athletes often keep playing.

• Playing through symptoms dramatically lengthens recovery.

In a retrospective study of about 300 kids, those removed from play right away recovered in an average of 18 days. Those who kept playing for just 15 minutes after symptoms began took 44 days. A follow-up dose-response analysis found that each minute played through the injury added roughly seven to eight days. He admits it wasn't randomized but says the gap is too large to ignore.

• Personal history shapes which pathway a concussion takes.

A history of migraine sends patients down the migraine pathway with less force. Car sickness predicts vestibular problems. Lazy eye or strabismus predicts ocular problems, and prior anxiety predicts the anxiety profile. Attia calls it 'concussive reserve.' Age matters too: high school athletes recover slowest, college athletes next and professionals fastest.

• Females are more vulnerable and recover more slowly.

Girls are more likely to be concussed than boys. Collins points to neck strength and hormones, and girls are about six times more likely to have migraine and car sickness. About 60% of his clinic's patients are female. His group has shown that menstrual cycles change after head injury and is starting a women's study on hormonal effects.

• Rest is the wrong treatment; targeted exposure is the right one.

The old advice was to rest an injured, energy-starved brain. Collins says that makes things worse. Anxiety is treated by exercise and regular sleep, which raise parasympathetic tone, and vestibular problems are treated by retraining. His clinic uses aggressive 'exertion therapy' plus exposure to busy environments. He stresses that this must be guided by a specialist, because the wrong approach can make patients worse.

• Early specialist care is the strongest predictor of good outcomes, but late cases are still treatable.

Across all the factors studied, being seen in the clinic within seven days best predicted recovery. Red flags such as an intracranial bleed must be ruled out first. Collins still says patients one to three years out can usually be treated effectively, and he follows patients every three to four weeks until they're normal.

• Medications are secondary and target the root problem, not downstream symptoms.

He tries behavioral treatment first. He avoids trazodone for sleep because the insomnia stems from nervous-system arousal. When drugs are needed, he says sertraline can help both vestibular and anxiety profiles, and he sometimes uses tricyclics, Wellbutrin, Effexor or escitalopram, often with an in-house psychiatrist. Untreated arousal can ripple outward. Attia asks about hypogonadism as one downstream example.

• Evidence on long-term brain disease is unsettled; the CTE picture suffers from selection bias.

Collins cites work from Grant Iverson's group, linked to Mass General, showing some relative increase in anxiety but no clear tendency toward dementia, Lewy body or other neurodegeneration after concussion. CTE brain-bank studies, he says, rely on people who donated brains because they had problems. UPMC is about two and a half years into a controlled study using neuropsych testing, imaging, lumbar punctures, CSF biomarkers and sleep studies. He also says there is no compelling evidence that APOE4 raises concussion risk.

EXAMPLES

• The race-car driver from Phoenix

Collins saw him the morning of the recording. He had a concussion in a crash, then a second crash with the same mechanism two weeks later. Two years on he had a vestibular profile with light and noise sensitivity, fog, dizziness with exercise and insomnia. He was no longer racing or working and had become reclusive. His plan: vestibular exercises morning and night, a 45-minute walk each morning, a 45–60-minute workout in the afternoon, fixed wake and bed times with no napping, and daily exposure to grocery stores, restaurants and parties.

• A cyclist who couldn't be in a room with a TV

Attia describes someone close to him riding at about 25 mph (40 km/h) who collided head-to-head with a runner who darted between cars. The runner fractured his face. The cyclist spent two years unable to tolerate a TV or noise, which Collins says is the classic vestibular-to-anxiety-to-migraine spiral.

• Equestrians, not boxers

Asked which sport carries the highest lifetime concussion risk, Attia guessed boxing. Collins says about 90% of equestrians suffer a concussion over their careers, from falls off a large animal. Football leads in raw numbers, women's soccer and basketball are also high, and the US sees about 1.8–3.6 million sports and recreation concussions a year.

• A 90-year-old who fainted

An elderly patient had a syncopal episode, likely from dehydration and stress, fell face-first off the toilet onto a linoleum floor and suffered a facial fracture, a small subdural bleed and a bad concussion. Eight weeks later the patient was highly motivated and was given walking plus balance and vestibular work after a fall-risk check.

• Nick Saban said yes

As a student, Collins asked Michigan State's medical staff about studying the football team and was sent to the head coach, Nick Saban, who approved it. The data fed a 1999 JAMA paper on college football. Collins started at UPMC in 2000 seeing two or three patients a week. The program now has about 20,000 visits a year and has trained 33 fellows.

OTHER RELEVANT

• Pull athletes at the first sign of dizziness or fog.

Teach kids and parents that sideline dizziness, fogginess, fatigue or blurred vision means stop now, because each extra minute may add days of recovery.

• Get seen early by a concussion specialist, not just any neurologist.

Collins says general neurologists and neurosurgeons often don't know this field. Specialty clinics now exist in most major areas, though rural access may be limited. Mild symptoms that are improving may not need a visit unless you risk another head hit soon.

• Expect an active plan: exercise, regular sleep, structured exposure.

Avoid prolonged dark-room rest and rumination. Treatments should be targeted to your profile and supervised.

• Be wary of unproven add-ons.

Collins won't prescribe hyperbaric oxygen because he sees no data showing it helps and says it feeds symptom-seeking. Attia adds the opportunity-cost argument: exercise time beats chamber time. Exogenous ketones at the time of injury are theoretically interesting, but neither knows of supporting human research.

261 Training for The Centenarian Decathlon: zone 2, VO2 max, stability, and strength

Date: 2023-07-10 · Duration: 1:11:27
URL: https://www.youtube.com/watch?v=NivjpZ0VBro

KEYPOINTS

• Exercise is the highest-leverage longevity tool for most people

Peter's view: if everything in your life is a 6 or 7 out of 10, raising exercise to a 10 does more for both length and quality of life than improving any other area. He says he would keep training even if it shortened his life by a year, purely for the quality of the years he has left. Severe problems like malnutrition still come first.

• Plan for the 'marginal decade' by training for specific late-life tasks

The marginal decade is the last decade of life, and for most people it is a period of poor health and function. The Centenarian Decathlon is a list of about 10 physical tasks you want to be able to do then, picked from about 50 options: about half are daily activities and half are feats of fitness. Peter's wall chart targets his late 80s, not 100.

• Peter's own list is concrete and measurable

His list includes picking up a 30 lb child from a squat or a crib, getting up off the floor with one point of support, lifting a 30 lb suitcase overhead and dead hanging for 30 seconds. It also includes a 1-minute farmer's carry with 25% of body weight in each hand, carrying 20 lb up four flights of stairs, pulling himself out of a pool onto a deck 12 inches above the water and drawing a 50 lb bow. Some items, such as a hex-bar deadlift of his body weight for five reps, are deliberately ambitious.

• Work backwards: today's targets must allow for the decline

Strength and VO2 max drop predictably with age. To still have a VO2 max of 30–32 mL/kg/min in 30–40 years, Peter, whose VO2 max is in the low-to-mid 50s, has to work hard now. That makes the bar even higher for someone 20 years younger. His archery analogy: practise at 100 yards and 50 becomes easy.

• Benchmarks for strength and grip

For a man in his 40s, the farmer's carry target is half his body weight in each hand for one minute (90 lb per hand for a 180 lb man). For a woman, it is about 75% of that. The dead-hang target is 2 minutes for men and 1.5 minutes for women in their 40s, minus about 10–15 seconds per decade. A 2-minute wall sit, thighs parallel and hands off, is another test. A VO2 max test costs about $100–150, and field tests can estimate it for free.

• Appendicular lean mass is a long-term record of training

Appendicular lean mass index (ALMI) is limb lean mass (kg) divided by height squared, taken from a DEXA scan. Peter wants patients at or above the 75th percentile for age and sex. He likens it to hemoglobin A1c: just as A1c reflects average glucose over three months, ALMI and VO2 max reflect years of training. He admits the link to outcomes is associative but strong.

• Minimum effective dose: about three hours a week if starting from nothing

Going from nothing to about 3 hours a week is an enormous improvement. A rough split: about 1 hour of steady zone 2, 1 hour of strength training, 20–30 minutes of VO2-max-style intervals across one or two sessions, and the remaining 30–40 minutes spent on stability in 10-minute daily chunks. Daily short stability work beats one long weekly session. Shift the balance based on weak spots, such as a strong lifter whose aerobic fitness is 'an atrocity'.

• Sports are great, but not a complete program

Tennis, basketball and weekly weights put you ahead of most people. But sports involve repetitive, asymmetric stress, such as a golf swing, which builds movement problems and imbalances over decades. So add deliberate training to counteract them.

• Split cardio roughly 80/20 between zone 2 and VO2 max

Both recreational athletes and elites follow about 80/20, and some elites run close to 90/10. Peter now does 4–5 hours of dedicated cardio a week, down from 14–20 hours in the past and not counting rucking. That includes four zone 2 sessions of 45–60 minutes. Following Iñigo San Millán's advice, sessions of at least 30–45 minutes are better spread across the week.

• Define zone 2 by lactate or effort, not heart-rate minutes

Zone 2 is the point just before you can no longer speak comfortably while exercising, roughly where lactate starts to accumulate. Heart rate is 'generally the worst approximation'. Forty-five minutes of heart-rate zone 2 scattered across a 3-hour ride is not physiologically the same as a steady 45-minute block. Good options include a bike, rower (if your form holds), stair climber, or brisk walking for beginners.

EXAMPLES

• VO2 max intervals

Intervals of 3–8 minutes work best. Peter's preferred workout is 4 minutes on and 4 minutes off, starting at about 105% of the target wattage. It should feel easy at first and very uncomfortable by minute three. Progress means more power for the same 4 minutes, for example going from 150 to 175 watts without gaining weight. Short studies suggest limited gains, but over a lifetime VO2 max can rise about 50%.

• Older women lifting heavy

In an Australian trial, women with osteopenia or osteoporosis, mostly in their 70s, lifted real weights. One reportedly deadlifted her own body weight, about 120 lb. Peter also cites Barry from Outlive, who traded health for wealth, retired in pain and now functions better than he did 20 years earlier.

• Bone density

Bone density peaks in the early 20s. Women lose estrogen sharply in midlife, so they face greater risk of osteopenia and osteoporosis. After that peak, heavy load-bearing work slows decline; walking doesn't count.

• His own early marginal decade

A back injury at 28 left Peter unable to walk for three months and in severe pain for about a year. He says this gave him an early taste of what lost function feels like.

OTHER RELEVANT

- **Write your own list of 10**
  Pick a mix of daily activities and fitness feats you want to manage in your 80s. Then work out what you need today to still be able to do them after the expected decline.
- **Don't let an injury stop all training**
  Work around it and get proper rehab. Peter told a friend whose shoulder hadn't improved in 6 months that it won't magically heal by 70, so it's worth investing in fixing it now.
- **Track progress with simple metrics**
  Watch your zone 2 output (watts or pace at the same effort), your 4-minute interval power, carry and hang times, and ALMI on DEXA.

260 Men’s Sexual Health: why it matters, what can go wrong, and how to fix it

Guest: Mohit Khera
Date: 2023-06-26 · Duration: 2:42:02
URL: https://www.youtube.com/watch?v=GNCpG1fkMBA

KEYPOINTS

• ED is common and largely untreated because of silence on both sides.
Khera, a Baylor urologist specialising in sexual medicine, cites a 1994 study finding about 52% of men over 40 have some ED. A rough rule: 40% at 40, 50% at 50, 60% at 60. He attributes this to accumulating health conditions more than age itself. In a recent survey of 1,500 men, about 40% had some sexual dysfunction, but only 51% had told their doctor and 44% their partner, mostly out of embarrassment. Busy primary-care doctors rarely ask. About a third of men with ED report depression and 37% anxiety because of it.

• First, tell psychological from physical ED.
Two screening questions: can you get an erection firm enough for penetration, and can you keep it until orgasm? Normal morning erections or erections during masturbation suggest a psychological cause, common in younger men, where anxiety ('I hope I don't lose it') becomes self-fulfilling. Khera uses sex therapy and daily tadalafil 5 mg to break the cycle, then often stops it. Physical causes follow the mnemonic VENT: vascular, endocrine, neurologic, trauma, plus medications like beta blockers and finasteride.

• Most physical ED starts as a 'venous leak.'
Erections depend on nitric oxide and cGMP; PDE5 inhibitors stop the enzyme that breaks cGMP down. As erectile muscle atrophies and scars with age (low testosterone and disuse contribute), the tissue can't press the veins closed, so blood flows in but won't stay. PDE5 drugs raise inflow to overcome the leak; constriction bands reduce outflow. Avanafil has the least effect on related enzymes (PDE6 affects vision, PDE11 the back) but isn't generic.

• Khera prescribes daily tadalafil as both prevention and treatment.
An as-needed pill treats one night while the disease progresses. Studies he cites suggest daily low-dose tadalafil helps maintain erectile muscle, and improved blood-vessel function persisted after stopping in a study by Aversa. 5 mg daily equals roughly 8 mg in steady state (a 1.6× multiplier). It's also FDA-approved for enlarged prostate, without the retrograde ejaculation of Flomax. Don't take it close to Flomax, which can drop blood pressure. Generic tadalafil can cost about $17 for 90 pills.

• ED is an early warning of heart disease.
In the Prostate Cancer Prevention Trial follow-up by Ian Thompson (2004), 15% of men who developed ED had a heart attack or stroke within seven years. In another study, about 50% of men with a cardiac event had ED roughly 39 months earlier. Endothelial dysfunction is the shared mechanism. In Esposito's 2004 JAMA trial of 110 obese men, a Mediterranean diet plus exercise raised ED scores by about 3 points without medication. Attia sees erections improve when patients' HbA1c falls from about 5.9 to 5.

• Peyronie's disease affects 7–9% of men and is usually linked to unnoticed trauma.
Scar plaque, often on the upper side of the shaft, causes curvature. Above 60° makes intercourse difficult. In the first year, about 15% improve, 40% stay the same and 45% worsen, so Khera waits until it stabilises before surgery. Collagenase injection (Xiaflex, 2015) is the first FDA-approved drug; vitamin E and colchicine don't work. The RestoreX traction device, used 30 minutes twice daily for 3 months, improved curvature 30–40% and can add up to about 2 cm in length (off-label, about $500). In a 2009 study, 74% of Peyronie's patients had low testosterone.

• Testosterone: treat symptoms, not just a number, and protect fertility.
Khera says total testosterone stays fairly flat in healthy men as they age, while SHBG rises and free testosterone falls. He prefers calculated free testosterone and notes androgen-receptor sensitivity varies genetically. He and Attia both decline to treat patients without symptoms. For injections he uses 50 mg cypionate under the skin twice a week (Sunday/Thursday, about $25/month), which causes less blood thickening than large doses every two weeks. Clomid raises levels but blocks estrogen, which men need for libido, in about 40%. Low-dose HCG (500 IU every other day) alongside testosterone helped preserve testicular function in Baylor studies. Nasal testosterone (Natesto) appears not to suppress sperm much.

• Khera avoids finasteride and considers post-finasteride syndrome real.
He notes that 5; ×&VGV7F 6R Ç6ò 6öàverts progesterone into allopregnanolone, a neurosteroid linked to mood and cognition. In his study of 25 men with persistent symptoms, two died by suicide. He acknowledges this is a minority view, and Attia notes randomised trials or better comparison groups are needed. For enlarged prostate he uses alpha blockers (alfuzosin has the least retrograde ejaculation) or daily tadalafil instead.

EXAMPLES

• Priapism
An erection lasting more than 4 hours needs the ER; after about 36 hours recovery is unlikely. Causes include over-dosing injections, trazodone and cocaine. Treatment: phenylephrine, draining old blood, then surgical shunts. A penile implant should go in within about 3 months, before scarring.

• Penile implants
Invented in 1973. Saline cylinders with a pump in the scrotum. Khera does about 60 a year with an infection rate near 1%, and advises choosing a surgeon who does at least 50.

• Shockwave and stem-cell clinics
Cheap radial 'shockwave' machines charge $500–$1,000 a session and, in his view, do nothing. Proper electrohydraulic or electromagnetic devices are still investigational but promising for mild–moderate ED. About 30% of men respond to placebo. No placebo-controlled stem-cell ED trial exists; his 30-man trial gained about 4 points for 6–9 months.

• Premature ejaculation
Affects up to 30% of men; about 9% of them seek care. Treatments include lidocaine spray, SSRIs (paroxetine strongest), and sex-therapy techniques (start-stop, squeeze), which can cure it. Tramadol works but is addictive. If ED and PE occur together,

treat the ED first.

OTHER RELEVANT

- **Testosterone and prostate cancer**
  The 2018 AUA guideline says there's no established link. Hopkins' bipolar androgen therapy and TRANSFORMER trial used high-dose testosterone in advanced prostate cancer, with similar survival to enzalutamide and better quality of life.
- **PSA saturation**
  PSA rises with testosterone only up to about 250 ng/dL, then levels off.
- **Orals and topicals**
  Oral undecanoate must be taken with food. Khera dislikes gels: about 20% of men barely absorb them, and they can transfer to others.
- **Testosterone reversal protocol**
  For men who want children after years on testosterone: HCG 3,000 IU plus FSH 75 IU three times weekly; sperm often returns in 3–7 months.

259 - Women's sexual health: Why it matters, what can go wrong, and how to fix it

Guest: Sharon Parish
Date: 2023-06-19 · Duration: 3:10:54
URL: https://www.youtube.com/watch?v=goLKqjUT93Q

KEYPOINTS

• Women's sexual medicine is a tiny field relative to the need

Sharon Parish has practised sexual medicine for about 30 years. She estimates the field's main annual meeting draws 500–600 people, which is probably most of the clinicians who work in it. By contrast, she jokes that the roughly 20,000 urologists at the main urology meeting all think they could handle a man's sexual problem. In the large PRESIDE survey (31,000 women aged 18–99), distressing low desire affected about 10–15% and distressing orgasm problems about 3–6%.

• Sexual function is linked to vascular and metabolic health

Peter treats erectile problems in men with prediabetes, for example an A1c of 5.9, as an early warning of blood-vessel disease. Parish says the 'female genital vascular district' may play a similar role in women and be a window into small-vessel disease, though the evidence is still being gathered. Metabolic syndrome, diabetes and obesity are associated with poorer sexual function in women too.

• Desire and arousal are different, and desire often follows arousal

Using Rosemary Basson's circular model, Parish explains that many women in long relationships don't feel spontaneous desire. Instead they start from neutral, and desire builds once arousal begins. Her first case, a married mother of two in her late 30s or early 40s who loves her partner but 'doesn't want to have sex', needs a full history covering sleep, stress, relationship, mood, menstrual and gynecologic history, and medications before any drug is considered.

• Antidepressants are a major, dose-dependent cause

About 30–40% of people on SSRIs or SNRIs develop treatment-emergent sexual dysfunction. Venlafaxine acts mostly like an SSRI at low doses (up to about 75 mg) and like an SNRI above about 100–150 mg. Parish says the best data for the fewest sexual side effects is for vilazodone, though the drug has its own drawbacks.

• Birth control pills can lower desire by raising SHBG

Every woman on combined oral contraceptives has a higher SHBG level, which binds testosterone. Ultra-low-dose (20 µg) pills are more strongly implicated than 35 µg pills. Claudia Panzer's study found that six months after stopping, former users' SHBG levels were still between those of current users and never-users. Parish wants informed consent about this before prescribing the pill, and often suggests switching to an IUD.

• Testosterone matters for women's desire, and the evidence is substantial

Women's testosterone at 18–24 roughly halves by the late 30s or early 40s, then levels off. A 2019 Lancet meta-analysis of 46 studies, 36 of them randomized, covering about 8,500 women, supports testosterone for low desire in postmenopausal women. A 300 µg patch (Intrinsa) raised testosterone and improved sexual function without worrying side effects, yet the FDA didn't approve it. Australia has an approved product, through Susan Davis's work.

• US women must improvise testosterone dosing off-label

Parish treats the syndrome, hypoactive sexual desire disorder, not a lab number. She checks baseline testosterone to rule out high levels and aims for physiological reproductive-age levels, about one-tenth of a male dose. In practice that means a roughly $200 tube of 1% gel divided into 10 piles, with blood levels checked after 3–4 weeks. She calls this 'not the kind of medicine I want to practice'.

• Two FDA-approved drugs exist for premenopausal women with low desire

Flibanserin is a daily 100 mg pill taken at bedtime that acts on serotonin and dopamine receptors. It carries an alcohol warning that has since been relaxed, and works in about 4 weeks (allow 8–12). Bremelanotide is a self-injected auto-injector used about 45 minutes before sex. About 40% of users get transient nausea on the first doses, it causes small rises in blood pressure, and rarely (about 1%) it causes focal hyperpigmentation, so she suggests no more than four doses a month.

• Orgasm problems are usually about knowledge and technique

Parish's rough split: about 30% of women reach orgasm through clitoral stimulation, about 30% through vaginal stimulation, and about 30% through either. For a 30-year-old who has never had an orgasm, she starts with education: anatomy, self-exploration, vibrators and communicating with a partner. She points patients to the OMGyes educational site (about $40 for standard programs).

• The fear of hormone therapy is largely unfounded

Parish says that even in the Women's Health Initiative, the increase in breast cancer incidence with conjugated equine estrogen plus MPA was only about 0.1% in absolute terms, with no increase in breast cancer deaths over 20+ years. Estrogen alone was associated with fewer breast cancers. Women aged 50–59 differ greatly from older starters. Hormone therapy can cut hot flashes by about 75–80%, and she calls the generation of women denied it a 'real tragedy'.

EXAMPLES

• Postpartum hormones

Breastfeeding can push estradiol down to postmenopausal levels (20–30 pg/mL), causing dryness and pain. Addressing vulvar and vaginal symptoms is often simple.

• A menopausal case

Two years after menopause (estradiol about 10, FSH about 75), Parish would discuss systemic hormone therapy (transdermal options with endometrial protection, possibly via a hormonal IUD) alongside local treatment.

• Genitourinary syndrome of menopause is progressive

Vulvar and vaginal tissue atrophy affects everyone after menopause to some degree. Local vaginal estrogen (creams, rings, inserts, tablets) or vaginal DHEA (Intrarosa) work, with no clear difference in effectiveness. Many women reach a threshold at

65–70 where lubricants are no longer enough.

- **Ageism in older women**
  Parish sees women in their 70s, 80s and 90s who want to stay sexually active. A man of 80 asking for an erectile-dysfunction drug is accepted, but a woman asking for help often isn't.

OTHER RELEVANT

- **Raise the topic with your clinician**
  Sexual problems are common, treatable and tied to overall health. If your doctor won't engage, seek out a sexual-medicine specialist or a pelvic floor physical therapist.
- **Review medications first**
  Check antidepressants and hormonal contraception before anything else. Switching contraceptive type or adjusting an antidepressant can help.
- **Don't wait for tissue damage after menopause**
  Starting low-dose local vaginal therapy early helps prevent painful sex and urinary symptoms later.

257 Cognitive decline, neurodegeneration, and head injuries: mitigation and prevention strategies

Guest: Tommy Wood
Date: 2023-06-05 · Duration: 2:20:33
URL: https://www.youtube.com/watch?v=zKFEUV911Zw

KEYPOINTS

• Some cognitive slowing with age is normal; dementia is an accelerated departure from that curve.
Attia describes names that come back ten minutes late, something he didn't notice in his late 30s. Tommy Wood, a physician-scientist whose interests span lifestyle medicine, brain health and performance, separates this ordinary age-related drift in processing speed and recall from the steeper decline some people experience on the way to a dementia diagnosis. The goal of prevention is to stay on the gentle slope.

• The brain responds to the right kind and amount of demand.
Wood argues cognitive function is use-dependent: novel, effortful and complex tasks build capacity, while retiring from all demand ('I'm 65, I'm done with spreadsheets') removes a key stimulus. Much of the evidence is observational, though he notes some interventional trials in older adults. There is also a threshold: overload, like Attia's unproductive 10 minutes of distracted work, achieves nothing.

• Task-switching carries a real cost.
Refocusing after a switch takes on the order of 20-plus seconds, so someone changing focus every minute or two spends much of their time re-orienting. Wood suggests short blocks of single-task focus (perhaps 20–30 minutes) and walking breaks rather than constant juggling.

• Formula 1 is a model of performance under extreme cognitive load.
Drivers hit straight-line speeds of roughly 200–220 mph while managing dozens of settings on the steering-wheel computer, and the jump in car complexity from F3 to F2 to F1 is large. Wood, who works in this environment, says the demands make it a natural laboratory for multitasking capacity and recovery.

• Alzheimer's is probably many diseases leaving the same 'tombstone'.
Wood questions the amyloid-and-tau-centric view, noting that even Alois Alzheimer reportedly doubted whether his cases belonged together and that later genetic analyses of the original patient conflicted (one 2013 report claimed a PSEN1 mutation, another sample found none). His unifying view: homocysteine, poor omega-3 status, glucose hypometabolism and microvascular disease converge on a final common pathway of neuronal damage, with plaques and tangles as the residue.

• Research money is skewed away from modifiable risk.
Wood cites the 2020 Lancet Commission estimate that about 40% of dementia may be attributable to modifiable risk factors, yet funding concentrates on late-stage pathology. He also notes the factors interact, so population-attributable risks shouldn't simply be added up.

• Lowering homocysteine slows decline and brain atrophy, especially with good omega-3 status.
Elevated homocysteine has a suggested population-attributable risk around 20% for late-onset Alzheimer's. In the VITACOG trial (B12 and folic acid), lowering homocysteine slowed cognitive decline and atrophy, but atrophy slowed only in those in the top tertile of omega-3 status, and a Dutch study (B-PROOF) pointed the same way. Wood's evidence-based cutoff is 11 µmol/L; Attia's clinic targets 8–9 even though lab ranges call 13–14 normal.

• Poor omega-3 status may account for a similar share of risk.
Another roughly 20% attributable risk has been assigned to low marine omega-3 intake. Both homocysteine and the omega-3 index are cheap and easy to measure. Wood frames moving homocysteine from 13–14 down to 9–10 while taking about 1–2 g/day of DHA as a potential 'winning lottery ticket', while stating it's not certain.

• Strength is one of the strongest protective associations.
Comparing the strongest roughly 10% of people with the weakest 10%, Wood cites about a 70% lower incidence of and mortality from all-cause dementia. Grip strength is a proxy for whole-body strength, and resistance training in people in their 70s improves brain measures, likely through multiple pleiotropic effects.

• After a TBI, the first 24–72 hours are about preventing fever.
Fever worsens secondary injury. Therapeutic hypothermia (33.5°C for three days) is standard for newborns with birth asphyxia, but in adult TBI the benefit seems to come from keeping core temperature at or below about 36.5°C. Wood suspects the early neonatal trials partly looked good because control babies were warmed quickly and left feverish.

• Hyperbaric oxygen is risky early and unproven later.
Attia calls much of the hyperbaric industry 'a racket' outside indications like wound healing. Wood says that in the acute phase, extra oxygen in an inflamed, impaired brain may drive oxidative stress, and he has heard of unpublished work showing more adverse effects; any trial in the chronic phase would wait at least a couple of weeks, with only pilot data so far.

EXAMPLES

• A crash and a two-year concussion
Wood describes a cyclist colleague hit at about 40 km/h whose concussion was so severe he wasn't himself for about two years, which pushed Wood into head-injury research.

• Angry Birds vs. Mario 3D
In a training study, playing a 3D game (Super Mario 3D) improved working memory and some response inhibition more than a 2D game, which Wood uses to show that novelty and complexity matter.

• Creatine loading as neuroprotection
Pre-loading creatine in rodents (equivalent to about 0.2 g/kg, or roughly 20 g/day for a week in humans) was significantly neuroprotective before a TBI. In people, 20 g/day for a week raises brain creatine on magnetic resonance spectroscopy, while 5

g/day eventually gets similar levels.

- **'37 of them are garbage'**
  Attia says patients arrive with 40 supplements and usually only about three are worth it; Wood's evidence-backed short list covers folate, B12, B6, EPA and DHA.

- **F1 forces prioritization**
  With 23 races a season, a driver will do only a few interventions, so Wood must be sure each one is worth more than the 99 alternatives. Solo endurance athletes, by contrast, will do 'all 100 things'.

OTHER RELEVANT

- **Test homocysteine and the omega-3 index.**
  Aim for homocysteine below about 11 (Attia targets 8–9), using methylfolate, methyl-B12 and sometimes B6, and consider around 1–2 g/day of DHA. These are reasonable but not proven to prevent dementia.

- **Keep the brain under the right demand.**
  Pick novel, challenging tasks, work in focused single-task blocks and avoid constant switching. Don't retire your brain when you retire.

- **Build strength across life.**
  Resistance training works even in your 70s and ties to dementia risk and survival; you can't jump from the bottom to the top in a year, but you can climb.

- **After a head injury, prevent fever.**
  Keep core temperature at or below about 36.5°C in the first 24–72 hours; be skeptical of early hyperbaric oxygen.

- **Consider creatine for high-risk athletes.**
  Wood sees a case for prophylactic creatine (5 g/day or a 20 g/day loading week) and post-injury creatine, DHA and choline, while noting much of it is preclinical.

256 The endocrine system: exploring thyroid, adrenal, and sex hormones | Peter Attia, M.D.

Date: 2023-05-29 · Duration: 0:57:36
URL: https://www.youtube.com/watch?v=5oxFK6poSXM

KEYPOINTS

• The thyroid mostly makes inactive T4, which has to be converted to active T3

The hypothalamus releases TRH, which drives the pituitary to release TSH, which drives the thyroid to make mostly T4 (four iodines) and a little T3 (three). T3 does the work: keeping you warm, supporting metabolism, and maintaining hair, nails and bowel function. Deiodinase enzymes D1 and D2 remove an iodine to turn T4 into T3. D3 turns T4 into reverse T3, which Peter describes as 'anti-T3' because it blocks T3's effects.

• Reverse T3 rises sharply in some states, including fasting

Peter says his free T3 to reverse T3 ratio can fall from a normal of about 0.25 to 0.05 or below in a 5–7-day fast. He measured this before and after week-long fasts, and most of the drop came from rising reverse T3. Insulin resistance and low-grade inflammation can also shift conversion toward reverse T3, down-regulating D1 and D2 and up-regulating D3.

• Why some patients feel worse on standard T4 therapy

The textbook approach is to give a patient with a TSH of 6–7 about 75 µg of T4 and expect TSH to fall to 2–3 and symptoms to improve. Often that works. But if conversion is skewed, the extra T4 just becomes more reverse T3, so TSH looks better while the patient feels worse. For them Peter adds T3 directly, bypassing the faulty conversion step.

• How Peter gives T3

Standard immediate-release T3 (Cytomel) is hard for many patients to tolerate. He prefers compounded controlled-release T3, typically 10–30 µg, taken in the morning so it lasts through the day and fades by evening. Desiccated thyroid contains both hormones at a fixed ratio (about 4.2 units of T4 to 1 of T3), which suits some people. He usually prescribes T4 and T3 separately so each can be adjusted.

• Test more than TSH when symptoms are present

He orders TSH, free T4, free T3 and reverse T3 to infer what the deiodinases are doing. If TSH, T3 and T4 are normal and the patient has no symptoms, he skips reverse T3.

• Measure free cortisol and its metabolites over the day in urine

Most cortisol in the blood is bound to proteins, and only the free fraction acts. Peter uses the four-sample DUTCH urine test, which captures free cortisol and cortisone across 24 hours plus their breakdown products (alpha- and beta-tetrahydrocortisol, tetrahydrocortisone). Those breakdown products show total adrenal output, which a blood test can't. The healthy pattern peaks a couple of hours after waking and is low at bedtime.

• 'Adrenal fatigue' is mostly a misnomer

People who feel run down may have low free cortisol, but when total metabolized output is counted, most have ample production. The problem is often the enzyme 11;"Ô…4@, which converts between active cortisol and inactive cortisone. Insulin resistance, obesity, inflammation, low thyroid function and leptin resistance push toward cortisol. Steroid use, hyperthyroidism, progesterone, PCOS and supplements like curcumin push toward cortisone. Peter calls lifestyle management the key fix.

• Perimenopause shows up in day 3–5 FSH before periods stop

In a 28-day cycle, estradiol rises in the follicular phase, LH surges to trigger ovulation around day 14, and progesterone peaks around day 21 before falling and triggering menstruation. As ovarian output falls, the brain drives FSH and LH higher. An early-cycle FSH creeping above about 10–12 is the 'canary in the coal mine'. FSH above about 25–40, with very low estradiol, confirms menopause, and FSH can exceed 50 years later.

• Start hormone therapy during the transition, not years after

Peter doesn't wait until a woman has flat-line estradiol and very high FSH. He starts a year or two before that point, giving enough estradiol to keep FSH around 20–30. The aim is not maximal estrogen but control of hot flashes, night sweats and vaginal atrophy, and above all protection of cardiovascular and bone health. For severe PMS in women who still cycle, he uses about 50 mg of oral progesterone from day 21 to day 28, or for the full 14 days after ovulation.

• Low testosterone isn't diagnosed from a number alone

Only about 1–3% of testosterone is free, and the rest is bound to SHBG or albumin. A small fraction becomes DHT, which is 2–10 times more potent, and less than 1% becomes estrogen. Androgen receptor numbers vary between people, so a man at the 30th percentile may or may not have symptoms caused by low testosterone. In trials, testosterone improves insulin resistance and mood, but Peter remains cautious.

EXAMPLES

• Licorice that looked like Cushing's

A medical-school story: a patient who seemed to have Cushing's disease turned out to eat about 10 packs of black licorice a day. Licorice disrupts the cortisol–cortisone enzyme system, and his cortisol activity had gone through the roof.

• Phosphatidylserine for evening cortisol

For patients whose cortisol stays high at night and can't sleep, and for himself when crossing time zones, Peter uses 400–600 mg of phosphatidylserine before sleep. He says the mechanism is unclear, but he sees the effect on cortisol.

• Why he avoids Clomid for men

Clomiphene raises LH, FSH and testosterone by blocking estrogen receptors in the brain. Peter dislikes it because estrogen feedback in the brain benefits mood, and some men on it feel no better despite soaring testosterone.

• Estradiol on testosterone therapy

Peter has never seen gynecomastia in 10 years of prescribing testosterone. He avoids anastrozole unless estradiol exceeds about 50–60 or causes symptoms, because estradiol supports bone and mood.

OTHER RELEVANT

- **Peter's TRT criteria**

  There needs to be a biochemical case (free testosterone below about the 50th percentile) and, more importantly, a symptomatic case, with informed consent. He trials 8–12 weeks, moving levels to about the 80th percentile, then reassesses symptoms.

- **Understand that testosterone shuts down your own production**

  Exogenous testosterone suppresses LH and FSH. Peter warns that within a year or two, natural production can be lost for good without very large doses of synthetic LH and FSH.

- **Women should time blood tests**

  Draw FSH and estradiol on days 3–5 of the cycle during the 40s to catch perimenopause early.

255-Latest therapeutics in CVD, APOE’s role in Alzheimer’s disease, familial hypercholesterolemia

Guest: John Kastelein
Date: 2023-05-22 · Duration: 2:04:18
URL: https://www.youtube.com/watch?v=Jduj5SL5FNs

KEYPOINTS

• Cardiovascular disease dwarfs every other killer.
Kastelein, a professor of genetic medicine at the University of Amsterdam who has spent decades running a large lipid clinic, frames the conversation with global numbers: atherosclerotic disease kills far more people each year than cancer (about 12–13 million), so it is 'not even close'. Early in his career he still saw fatal or severe heart attacks in FH patients aged 20–30.

• Familial hypercholesterolemia is common and starts in childhood.
Heterozygous FH is now thought to affect about 1 in 250 people, making it the most frequent autosomal dominant disorder. More than 3,500 mutations can produce the phenotype. In children with a clinical diagnosis a mutation is found about 95% of the time (roughly 95% LDL receptor, 4.5% APOB, 0.5% PCSK9 gain-of-function), versus maybe 50–60% in adults.

• FH is a syndrome diagnosis, not a single LDL number.
An LDL cutoff of about 190 mg/dL is common, but many people at 200 have secondary causes like high triglycerides, type 2 diabetes, untreated thyroid or kidney disease. Heterozygous and homozygous FH distributions overlap, so diagnosis needs family history, pedigrees and physical signs. Referral bias meant his early patients all had LDL over 300.

• Physical signs appear as cholesterol deposits.
Tendon xanthomas on the backs of the hands and the Achilles, the corneal arcus and eyelid deposits (xanthelasma) are classic, though the first real symptom used to be a heart attack. A milder genetic subset exists; among about 25,000 heterozygous patients found, he has never seen that subset have heart attacks in their 20s or 30s.

• Treating early likely adds 15–20 years of life.
Children start statins (plus ezetimibe if needed) with a modest pediatric target below 130 mg/dL. Attia pushes back that healthy kids have LDL around 20–30 and newborns roughly 10 mg/dL, a natural experiment showing low LDL is safe. Their pediatric cohort, followed for 10 years after a NEJM trial, supports early treatment.

• About 10% of heterozygous FH is 'severe' and resists triple therapy.
Starting from 300 mg/dL, a statin's roughly 45% cut plus ezetimibe and a PCSK9 inhibitor may still leave some patients above 100–120. For homozygous FH the state of the art is high-dose statin, ezetimibe, evolocumab and evinacumab (Regeneron's ANGPTL3 antibody), with apheresis as an option.

• LDL causality is settled.
Kastelein says he 'doesn't even listen' anymore to claims that LDL isn't causal; Mendelian randomization across many genes, not just FH, shows the same dose-response. The thrifty-gene idea: FH may have protected against infection and was less dangerous around 1860, before modern diets.

• CETP inhibitors failed for clear reasons.
Pfizer's torcetrapib raised blood pressure in phase 2 and in the large trial 'killed more people than it saved' (2006). Others failed on HDL-focused thinking. Merck's anacetrapib REVEAL trial, done by Oxford with 30,000 patients, worked only modestly because it lowered LDL just 17% from a baseline of about 60, an absolute drop of only about 11 mg/dL.

• Obicetrapib is far more potent.
At 1 mg in phase 1 it lowered LDL 27%; at 10 mg it inhibits CETP about 97%, cutting LDL roughly 50% on top of high-intensity statins, raising HDL about 165% and lowering Lp(a) 56% (43% at 5 mg) in the ROSE trial. Kastelein is directly involved in its development, so treat his optimism accordingly. Phase 3 includes BROADWAY (~2,400 patients, 52 weeks), BROOKLYN (~300 heterozygous FH) and PREVAIL (~9,000 with established ASCVD and baseline LDL near 100).

• APOE4 fails at moving cholesterol in the brain.
About 65% of Alzheimer's patients carry at least one E4. Kastelein cites roughly 16-fold risk for E4/E4 and 4.5-fold for E3/E4; Attia thinks the data suggest closer to 10-fold and four-fold. Mechanistically E4 is a poor acceptor and a poor donor of cholesterol, failing both to clear excess and to supply deficient brain cells.

EXAMPLES

• The untreated aunt
Cascade screening of one family turned up a 76-year-old aunt who had never been treated and had LDL of about 250, alongside siblings with wildly different cholesterol, which shows how variable FH can look.

• The man whose doctors said it was too high
A patient with LDL around 200 since his late teens ignored warnings for decades and presented at 50 with disease, a common pattern in men first measured at military entry.

• Attia's PCSK9 misprediction
Attia thought a trial adding a PCSK9 inhibitor to patients already at LDL 70 couldn't run long enough to show a difference; it stopped early at about 2.3 years with benefit, which Kastelein uses to argue PREVAIL can also succeed.

• A planned Alzheimer's proof-of-concept
Kastelein's group is running an obicetrapib trial in E4 carriers that taps cerebrospinal fluid and tracks about 50 biomarkers, hoping CETP inhibition improves brain cholesterol transport.

• Diabetes signal
Higher HDL from CETP inhibition may protect pancreatic beta cells from apoptosis, and trials have shown roughly 16–20% fewer new-onset type 2 diabetes cases. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

OTHER RELEVANT

- **Screen families.**
  If you or a relative has LDL near or above 190 mg/dL or early heart disease, look for FH and test children; diagnosis is easiest and most accurate in kids.
- **Rule out secondary causes first.**
  Check triglycerides, glucose, thyroid and kidney function before labeling high LDL as genetic. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Lower is better, earlier is better.**
  Adult targets keep falling (below 70, 55, even 20), and lifetime exposure drives risk. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Know your APOE status in context.**
  E4 raises both cardiovascular and Alzheimer's risk; metabolic factors like insulin resistance and fatty liver compound it, so manage apoB and metabolic health aggressively.

253 Hormone replacement therapy and the Women’s Health Initiative: re-examining the results

Guest: JoAnn Manson
Date: 2023-05-08 · Duration: 1:20:48
URL: https://www.youtube.com/watch?v=8bRuzA-qd0s

KEYPOINTS

• The WHI tested hormone therapy for preventing disease in older women, not for treating menopause symptoms.
Manson, a Harvard endocrinologist and epidemiologist and a principal investigator of the Women's Health Initiative, explains the background. By the early 1990s, observational studies suggested women on hormones had less heart disease and cognitive decline and lower mortality. Doctors had started prescribing hormones for prevention, sometimes to women 10–30 years past menopause. Hormones were already accepted and FDA-approved for hot flashes. The open question was whether they prevented chronic disease, and no randomised trial had tested it.

• Design: two trials, about 27,000 women, average age 63.
Women aged 50–79 were enrolled: close to 17,000 with a uterus got conjugated equine estrogen plus medroxyprogesterone acetate (MPA) or placebo, and close to 10,000 without a uterus got estrogen alone or placebo. The main outcome was coronary heart disease, and the main safety outcome was breast cancer. The trial was powered to detect about a 20% heart-disease reduction. Manson corrects a common misconception: women with hot flashes weren't excluded. About 45–50% had mild to moderate symptoms, though women with severe symptoms tended to opt out. These were the formulations behind the observational data, partly because a pharmaceutical company dominated with pregnant-mare-derived estrogen.

• Manson expected a small heart benefit, not the 40–50% the observational studies showed.
Women on hormones tended to be wealthier, better educated and more health-conscious. Manson thought starting estrogen early in menopause might modestly reduce heart risk, since women's own estrogen seems to delay heart disease by about a decade compared with men. She doubted the large observational effects would hold up in a randomised trial.

• The combined-therapy arm was stopped early; the absolute breast-cancer increase was small.
Estrogen plus MPA was halted after 5.6 years, 3.3 years early, because of more breast cancer, no heart benefit, and an unfavourable overall balance across all outcomes. The relative increase in breast cancer was about 25%. Attia emphasises the absolute figures: roughly 4 versus 5 cases per 1,000 women. Manson describes most harms as about one extra case of breast cancer, heart attack or blood clot per 1,000 women per year. That's low, but it can add up with long-term use.

• Estrogen alone did not increase breast cancer; with longer follow-up it was linked to a reduction.
With estrogen alone, breast cancer fell by about 20% with longer follow-up, and breast-cancer deaths were significantly lower. With estrogen plus MPA, breast-cancer deaths trended higher but weren't significant. Breast density rose more with the combination. Manson and Attia agree the excess risk is mostly attributable to MPA. But Manson cautions that this result may be specific to conjugated estrogen, which may act partly like tamoxifen, and that other evidence (such as ovary removal lowering recurrence) still points to a role for estrogen. Total invasive cancer didn't rise in either arm, and the combination reduced endometrial cancer.

• Timing matters.
In the 2017 JAMA mortality analysis, women aged 50–59 had about a 30% lower all-cause mortality on either regimen. This wasn't significant in either trial alone. Results were neutral at 60–69. Women aged 70–79 on estrogen alone had about 22% higher mortality, borderline significant. Women in their 50s on estrogen alone also had favourable heart-attack signals. Both arms raised stroke risk, and cognition worsened in women 65 and older.

• The practice changed in a good way and a bad way.
Hormone use fell by 70–80%. Ending prescriptions for disease prevention in older women was appropriate. Extending the fear to healthy women in their 40s and 50s with distressing hot flashes was not, because their absolute risks are even lower. Attia calls it one of medicine's greatest missteps and speaks of a 'lost generation' of women, including his mother and mother-in-law. Manson says the pendulum is settling: hormones are good for some women, not all. The best candidates are healthy women in early menopause with moderate to severe symptoms.

• Manson questions Attia's case for long-term use to prevent fractures.
Attia argues that hip-fracture protection, which he estimates at about 1.5% absolute, would far outweigh a small breast-cancer increase over 30 years of use. Manson points out that bone loss resumes quickly after stopping. No subgroup at high fracture risk had a clearly favourable overall balance on combined therapy for prevention. And women who stay on hormones long-term in observational studies are a self-selected, healthier group. A 30-year trial has never been done.

EXAMPLES

• Statin use during the trial
Only 7% of participants took statins at the start, rising to over 25% during the trial. Attia notes hormones would no longer be considered for heart prevention today.

• Mammography bias
Observational studies may have overstated breast-cancer risk because women on hormones had more frequent mammograms. The WHI required one every year for everyone.

• Oral estrogen and clots
Oral estrogen passes through the liver and raises clotting proteins. This was known beforehand and was expected to be outweighed by benefits.

• Manson's H-index
About 305, one of the highest in biomedical science, according to Attia. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

OTHER RELEVANT

- **Today's formulations**
  Most women now use transdermal estradiol with micronized progesterone, or a progestin IUD. Manson favours this shift because of effects on clotting and blood pressure. But long-term outcome trials are lacking, and a new WHI-scale trial would need 40,000–50,000 women.
- **Finding a clinician**
  menopause.org (North American Menopause Society) has a zip-code search for certified menopause practitioners.
- **Non-hormonal options**
  SSRIs/SNRIs and gabapentinoids cut hot flashes by about 40–50%. A new drug that acts in the brain was awaiting FDA approval at the time.
- **Personal choice**
  Manson respects a woman's fear, for example after her mother's breast cancer, as part of the decision. Attia worries many refusals are based on misinformation.

252 Latest insights on Alzheimer’s disease, cancer, exercise, nutrition, and fasting

Guest: Rhonda Patrick
Date: 2023-05-01 · Duration: 2:53:27
URL: https://www.youtube.com/watch?v=zkp0DRUQ33g

KEYPOINTS

• Patrick increasingly sees blood-brain barrier breakdown as an early driver of dementia, ahead of amyloid.

Patrick, who carries one APOE4 allele and has Alzheimer's and Parkinson's in her family, cites work by Berislav Zlokovic (USC) and Axel Montagne (Edinburgh). Their research found markers of barrier leakage decades before cognitive decline, in more than half of dementias, independent of amyloid and tau. A leaky barrier lets substances like fibrinogen into the brain, where it damages myelin-making cells, and impairs the glymphatic clearance of debris during sleep. It also disrupts GLUT1 transporters, which carry glucose into the brain without needing insulin. That may explain the brain's reduced glucose use better than 'brain insulin resistance' does.

• Type 2 diabetes and APOE4 both damage the barrier, and diabetes is preventable.

Patrick says 50–80% of people with Alzheimer's also have type 2 diabetes. Attia estimates diabetes roughly doubles risk, about the same as carrying one APOE4 copy (two copies raise risk up to about tenfold). High glucose produces advanced glycation end products that damage tiny blood vessels, as in the eyes and kidneys. Attia sees atherosclerosis and cancer as eventually inevitable for humans, but not type 2 diabetes, which he calls 'gasoline on the fire of aging.'

• The omega-3 DHA transporter may be key to barrier health.

In animals, disrupting the DHA transporter MFSD2A causes about 50% barrier breakdown and more than 50% loss of brain omega-3. In humans it declines with age, faster in Alzheimer's and with APOE4, and genetic defects cause small heads and cognitive impairment. Patrick has joined Bill Harris's Fatty Acid Research Institute to study omega-3 and barrier integrity. She calls trials giving 500 mg–2 g to people who already have Alzheimer's far too little, too late. EPA may help through inflammation; small trials suggest EPA helps depression.

• Blood pressure damage builds up over a lifetime.

About half of US adults and about 20% of 18–39-year-olds have hypertension. Patrick says high blood pressure in midlife, before about 50, is linked to dementia, while starting at 70–80 is much less so. She aims for systolic below 130; Attia cites SPRINT's 120. Exercise and sauna both lower blood pressure, and some people are genetically salt-sensitive.

• Patrick trains hard specifically to raise lactate for her brain.

Lactate, once seen as waste, is used by the brain as fuel and as a signal. George Brooks's 'lactate shuttle' work shows it raises VEGF, which repairs and grows vessels at the barrier, and BDNF, which supports neuroplasticity. Patrick does Tabata-style intervals (16 rounds of 20 seconds on, 10 off) on a Peloton five days a week, reaching about 7–8 mmol. Attia combines zone 2 rides at about 1.9 mmol with 4-minute all-out VO2 max intervals reaching 15–16 mmol, describing fitness as a pyramid needing a wide base and a high peak. He suggests she rest completely in the 10-second off periods to push the 'on' periods harder, and that blood flow restriction training can also spike lactate.

• Exercise and cancer: real but more modest, with stronger effects after diagnosis.

Studies of Olympians found they lived about 5–6 years longer than the general population, about two of those years from fewer cancer deaths. In observational data, aerobic exercise is linked to roughly 10–20% lower risk of breast and colorectal cancer. After diagnosis, active patients had about 50% lower mortality and recurrence. Patrick thinks preventing cancer may require more exercise, toward the upper end of the guidelines (300 minutes a week of moderate exercise), than heart benefits do. One proposed mechanism: shear stress from fast blood flow kills circulating tumour cells. Trials show exercise reduces them.

• Both changed their minds on protein: muscle matters more than results in lab mice.

Low-protein longevity results come from mice in sterile labs that die of lymphomas, not from infections, falls or bed rest. Worm daf-2 mutants live longer only by entering a dormant state humans don't have. Stuart Phillips's newer tracer studies suggest a minimum of about 1.2 g/kg, not 0.8, and more for older or active people because of anabolic resistance. Attia targets about 1 g per pound (2.2 g/kg), spread over four meals and snacks of about 40–50 g each. He notes that in Levine's study, protein intake wasn't linked to IGF-1 in people over 65. Attia cites a 70% lower dementia risk with strong versus weak grip.

• Exercise 'forgives a lot of sins.'

Patrick's continuous glucose monitor as a new mother showed broken sleep pushing her glucose into the prediabetic range. Exercise largely blunted this for about 48 hours. She also cites data where poor sleep raised mortality only in inactive people. Because of her APOE4, she drinks rarely. Attia argues no amount of alcohol is healthy and the J-curve is due to confounding, though harm at a few drinks a week is probably too small to measure. He says APOE4 carriers are more vulnerable, partly through poorer sleep.

EXAMPLES

• Fitness vs questionnaires

In a decades-long study, women with the highest measured cycling fitness had dramatically lower Alzheimer's risk. Studies based on self-reported activity often find no link.

• Sauna routine

Patrick uses 175–180°F for 20–30 minutes after workouts, often rehearsing talks because she finds she remembers them better. She uses a hot tub at night for sleep, and avoided heat during pregnancy because of neural-tube concerns.

• Time-restricted eating

Eating one meal a day usually means too little protein. Attia adds low-calorie protein snacks outside the eating window. Patrick still values not eating late, since melatonin impairs glucose handling.

• GLP-1 drugs

Attia insists on high protein for patients on semaglutide or tirzepatide. Some patients barely eat and lose muscle.

OTHER RELEVANT

- **Vitamin D trials**
  Attia argues trials should dose to a target blood level, as blood-pressure trials do, rather than give a fixed dose.
- **Precision nutrition**
  Patrick expects gene-diet interactions, for vitamin D, omega-3 and sodium, to become clearer within a decade.
- **Alcohol and breast cancer**
  Patrick notes women fear hormone therapy far more than regular drinking, though she says drinking raises breast-cancer risk more.
- **Ketones and lactate**
  Both use the same brain transporter. Patrick hopes for more research in brain injury and Alzheimer's.

250 Training principles for longevity | Andy Galpin, Ph.D. (PART II)

Guest: Andy Galpin
Date: 2023-04-10 · Duration: 3:10:02
URL: https://www.youtube.com/watch?v=UA5z1lAn2mc

KEYPOINTS

• Muscle fiber makeup differs by muscle and by job.
Galpin, an exercise physiologist, contrasts the calf's two main muscles: the gastrocnemius is often 60–80% fast type 2A fibers for sprinting and jumping, while the soleus underneath is built to be 'on all day' for standing and walking. Muscle also does non-movement work, such as pumping blood back toward the heart and acting as the body's largest glucose reservoir.

• Hypertrophy comes in more than one form.
Bodybuilders long claimed higher-rep training produces 'sarcoplasmic' growth (more fluid and stored energy) while lower reps (around 5–10) add contractile units. Galpin calls this a vindication of 'bro science': Mike Roberts' lab at Auburn found sarcoplasmic hypertrophy really happens, alongside contractile hypertrophy. Just because science hasn't studied something yet doesn't mean it's wrong.

• Strength trumps size, but size still matters metabolically.
Attia's reading is that strength predicts longevity more strongly than muscle size, though both correlate with lifespan, as does VO2 max. Size still matters because of muscle's metabolic role as a glucose sink that helps keep inflammation low. Galpin also rejects the myth that being very strong becomes harmful with age.

• Powerlifters train strength by accumulating reps in percentage zones.
Programs prescribe accumulating set numbers of reps between 70–80%, 80–90% and 90%+ of a one-rep max. A one-rep max can be estimated with online calculators from a 3–10 rep set, and effort can be rated with RPE scales (the original Borg 6–20, or 1–10). Elite 'light' days are still enormous: a 1,000-lb squatter's 70% day is a 700-lb squat.

• Velocity tracking adds objective feedback.
Attia uses a bar velocity transducer that measures each rep's speed in meters per second, projecting his one-rep max and showing fatigue as velocity drops across sets. Galpin agrees velocity is a useful lens on power training.

• Power is force times velocity, and the best load depends on the lift.
A medicine-ball throw is fast but light; a snatch moves heavy load fast. Peak power appears around 30% of max for simple movements, 40–50% for squats, and 80–90% for highly technical lifts like the clean and jerk and snatch, which most people can't reach without technical skill. Cluster sets (single reps with 5–20 seconds rest) preserve quality.

• Post-activation potentiation draws on the size principle.
Henneman's 1950s papers established that motor units, each made of a nerve and fibers of a single type, are recruited from small to large. A heavy prior effort can temporarily enhance subsequent power output; Galpin also describes the reverse, assisted jumps with body weight reduced 5–20% by a harness, to train speed.

• Strongman and CrossFit reward different blends.
Strongman demands broad strength and stamina with odd objects, like flipping a 450-lb tire for 25 reps, but never 65-rep sets. Competitive male CrossFitters cluster around 5 ft 9 in to 5 ft 11 in and 190–210 lb because heavy lifting must coexist with gymnastics like 100 pull-ups, while top strongmen often weigh 330–400 lb.

• Heart rate recovery is a strong fitness metric.
Good VO2 max testing centers check 1-, 2- and 3-minute recovery. Galpin's rough target: within two minutes, heart rate should be at least 20% below peak, so below 160 if you hit 200. A max test is only valid if you get near predicted max heart rate.

• Most training injuries are joint injuries from repetition of poor movement.
Galpin says it's rare for the muscle itself to be the problem. Injuries come from global overreaching (frequent illness, disrupted cortisol, testosterone or estrogen, poor mood, sleep and appetite) or from joints repeatedly moving badly. Attia stresses that for older people avoiding interruptions matters most, because regaining lost fitness gets so costly.

EXAMPLES

• A 119-lb deadlift of 525
Galpin describes a female powerlifter with 25–27 world records who deadlifted 525 lb at about 119 lb body weight, likely benching 200-plus and squatting over 400.

• Swedish skiers in their 80s and 90s
In Galpin's study of lifelong cross-country skiers competing since the 1940s–50s, average max heart rate was about 148–150 in 89-year-olds, and VO2 max stayed in the mid-30s; a 92-year-old measured about 38.

• Mile pace as sprint pace
Attia and Galpin break down an elite four-and-a-half-minute mile into 65-second 400 m laps, roughly 16-second 100 m repeats, a pace most people can't run once.

• Six hours at 250 watts
Galpin uses a cyclist averaging 250 W for six hours, when most people couldn't hold that for two minutes, to show how hard it is to compare endurance and strength demands.

• Blood pressure under a max lift
Galpin notes reports of blood pressure around 450/350 mmHg during one-rep-max deadlifts, illustrating the acute strain of maximal lifting.

OTHER RELEVANT

• Train for the 90-year-old you.
Attia's 'centenarian decathlete' framing: work backward from tasks like carrying luggage up a broken escalator and build

strength, power and endurance now, since decline is steep later.

- **Prioritize strength, keep enough size.**
  Strength predicts longevity best, but muscle mass supports glucose control and metabolic health. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Use objective markers.**
  Track estimated 1RM, bar velocity, RPE and heart rate recovery to steer training and spot fatigue. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Match load to the goal.**
  For power, use lighter loads on simple movements and heavier loads only on lifts you can perform with good technique; for strength, accumulate quality reps at 70–90%+ of max and use cluster sets so fatigue doesn't degrade form. Don't judge an elite lifter's 'light' day by your own standards.
- **Protect your joints to avoid layoffs.**
  Fix movement quality before adding load and watch for signs of global fatigue; the cost of rebuilding after injury rises with age.

249 How the brain works, Andrew’s fascinating backstory, improving scientific literacy, and more

Guest: Andrew Huberman
Date: 2023-04-03 · Duration: 3:03:33
URL: https://www.youtube.com/watch?v=OGe1bTccCyg

KEYPOINTS

• Adrenaline briefly takes the forebrain offline, and getting familiar with that state makes you less likely to be hijacked by it.

Huberman says that after a jolt of adrenaline (an ice bath, a car crash, a troubling text), the forebrain quiets for about 20–30 seconds. Meanwhile heart rate and breathing rise, pupils dilate and vision tunnels. Glucose and lactate are shunted toward survival centers. The more often you practice these states, through deliberate cold or blood-flow-restriction training, the more you learn they pass. He frames this as stress inoculation.

• Lactate is a fuel, not a poison.

After putting Huberman through blood-flow-restriction cycling, Attia explains that repeated lactate exposure leads cells to make more MCT transporters, so they clear and use lactate more efficiently. The liver can also turn it back into glucose. Huberman adds that the hypothalamus and brainstem areas that control breathing appear to prefer lactate under high exertion or stress. BFR's appeal: growth hormone and metabolic stress with little soreness, but only with proper cuffs, not homemade tourniquets.

• The prefrontal cortex sets rules by context, and stress shrinks those rules.

Huberman uses the Stroop task (name the ink color, not the word) to show how the PFC switches rules. Under even mild stress, he says, everyone fails at novel rule-switching, 'Seal Team Six guy' or not. People fall back on what they've practiced. When calm, they can draw on far wider rule sets, which he links to creativity.

• Mood circuits run 'north to south' in health and 'south to north' in distress.

Huberman cites Nolan Williams's work, not his own. In calm, healthy states the prefrontal cortex drives the insula and amygdala from the top down. In depression, activity in the left dorsolateral PFC is weak, so thinking is driven bottom-up from the insula and amygdala. Williams's lab uses TMS to activate that region, and new ideas seem to emerge, partly by temporarily dampening interoception. The insula holds a map of the internal body and merges outside information, rules and internal state.

• The amygdala isn't the only seat of fear.

People or monkeys with damage to both amygdalae still panic when made to breathe CO2. Yet they lose learned fears such as snakes and behave inappropriately with food and sex, for example tasting a pen.

• Humans are visual animals, but other animals see better in specific ways.

About 40–42% of the human brain responds to visual input. With good vision, people resolve about 60 cycles per degree, meaning 60 black lines on a thumbnail at arm's length. A red-tailed hawk resolves about 120, enough to spot a gopher lift its head from a light pole. Huberman says color vision evolved late: dogs see roughly brown-red-orange tones, while a mantis shrimp distinguishes far more shades of red than we can.

• Belief changes physiology, not just how things feel.

Huberman describes Alia Crum's research, which separates mindset effects from placebo. Drinking the same milkshake labeled low- or high-calorie produced different hormonal and satiety responses. Hotel housekeepers told their work burns calories and lowers blood pressure lost about 8–11 pounds over three or four weeks. People told about stress's performance-enhancing effects responded differently from those told its harms. He relays her estimate that belief accounts for roughly 8–20% of the effects of things like a food or behavior.

• Teaching mechanisms changes people more than listing facts.

Huberman says 50 brain facts don't change anyone, but explaining the process behind a few daily experiences, like fatigue and stress, makes the tools stick. He warns against promising 'works the first time, every time' unless it truly does, such as morning sunlight viewing working within two or three days. Both agree the world would benefit more from freshman statistics and probability, especially standard deviation, than from calculus.

EXAMPLES

• From truancy to residential treatment

Huberman grew up near Stanford. His father, an Argentine physicist, worked at Xerox PARC. After his parents' high-conflict split around age 12–13, he fell into the underground skateboarding scene and stopped going to school. The school system placed him in a residential treatment program for truancy, not drugs or violence. He says it 'wasn't jail but it wasn't far off.' The conditions for release were a new high school and therapy.

• A therapist for more than 30 years

His therapist, trained mainly in psychoanalysis, was the first person who really paid attention to him. He still sees that person one to three times a week, and in graduate school he sometimes needed budget help to keep going.

• Ben Barres's lab

Huberman did his postdoc from 2005 to 2010 in Ben Barres's 32-person Stanford lab, which held four-hour lab meetings. Barres, who had taught Attia neuroscience in medical school, transitioned during Attia's year and had a mild face-recognition deficit. To pay Bay Area rent on a roughly $45k salary, Huberman wrote for Thrasher and Slap under a pen name, earning an extra $500–$1,000 a month.

• Losses that destabilized him

A close colleague with BRCA1 and BRCA2 mutations died of early-onset breast cancer. He says it felt like losing his mother. Barres died of pancreatic cancer in 2017. Huberman reacted by working twice as hard and taking risks again, including cage diving with great white sharks, and felt joyless despite tenure and a 2018 Nature paper.

• Hoffman, a SEAL and a seed question

In 2017 he did the week-long Hoffman Process (he notes it costs about $4–5k, with scholarships) and met Pat Dossett, who served 13 years in the SEAL Teams. Around the start of 2019 Dossett asked, 'What are you gonna do for the world?' That led to Instagram clips, about 30 podcast guest appearances in 2020 including Rogan and Lex Fridman, and the launch of the Huberman Lab podcast in 2021.

OTHER RELEVANT

- **Practice controlled stress.**
  Short, deliberate cold or hard intervals let you rehearse the adrenaline window and learn that it ends.
- **Do novel or creative work when calm.**
  Rule-switching collapses under stress, so protect relaxed time for hard thinking.
- **Frame your activity accurately and positively.**
  Mindset effects are real but limited; true beliefs about the benefits of exercise and stress may add to the physiological effects.
- **Learn statistics.**
  Understanding probability and standard deviation protects you from confusing health messaging.
- **Seek sustained help.**
  Huberman credits long-term therapy and deliberate inner work, not willpower alone, with turning his life around.

248 OUTLIVE book: A behind-the-scenes look into the writing of this book, motivation & main themes

Guest: Bill Gifford
Date: 2023-03-28 · Duration: 1:58:07
URL: https://www.youtube.com/watch?v=Kx8Tag0Qwmw

KEYPOINTS

- **The title 'Outlive' replaced earlier working titles and was never seriously questioned.**
  Attia's first idea in 2016 was 'The Longevity Manifesto', scrapped almost immediately; the working title while shopping the proposal was 'The Long Game'. 'Outlive' stuck because it is simple, evocative and an action — outliving your expectations, your parents or your grandparents, the idea that your fate isn't set in stone. 'The Science and Art of Longevity' was added because, unlike mouse research where definitive experiments are possible, human longevity requires judgment under uncertainty.
- **The book took about six years and went through three distinct versions.**
  Version one was Attia writing alone in 2016, submitting a first section of just under 40,000 words. Version two was written with Bill Gifford from early 2018 to early 2020. In February 2020 the project was effectively dead — the publisher dropped it — until Michael Ovitz asked about it around Christmas 2020, read the long manuscript in two weeks, and helped revive it with a new publisher and editor through 2021–2022.
- **The final structure has three parts that build on each other.**
  Part one explains 'Medicine 3.0', the vehicle for pursuing longevity. Part two covers the diseases that come to take us — the 'horsemen' of heart disease, cancer, neurodegeneration and metabolic disease — because you can't delay them without knowing the enemy intimately. Part three covers the tactics. Attia says that architecture didn't really crystallize until around 2019.
- **Centenarians revealed the strategy: delay every chronic disease.**
  While working on the centenarian chapter, Attia and Gifford realized it isn't a mystery how people reach 100 when most reach 80: they get heart disease much later if at all, cancer much later or never, and neurodegenerative disease later or never. That became the ball game — Medicine 2.0 waits for disease and drags you through it, while Medicine 3.0 acts years earlier.
- **Objective, strategy, tactics — in that order.**
  Attia argues most people jump straight to tactics, such as taking 27 supplements to 'hack' something, without a clearly stated objective. If you can't state the objective, there's fog around everything. His favourite chapter-opening quote is Sun Tzu's: strategy without tactics is the slowest route to victory; tactics without strategy is the noise before defeat.
- **Frameworks are meant to outlast the specific science.**
  Asked how a book can still apply in 10 years, Attia says tactics will change — he will likely take things in a decade he doesn't know about now, and drop things whose evidence turns out weak — but each tactic should anchor back to the strategy. A framework-focused book is more timeless than a list of protocols.
- **Cancer screening is where he expects the most change.**
  Attia takes an aggressive posture on screening because treating a cancer at around a billion cells versus 100 billion cells with the same therapy produces dramatically different outcomes. He hopes liquid biopsies will be far better in 10 years. He contrasts guidance like a colonoscopy every 10 years — which he says fewer than 40% actually get — with his own practice: at 50 he'd already had three, every three years.
- **Immune-cell reprogramming excites him but isn't ready.**
  Something he deliberately left out as too early is reprogramming immune cells, which he considers much easier to reprogram than organs like the heart or liver.
- **Learning to 'kill your babies' was the hardest writing lesson.**
  Attia recalls advice from a lab colleague (he thinks Dan Powell) that you throw out 90% of what you know. As a scientist he struggled to believe readers could appreciate the tip of the iceberg without everything beneath it; the manuscript reached about 190,000 words a year before publication and had to be cut hard.
- **The book reflects his evolving thinking, including emotional health.**
  Attia notes that a version written five years earlier would have contained nothing on emotional health. There isn't a lot on it, but it's there and he believes it's relevant — part of how the podcast interviews and patient conversations shaped the book.

EXAMPLES

- **The 7-out-of-10 cover**
  Exhausted, Attia was ready to accept a cover he rated a solid seven out of ten. Gifford insisted they'd worked too hard for that; a designer produced about 30 covers within three days, each picked a top five or six, and the final design was in everyone's list, for different reasons.
- **The marathon analogy**
  Attia compares the final stretch to a marathon: physiologically you hit the halfway point around mile 20, so the last 6.2 miles hurt as much as the first 20. The last nine months of edits were similarly more work than everything before.
- **Reading the audiobook himself**
  Following Sam Harris's old advice to read edits aloud, Attia narrated the audiobook — and in doing so made several hundred line edits late in the process, to his team's dismay. A director reminded him an audiobook must sound slow at 1x, since he usually listens at 1.8–2x.
- **Talks road-tested on patients**
  Many of the book's explanations come from conversations Attia has with patients repeatedly; some versions land better than others, and he would sometimes ask patients whether he could use their stories.
- **The final chapter**
  The 17th and final chapter, initially disliked by Gifford and editor Diana, became the most improved — Gifford's favourite by

the end.

OTHER RELEVANT

- **Define your objective before choosing tactics.**
  Before adding a supplement or protocol, state what you're trying to achieve and which strategy it serves; if you can't, drop it.
- **Think in terms of delaying all chronic diseases.**
  The centenarian lesson suggests prevention should target heart disease, cancer, metabolic disease and neurodegeneration together, years before symptoms.
- **Discuss earlier and more frequent cancer screening with your doctor.**
  Attia's case rests on catching tumours at far smaller cell counts; his personal colonoscopy cadence is more aggressive than standard guidelines and is his choice, not a universal rule.
- **Expect tactics to change.**
  Hold specific protocols loosely: evidence will strengthen some and undercut others over a decade.

247 Preventing cardiovascular disease: the latest in imaging, blood pressure & metabolic health

Guest: Ethan Weiss
Date: 2023-03-20 · Duration: 2:24:55
URL: https://www.youtube.com/watch?v=vxA2jKZylnE

KEYPOINTS

• A calcium scan is cheap and useful, but a zero doesn't rule out disease, especially in younger people.
Weiss, a cardiologist who now volunteers as clinical faculty at UCSF after leaving his lab to start a biotech company, says he did 'a full 180' on CAC scans. They're low-risk, need no dye, and can cost about $200, though some places charge $2,000. His two-by-two: a zero in a 40-year-old with risk factors teaches little and shouldn't stop aggressive treatment, and a zero in a high-risk 80-year-old has its own false-negative problem. Attia cites data that about 15% of people with a zero score have something on CT angiography, and about 1.5–2% have an unstable plaque.

• CT angiography sees soft plaque and small calcium that CAC misses, at higher cost and some radiation.
Attia says CTA often runs $700 to $2,000–2,500. Prices can differ tenfold between institutions, and fewer than half of Weiss's patients have coverage. A modern scan delivers about 2 mSv, roughly 4% of the annual allowance mentioned, but some older scanners use about 20 mSv. Attia advises shopping for both price and dose.

• Weiss treats causal risk factors, not end-stage findings.
Waiting for 30% stenosis or a calcium score of 200 before acting is 'insane,' he says, comparing it to waiting for lung damage before telling someone to quit smoking. He describes 'eye-bleeding' fights with insurers who want a heart attack before approving PCSK9 inhibitors. With low enough apoB over a long enough runway, both argue, atherosclerosis could become largely irrelevant.

• For stable plaque, optimal medical therapy usually beats stenting.
COURAGE, ISCHEMIA and ORBITA showed that optimal medical therapy works well even in mildly symptomatic patients. Clear stent cases are an active MI, rest or unstable symptoms, heart failure, or chest pain that doesn't respond to medicine. FAME and FAME 2 used fractional flow reserve (the pressure drop across a lesion) to show which lesions matter. Weiss notes that the plaques that rupture and cause sudden death are often smaller ones of about 30%, not 80–90% blockages.

• Statins can increase calcification while lowering events, so calcium isn't always a direct proxy for risk.
Weiss calls it 'incontrovertible' that statins probably increase calcification even as they cut event risk, likely by stabilizing plaque. Whether heavy endurance exercise is similar is unknown. He wouldn't tell anyone not to exercise but is 'on the fence' about the most extreme volumes.

• Statin fear far exceeds actual statin harm.
Weiss estimates that about 5% of patients have muscle side effects real enough to stop. A similar or larger group refuses statins out of fear fed by documentaries and online claims that they are 'poison,' even after 25–30 years of successful use. Liver enzyme rises also occur, especially combined with ezetimibe.

• Normal blood pressure is about 120/80 at any age, and drifting higher with age is disease.
The old view allowed 'permissive hypertension' in older people. Weiss now tells patients the goal is to get as close to 120/80 as possible without side effects. He traces the definitions from JNC 6 to JNC 7, which called 120–140 'prehypertension,' and says the evidence, not opinion, now ties lower pressure to lower mortality.

• SPRINT showed a mortality benefit from intensive control, with manageable costs.
The NIH-funded, drug-agnostic trial compared targets of about 120 against about 140 systolic and achieved roughly 121 versus 136. The results were strong enough that the trial was stopped early. Blood pressure was measured with automated cuffs, seated and alone, three readings five minutes apart. The intensive arm had more falls, syncope and kidney dysfunction, all reversible. STEP, published the year before this conversation, eased worries that SPRINT's early stop had overstated the effect.

• Fat storage capacity, not body weight alone, drives metabolic risk.
Weiss uses a bathtub analogy. Each person's genetically set capacity to store fat safely under the skin differs, and overflow into the viscera, muscle, pancreas and pericardium does the damage. People with congenital lipodystrophy or severe insulin resistance have extreme coronary risk; he mentions women needing bypass surgery in their 30s and 40s. Gerald Shulman's insulin-resistant mice got fatter and healthier when given more subcutaneous fat. A DEXA fat-mass ratio (central versus peripheral fat) helps identify this pattern.

EXAMPLES

• Attia's own scans
At 35, training at least 24 hours a week with LDL-C around 110–120 and apoB around 85–90, he had a CAC score of 6, a single speck in the proximal LAD and around the 75th–90th percentile for his age. Nobody seemed concerned. In 2016 his CAC was 0, but CTA found the same tiny speck. Radiologist Bob Peters told him a speck that small could be missed on half of repeat scans. In 2022 his CAC was 2 and his CTA was unchanged. He now targets an apoB of 30–40 mg/dL with medication.

• Measuring blood pressure honestly
Attia's resting readings averaged about 110/70 and then crept to 125–130/80 from August on. A reading right after climbing stairs might be 140/90, then fall a few minutes later. He averaged below 120/80 for six months but felt he was 'cheating' by resting five minutes first. Weiss recommends 24-hour ambulatory monitoring, because pressure varies with sleep, stress and exercise and is normally checked only briefly once or twice a year.

• ALLHAT's verdict on drug classes
The early-2000s NIH trial compared calcium channel blockers (amlodipine), ACE inhibitors and thiazide diuretics (chlorthalidone, which is more potent than hydrochlorothiazide). Alpha-blocker and beta-blocker arms were stopped early because they did worse. The remaining classes became first-line options for primary hypertension.

• The control gap

According to Weiss, in the 1970s national survey only about 50% of people with hypertension knew it, 30% were treated and 10% were controlled. Today he estimates awareness is above 80%, treatment is about 75–80% and control is only about 50%.

- **Kidneys and the 'phase shift'**

  Weiss tells patients that living an extra decade means a 50-year-old should meet the standard of a healthy 40-year-old in heart, brain, bone and kidneys. That includes using cystatin C rather than creatinine for eGFR. An eGFR of 70 in a 55-year-old shouldn't be accepted as 'good enough.'

OTHER RELEVANT

- **Use CAC as a cheap first look, not a final verdict.**

  With a family history, a zero shouldn't lead to complacency; consider CTA if it would change decisions.

- **Shop CTA for price and radiation dose.**

  Ask what the scanner's dose is and what you'll pay before the scan.

- **Measure blood pressure the way trials did, and over 24 hours.**

  Use a validated automated cuff, sit quietly, take several readings five minutes apart, and consider ambulatory monitoring.

- **Lower pressure toward 120/80 while watching for side effects.**

  Dizziness, falls and kidney changes are signs to back off. Older patients need special care with orthostatic drops.

- **Separate statin facts from fear.**

  Expect about 5% to have true intolerance, and don't let documentaries decide for you.

245 Overcoming trauma, finding inner peace, & living a meaningful & fulfilling life | Lewis Howes

Guest: Lewis Howes
Date: 2023-03-06 · Duration: 1:39:28
URL: https://www.youtube.com/watch?v=oWDpSjxiiyk

KEYPOINTS

• Childhood adversity can stay buried for decades and then erupt.
Howes was sexually abused at age five by a babysitter's son of about 16 or 17, and kept it secret for roughly 25 years. Growing up in the 1980s and 90s, he never heard a male perspective on abuse and believed he was essentially the only one it had happened to. The pain surfaced as insecurity, shame and anger rather than as a memory he talked about.

• Success built on proving people wrong didn't bring peace.
Howes says he was fuelled to win, look good and be acknowledged, assuming that would bring joy and fulfilment. Instead, the more successful he got the angrier and more upset he felt. Around age 30 he had several breakdowns at once — in an intimate relationship and in a business partnership where he felt he was doing about 80% of the work.

• Ego was the barrier to getting help.
Already working in personal development and making money, he thought he had the answers and that people just needed to understand and accept him. Only after friends repeatedly recommended it did he try therapy and workshops; he now approaches every therapeutic experience with a beginner's mind.

• Telling the secret in a room of men was the turning point.
At a 2013 emotional-intelligence workshop he stood in front of about 40 people and told the story for the first time, reliving it vividly. Afterwards a man in his late 50s — married 25 years with four kids — told him the same had happened to him at 11 and no one knew. About 12 or 13 men came forward; several said they'd never told anyone.

• Being authentic deepened his relationships, including with family.
Howes says he'd been missing 25 years of true intimacy and connection because he was inauthentic about who he was. Opening up strengthened bonds and gave him a sense of inner peace he'd never had.

• Adversity and trauma are different, even if both can carry meaning.
Playing football with a broken wrist for 14 games or with three broken ribs was adversity that also produced good. Attia pushes back on framing abuse at five the same way: no parent would choose that for a child, even if meaning can later be found in it.

• Adverse childhood events predict adult disease.
Attia describes the ACE (adverse childhood events) score, a standardized 10-question test his practice gives patients when relevant. Its histogram shows how scores from zero to ten predict physical and mental health outcomes in adulthood. He notes that Howes' brother's imprisonment would likely count, since an 11-years-older sibling functions almost like a parent figure.

• Unresolved trauma can show up as physical symptoms.
Even after a decade of work, Howes had sharp chest pain unrelated to exercise and a throat-clenching feeling 'like someone was strangling me' when emotionally triggered. A five-month intensive therapy and coaching programme about two years earlier, focused on intimate relationships, is when he says the pain lifted.

• He chose partners he could 'fix'.
Howes realized he sought partners with a hole he felt he could fill — subconsciously trying to fix his parents' unhappy marriage through his own relationships.

• Healing is gradual, not a switch.
Attia stresses these changes aren't digital, zero-or-one switches. Howes describes re-parenting his five-, 10- and 18-year-old selves, and having compassion even for the 11-year-old who stole.

• Mortality can be a motivator.
After his father's accident, Howes went after everything, knowing life could change suddenly. Attia shares a 'life in weeks/ months' chart: at about 50 with a life expectancy near 88, he's more than halfway through.

EXAMPLES

• His brother's prison sentence
Howes' brother, 11½ years older and a violin prodigy who was in the Columbus Symphony at 16, sold LSD to an undercover cop at 18 and received six to 25 years on a first offence. The family visited weekly for about four years, sitting in a room with some 40 inmates and their families; he was released after about four and a half years and later played with Les Paul for a decade in Times Square.

• Leaving home at 13
Amid turmoil at home, Howes begged to go to a boarding school in St Louis and essentially lived with roommates from 13 to 18; at 8–12 he'd had no friends for years while dealing with his brother's imprisonment.

• His father's brain injury
When Howes was about 20–21, his father was hit by a car and suffered a traumatic brain injury. For 17 years he couldn't work, often repeated the same conversation and sometimes called Lewis by his brother's name, until he died a year before this conversation.

• The life-percentage shirt
Howes describes someone who wears a shirt displaying how much of his expected life he's lived, updated each year — a constant reminder of mortality.

OTHER RELEVANT

- **Consider taking the ACE questionnaire.**
  It's a quick way to see whether childhood adversity may be relevant to your health; discuss results with a clinician or therapist.
- **Try therapy or coaching even if you think you don't need it.**
  Howes credits workshops, therapy and coaching, over a decade, for changes success alone never gave him. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Notice physical symptoms tied to emotional triggers.**
  Recurrent chest tightness or other symptoms during emotional stress can be worth exploring — after medical causes are ruled out. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Speak up to break isolation.**
  Howes' disclosure prompted others to share; telling a trusted person can be a powerful first step. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

244 The history of the cell, cell therapy, gene therapy, and more | Siddhartha Mukherjee

Guest: Siddhartha Mukherjee
Date: 2023-02-27 · Duration: 2:00:14
URL: https://www.youtube.com/watch?v=-_2SPU3GqB4

KEYPOINTS

• Cell biology advanced steadily, while genetics stalled for decades.
Mukherjee contrasts the two histories. After Mendel's paper, genetics had roughly 40 years of silence. Cell biology grew steadily from the 17th-century microscope to Rudolf Virchow's 19th-century claim that every function, and every illness, comes down to how cells behave. Attia says the early figures impressed him even more than the genome decoders because they had so few tools.

• Germ theory and the cell powered the leap from 'Medicine 1.0' to 2.0.
Attia frames the shift as two processes: a new way of thinking (the scientific method) and new tools for seeing, such as microscopes that revealed germs. Mukherjee agrees that seeing microbes and linking them to disease changed medicine. He adds a clinical lesson: the most important question is often what the patient thinks is wrong.

• Multicellularity may evolve more easily than once assumed.
Single-celled organisms remain wildly successful, living even in boiling water and volcanic vents. So the puzzle is why multicellular life exists at all. William Ratcliff and his advisor Michael Travisano repeatedly selected yeast that settled fastest in a tube. Within about 30–40 cycles, perhaps 60–90 days, clusters of cells emerged that stayed together, a new form of life evolved by simple selection. Mukherjee also notes size limits set by the ratio of volume to surface area.

• There are four ways to use cells as medicine.
First, drugs that change a cell's behavior, such as antibiotics killing microbes but sparing human cells. Second, transferring unmodified cells, as in blood transfusion. Third, using cells as factories for products like insulin or antibodies such as Herceptin. Fourth, genetically modifying cells and putting them into the body. Mukherjee stresses that 'gene therapy is really cell therapy': the right gene in the wrong cell is useless or dangerous.

• CAR-T cells can cure some blood cancers, but cost is a structural problem.
T cells are taken from a patient, engineered with a virus to target cancer (for example, CD19 on B-cell cancers) and infused back. They work in lymphoma, leukemia and myeloma, but not yet well in solid tumors. US costs run about $500,000 to $1 million per patient. Mukherjee's team in India has treated about 11–12 patients with very good early data and aims for 20–50-fold lower costs. He links US prices partly to the roughly 90% of drugs that fail, which companies cite to justify pricing; he calls that argument somewhat specious.

• CRISPR is like editing one word in a vast library.
Picture the genome as about 80,000 books. Old viral gene therapy slipped a new page in, sometimes into the wrong book. CRISPR, from the work of Jennifer Doudna, Emmanuelle Charpentier, Feng Zhang and others, can go to one book, one page and one word and change 'verbal' to 'herbal.' Mukherjee's group is editing bone marrow, and he discusses gene editing for sickle cell disease, which is caused by a single amino-acid change.

• Gene editing crosses an ethical line when it moves from disease to desire.
Mukherjee recounts He Jiankui editing CCR5 in embryos so that twins would be HIV-resistant. Because they were conceived by IVF with washed sperm, their risk of getting HIV from their father was essentially zero. He says the change served the desire to be first, not to treat disease, and made unintended, imprecise germline changes. Editing for Huntington's (100% penetrant) sits clearly on the disease side. Less penetrant genes such as APOE4 or Lp(a), and traits like height, move toward desire.

• Most mental illness is 'death by a thousand cuts,' which makes it hard to edit.
A few rare, highly penetrant variants run in families. He mentions a book about a family with several children with schizophrenia. But like height, most risk for depression, schizophrenia and autism comes from many small genetic nudges, many not yet identified. Current editing handles only one to three genes.

• Science has two kinds of anomaly: an 'eye in the sandstorm' and 'sand in the eye.'
In the first, nothing fits, as with the move from Newtonian to quantum physics. In the second, a theory is almost right but one fact won't fit. His example is the gap between neurons, the synapse: why convert electrical signals to chemical ones and back? The answer was weighting. Adjustable synaptic weights make learning networks possible, like artificial neural networks, rather than a 'box of wires.'

EXAMPLES

• Semmelweis's two maternity wards
In 19th-century Vienna, one ward run by doctors had maternal mortality of about 20–30%, around one in five women. The doctors went from autopsies to deliveries without cleaning their hands. A ward run by nurses, who didn't handle dead tissue, had almost none. Mothers reportedly begged to be admitted to the safer ward.

• Jesse Gelsinger
Around 2000 at the University of Pennsylvania, a teenager with an inherited enzyme defect in ammonia processing received an adenovirus engineered to deliver the correct gene to his liver. His immune system reacted violently to the flood of virus particles and he died. Gene therapy was frozen for almost a decade. Today's strategies dampen the immune response or use viruses the body hasn't seen.

• A CAR-T cure
Mukherjee describes a girl treated with CAR-T therapy who, he says, is now about 16 or 17, applying to college and completely cured.

• Making a Leeuwenhoek microscope
Mukherjee tried to build one of van Leeuwenhoek's single-lens microscopes, about half the size of a sheet of paper with a

lens smaller than an eyeball, and calls it a disaster. Van Leeuwenhoek made 500.

- **Speaking openly about depression**

  Mukherjee chose, after talking with his family, to write about his own depression. He argues it can be an organic disorder of mood-regulating circuits, like type 1 diabetes in beta cells, and that we wrongly attach a punitive 'victimhood' to it. Attia notes that no one blinks at 10 mg of Lipitor, yet antidepressants still carry stigma.

OTHER RELEVANT

- **Ask patients what they think is wrong.**

  Mukherjee calls it the most important and most forgotten question in medicine.

- **Learn by doing.**

  He says his Oxford doctoral training under his mentor taught what textbooks can't, like choosing and managing patients for trials or troubleshooting experiments.

- **Take falls in older adults seriously.**

  Attia notes that falls are the leading cause of accidental death. He says femur fractures after 65 carry about 10–30% one-year mortality depending on the study, and that Virchow died within months of a broken femur.

- **Judge gene editing by disease versus desire.**

  Weigh penetrance and medical need before accepting germline changes.

243 The fentanyl crisis and why everyone should be paying attention | Anthony Hipolito

Guest: Anthony Hipolito
Date: 2023-02-20 · Duration: 1:13:28
URL: https://www.youtube.com/watch?v=i2K-_UTLNR4

KEYPOINTS

• Fentanyl is dosed in micrograms, and street pills are off by orders of magnitude

Peter explains that hospitals give morphine in milligrams (1–5 mg IV) but fentanyl in micrograms. About 100 µg is a typical dose for something like a colonoscopy, and even clinicians occasionally over-sedate someone by misjudging sensitivity by 25–50 µg. Deputy Anthony Hipolito says about 2 mg can kill. Illicit manufacturers can match colours and stamps perfectly, yet they are off by as much as 'a dose of a thousand' on the active ingredient: far beyond a lethal dose, 'you might as well have cyanide'.

• The crisis grew out of prescription opioids

Hipolito dates widespread opioid addiction to around 2010–11, when some pain-management doctors prescribed oxycodone, Vicodin and Percocet recklessly and patients went 'doctor hopping'. As an Austin police interdiction sergeant along I-35, he began seeing fentanyl around 2017–18, mostly ordered on the dark web from China and shipped through FedEx, UPS and USPS. Mexican cartels now dominate the trade.

• Accidental overdose is now the leading killer of young adults

By Peter's reading of the last 12 months of CDC data, someone in the US dies of an accidental overdose roughly every five minutes, more than 100,000 a year, excluding suicides. Hipolito estimates about two-thirds involve fentanyl. In 2021, fentanyl was the number one killer of Americans aged 18–45, and he expects the 2022 data to push the lower bound down to 13 or 14. Ten years ago Peter would have said only two things threatened people under 40, car accidents and suicide; now accidental overdose dwarfs both, making them 'rounding errors'.

• Call it poisoning, not overdose

Most victims are not trying to get high on fentanyl or end their lives. They believe they're taking Xanax to sleep, Adderall to study, a Percocet, or cocaine. Hipolito says six in every 10 counterfeit pills contain a potentially lethal dose. By his estimate, street cocaine is laced 90–99% of the time, and most users survive only because a given dose happens not to be lethal: 'Russian roulette'.

• Seizures show the explosion in supply

Fentanyl seizures went from about 200,000 to 1.5 million to 4.1 million to almost 10 million over 2018–2021. Border agents are thought to intercept only 5–10% of narcotics. Because it is synthetic and needs no poppy fields, fentanyl is cheap compared with a kilogram of cocaine or heroin, and smugglers use methods that can evade X-rays and drug dogs.

• Dealers are targeting younger kids

Hipolito says the DEA believes cartels are deliberately pursuing younger buyers to create long-term customers. 'Rainbow' or candy fentanyl looks like sweets and is smuggled inside real Skittles or Nerds boxes. Sales happen on Snapchat, Instagram and Facebook, and on encrypted apps like Telegram and Signal where messages disappear. In Hays County, the most recent death was a middle school student.

• How fentanyl kills

It suppresses breathing. As breathing slows, heart rate falls, and death can come quickly while the person feels euphoric. Surveillance footage Hipolito shows students includes a passenger who waited 20–25 minutes before calling 911, delays that cost lives.

• Narcan works, but street doses may need many

Naloxone reverses opioid effects. Hospitals use it after an accidental fentanyl overdose of, say, 120–125 µg. In Hays County, a single dose often isn't enough: one teenager needed 15 doses. All deputies there carry it. It is sold without a prescription at pharmacies such as Walgreens and CVS, and the federal government will mail it.

• Policy is unresolved; the 'why' matters most

Peter notes Portugal decriminalized personal possession and reports one of Europe's lowest overdose rates, while Oregon and British Columbia are trying similar approaches. He says he hasn't decided where he stands and worries it may be a band-aid. Both agree the root question is why someone needs the drug, whether that's anxiety, insomnia or academic pressure, and without answering it the person won't get help.

• Stronger opioids are coming

Peter says he has heard that the FDA deeply regrets approving the medical opioid sufentanil because it 'makes fentanyl look weak'. Hipolito warns that manufacturers are altering molecular structures to create compounds stronger than fentanyl, and that a 'super Narcan' is being developed in response.

EXAMPLES

• Kevin McConville, 17

His mother found him dead in bed the morning after he said goodnight. A light-blue pill stamped 'M30', believed to be fentanyl, was in an Altoids tin beside him. A friend said he had been taking what he thought was Xanax to help him sleep. Hipolito opens his school presentations with her video.

• Noah Rodriguez, 15

Noah was a sophomore at Johnson High School who died in August. Toxicology found about 8 mg of fentanyl in his system.

• A daughter thanks him for removing TikTok

About two months after Hipolito took away social media, his daughter thanked him, saying she was much happier and hadn't realized how much scrolling alone in her room had affected her.

• The starfish

Hipolito ends with the parable of throwing stranded starfish back into the sea one at a time: reaching one student out of 300 is worth it. Taking 10 pills off the street potentially saves six lives.

OTHER RELEVANT

- **Talk to kids early and plainly**
  Hipolito wants these conversations to start in elementary school: any pill not from a pharmacy may contain fentanyl, and there is no such thing as a safe 'just once'.
- **Keep Narcan in the house**
  Keep it somewhere everyone knows about, like the kitchen drawer. A visiting friend could be the one at risk.
- **Know the apps and limit social media**
  Know which apps and games your children use, including encrypted messengers, and consider delaying or removing social media.
- **Call 911 immediately**
  If someone becomes unresponsive or their breathing slows, call 911 immediately and give naloxone. Don't wait to see whether they sleep it off.

241 Living intentionally, valuing time, prioritizing relationships, & more keys to a rich life

Guest: Ric Elias
Date: 2023-02-06 · Duration: 1:31:25
URL: https://www.youtube.com/watch?v=qb4_WiSFHvU

KEYPOINTS

• Parenting teenagers is a tug of war you must eventually lose

Ric Elias says this was the last meaningful lesson from his mother, given over coffee while she had Alzheimer's and he was asking for advice about his teenage daughter. You can't drop the rope right away, but by the time children leave for college they should have pulled you over the line. His version: they will always be your kids, but you won't always be their parent.

• Memories made with people you love are what a year leaves behind

When Ric looks back over a year, what he actually remembers is time spent with people. So he started creating those experiences on purpose. One was a 'friends summit': about 30 friends, each personally chosen by him, who arrived open-minded because the only thing they had in common was knowing Ric. Peter, who attended, says he left with a list of men he couldn't wait to see again.

• People who finish life well keep looking forward

Ric has studied people in their 70s, 80s and 90s who are thriving. The common thread is that they keep planning and building instead of retreating into the past. Staying 'in the arena', even at a slower pace, keeps the mind engaged and keeps them feeling relevant. He connects this with Arthur Brooks's idea that crystallized intelligence takes over as fluid intelligence declines, so older people stay productive by teaching and advising.

• Live with complete intention, and count your time

Since Flight 1549, Ric has tried to live with full intention. He knows, for example, that he has 242 weeks left until he turns 60. Each week he sets his big intentions, because he expects lower energy and some physical debts to come due after 60. He says this way of living is what makes his life feel rich.

• The most important relationship is with yourself

Ric calls this his biggest growth since the plane. If that relationship is wrong, every other one carries friction. He argues that most religions and much of society use guilt to teach or control us, and that guilt is 'the most useless emotion'. He has spent five years getting rid of it. The alternative is to own mistakes quickly. When he snaps at someone, he apologises within about 20–30 minutes and asks for forgiveness, rather than carrying the guilt around.

• Happiness and wealth are only as linked as you decide

Ric points out that some of the happiest people in the world have no wealth, so the two can't be tied together. But many people chase wealth for their whole lives because society tells them to, then arrive feeling empty and guilty about what they sacrificed. He calls that the worst place to be: getting what you wanted and finding it was a mirage.

• Play the infinite game

At the friends summit, Simon Sinek spoke about finite and infinite games. Ric says the book put into words what he already believed: in an infinite game there is no winning, and the goal is to stay in the game and ultimately keep it going. After the plane, he decided to 'run a different race' than everyone else. He says he feels no jealousy and rarely reads comments about himself.

• Struggle builds greatness, and that is hard on privileged children

Peter recalls an old interview in which a young Arnold Schwarzenegger said his drive came from hardship and a need to escape. Ric agrees and adds that perfect 4.0 students who never faced adversity often struggle to be productive later. He notes that his generation came from little while their children come from plenty.

• The twenties are an apprenticeship that remote work may erode

Ric thinks something special about the US is that companies, hospitals and other employers spend the decade from 20 to 30 training people for the rest of their lives. He loves the flexibility of hybrid work and doesn't want to lose it. But he worries that if young people no longer learn alongside experienced colleagues, the country could lose much of its edge in 10–30 years.

EXAMPLES

• Flight 1549 and the last seconds

Ric was on the US Airways plane that landed on the Hudson in January 2009. He has said that if he had died, he would have felt only sadness rather than gratitude. Peter asks whether he has asked other passengers what they thought in the final seconds. He hasn't yet, but plans to.

• Marshall at 96

Ric has known Marshall, a former North Carolina state senator of 26 years who played basketball at Duke around 1939 and served in World War II, for about 20 years and over roughly 100 lunches. At 96, Marshall brought Ric a serious business idea based on where trends would be in 10 years. Peter compares this to his 85-year-old father, who in his 60s bought undeveloped limestone land expecting demand over the next 30 years and still works at a quarry every day.

• Red Ventures and the Giving Pledge

Red Ventures has grown from about 1,200 employees around 2014–15 to about 4,500. Ric expects that by 80 he'll have about 15 people and will be giving the money away. About 18 months before the interview he signed the Giving Pledge, which commits signers to give at least half their wealth away during their lifetime or at death. He says he and his wife did this with real trepidation while their children were still in high school.

• Golden Door Scholars and Road to Hire

Golden Door Scholars funds college for undocumented students who can't get in-state tuition. Ric says about 80,000 such students graduate from high school each year and can no longer obtain DACA permits. The latest round had about 1,200 applicants, more than 300 of them with GPAs close to 4.0, and about 520 students are in the programme. A sister programme, Road to Hire, teaches mostly Black and brown students from Title I schools to code through paid apprenticeships; more than

220 graduated this year, all with jobs.

- **A learning list to stay humble**
  Ric works out with a coach twice a week and keeps a list of eight or nine things he wants to learn. One is salsa: as a Puerto Rican, he says he can't die without knowing how to dance it.

OTHER RELEVANT

- **Plan the year around shared experiences**
  Deliberately create gatherings and trips with people you love. Those are the memories that remain.
- **Count the weeks to your next milestone**
  Pick a horizon, work out how many weeks remain, and set a few clear intentions each week so time is spent on purpose.
- **Replace guilt with a fast apology**
  When you've wronged someone, own it quickly and ask forgiveness instead of carrying guilt.
- **Keep a beginner's list**
  Choose a handful of skills you're bad at and practise them. It keeps you looking forward and keeps you humble.

240 The confusion around HDL and its link to cardiovascular disease | Dan Rader, M.D.

Guest: Dan Rader
Date: 2023-01-30 · Duration: 1:54:09
URL: https://www.youtube.com/watch?v=cBDrK3xOZ7U

KEYPOINTS

• HDL biology is far more complex than LDL biology, which is why it is so poorly understood

Dan Rader, a lipidologist at the University of Pennsylvania, explains that apoB stays with its particle for life. ApoB100 is made in the liver and apoB48 in the gut. HDL's main protein, apoA1, behaves differently. It is secreted lipid-poor and picks up cholesterol and phospholipids from cells through the transporter ABCA1, and its other proteins swap on and off between particles. People who lack ABCA1 make plenty of apoA1 but have almost undetectable HDL, because the apoA1 can't acquire lipid and is cleared quickly.

• Humans are unusual in carrying most cholesterol on apoB particles

In a normal mouse, more than 90% of blood cholesterol is in HDL. Rader and Peter note that if humans had primate-like or mouse-like apoB levels, around 20 mg/dL instead of about 100, that five-fold difference would roughly separate developing atherosclerosis in a lifetime from never developing it. This is one reason mouse HDL research translates poorly to people.

• HDL subfraction labels are mostly noise for clinicians

HDL2 and HDL3 refer to particle size and number of apoA1 molecules (about four in HDL2 and three in HDL3). They have nothing to do with apoA2 or apoA4. Rader considers fractionation interesting biologically but relatively unimportant clinically. Peter says his practice stopped paying attention to HDL fractionation around 2016, and Rader agrees that was reasonable.

• High HDL cholesterol is not a free pass

The inverse link between HDL cholesterol and heart disease goes back to early Framingham data from the late 1970s and early 1980s. But a high HDL-C does not offset a high LDL-C or apoB. Peter calls the idea that a high HDL means you can ignore heart disease risk 'bunk' and cites two Mendelian randomization studies that fail to support a causal protective role. Rader says he would not change the treatment he'd otherwise give just because HDL is high. Both say HDL-C above about 90 deserves a closer look rather than reassurance.

• Raising HDL-C with CETP inhibitors has repeatedly failed

CETP moves cholesterol ester from HDL to apoB particles, and people deficient in it can have HDL-C above 100 mg/dL. Pfizer's first inhibitor, torcetrapib, was tested on top of Lipitor, and in September 2006 the combination did slightly worse, which Peter calls a bombshell. After three failures, Rader's reading is that raising HDL-C with CETP inhibition neither helps nor hurts. A CETP inhibitor might still be useful for lowering LDL and apoB, and that is being tested.

• Niacin raised HDL and lowered apoB, but outcome trials found little benefit

Niacin modestly lowers triglycerides, apoB, LDL and Lp(a) (roughly 15–20%) and could raise HDL-C from about 50 to 90 mg/dL at strong doses. Rader once prescribed it widely and says he has had to 'eat crow'. AIM-HIGH showed little benefit, and a large, well-powered Merck trial was also disappointing; together they 'killed niacin'. He has had to tell patients it probably wasn't helping them.

• HDL-C tracks triglyceride metabolism and insulin resistance

Rader calls HDL-C an 'integrator' of triglyceride handling, a little like HbA1c for glucose. After a fatty meal, triglycerides might rise from 100 to 400 mg/dL before clearing. Each excursion lowers HDL-C slightly (for example, 40 to 37–38), and repeated meals push it to a lower steady state. That is why a high triglyceride-to-HDL ratio (both in mg/dL) is reasonably associated with insulin resistance, though not in African-American patients, where it has long been found unhelpful.

• What matters may be HDL function, especially cholesterol efflux

Macrophages in the artery wall use ABCA1 to unload cholesterol onto apoA1. The cholesterol eventually returns to the liver through SR-B1, a process called reverse cholesterol transport. Rader's garbage-truck analogy: HDL collects cholesterol where you don't want it and dumps it at the liver. Two people with the same HDL-C of 50 can have very different flow through this pathway. A static concentration tells you nothing about velocity.

• Efflux capacity predicts events, and a trial is testing it

Rader's lab measures efflux capacity in macrophage-like cells (J774 cells and human macrophages). Using many thousands of baseline samples from EPIC-Norfolk with 10+ years of follow-up, they found efflux capacity predicted incident cardiovascular events. That is still association, not proof of causation. CSL112, an infusion of apoA1 complexed with lipid, was being tested in patients after acute coronary syndrome: four weekly infusions, with events measured at 90 days. If positive, it would be the first evidence that promoting efflux reduces events.

EXAMPLES

• The woman with HDL of 150

Rader recalls a published case of a woman with an LDL-C of about 100 and HDL-C of 150, initially assumed to be low risk. Humans who lack SR-B1 have very high HDL because they can't 'unload the garbage trucks', yet they have increased heart disease risk. That is why he suggests checking very high HDL-C, though he notes SR-B1 deficiency is not common.

• The ratio argument Peter hears from doctors

One of Peter's most vexing conversations is with physicians who say a patient's LDL-C of 140 is fine because the HDL is 80. Rader says he looks at the whole patient and calculated risk, but not in a way that lets a high HDL cancel out apoB.

• ApoE, apoA1 and the brain

ApoE4 is the major genetic risk factor for Alzheimer's disease in a dose-dependent way. ApoE2 is bad for lipids but carries about a 20% relative risk reduction. ApoA1 isn't made in the brain yet appears in cerebrospinal fluid. Rader says a fair amount of observational data suggests apoA1 protects against neurodegeneration, but it is associative and not yet clinically useful.

• HDL and nitric oxide

Rader cites Philip Shaul's work in Dallas showing in cells and mice that HDL, acting through SR-B1 on endothelial cells, promotes nitric oxide production. That could plausibly lower blood pressure and protect arteries, but its relevance in humans remains unproven.

OTHER RELEVANT

- **Focus on apoB, not HDL-C, when judging risk**
  Lowering apoB has hard-outcome evidence. Raising HDL-C with drugs does not, so don't let a high HDL-C talk you out of treating elevated apoB.
- **Treat very high HDL-C as a question**
  HDL-C well above 90 mg/dL may reflect genetic variants that don't protect the heart. Discuss it in the context of your overall risk.
- **Use the triglyceride-to-HDL ratio as a rough metabolic clue**
  A rising ratio in non-African-American patients can point to insulin resistance, which deserves attention.
- **Demand outcome trials**
  Rader's broader lesson from CETP inhibitors and niacin is that improving a lipid number is not the same as preventing heart attacks.

239 The science of strength, muscle, and training for longevity | Andy Galpin, Ph.D. (PART I)

Guest: Andy Galpin
Date: 2023-01-23 · Duration: 2:55:15
URL: https://www.youtube.com/watch?v=ED8pq0uBct8

KEYPOINTS

• Strength, power and endurance are distinct qualities.
Galpin, a professor of human bioenergetics at Cal State Fullerton since 2011, separates force production (strength), force times velocity (power) and repeated output (endurance). The distinction shows in sport: a World's Strongest Man event may be won in 5–15 reps, while CrossFit can demand 90. Training for longevity means deliberately building each, not just one.

• Adding muscle won't transform your metabolic rate.
People imagine five pounds of new muscle will lift basal metabolic rate from 1,500 to 2,500 calories a day; Galpin says that's far outside reality. There are many reasons to build muscle, but large calorie burn at rest isn't one.

• Fiber types sit on a spectrum, and hybrids are common.
Humans have type 1 (slow), 2A and 2X fibers; the old '2B' label was a misidentification in humans, though animals like bears and cheetahs (20–60% 2B) have them. A type 2A fiber generates roughly 5–6 times the power of a type 1. Hybrids (1/2A, 2A/2X, even triple) are common, while pure 2X fibers are extremely rare, around 0.1% of the hundreds of thousands Galpin's lab has analyzed.

• Muscles' composition matches their job.
The soleus can approach 100% slow twitch because we're ambulatory so much, while the vastus lateralis is typically about 50-50 fast and slow. Some elite athletes in Galpin's lab exceed 80–85% fast twitch. Unusual 2X levels appear in people with long-term spinal cord injury (up to 50–60%), and sometimes in older adults, for unclear reasons.

• Training shifts fibers, especially away from hybrids.
With any physical training, hybrid fibers tend to decline and fibers settle into pure 2A or type 1, the forms Galpin says you want to 'train into'. A strength-trained person might be about 70% 2A and 30% type 1, while long-term endurance training can drive the composition toward nearly all slow twitch.

• Slow fibers get trained by daily life; fast fibers need specific work.
Hypertrophy is fairly non-specific as a training outcome, but targeting fast fibers requires heavy or explosive work, because slow fibers are activated by any activity of daily living or cardio zone. This matters for aging, since fast-fiber function is what declines and what prevents falls.

• Falls after 60 are often about foot speed and eccentric strength.
When you catch a toe or slip, you need the foot speed to get a foot back underneath you and the eccentric strength to stop the fall, so you don't break a hip. That's why Galpin opens Attia's hypothetical program with 10–15 minutes of power and speed work, like jumps and playful drills.

• Aim for high lean mass, but make it functional.
Attia's DEXA showed his appendicular lean mass index around the 40th percentile; he thinks at or above the 75th percentile is a better place, but wants strength and capability, not just size.

• Program design: 60/20/20.
For a client with three 60-minute sessions a week, Galpin splits the effort into about 60% what you need now, 20% long-term development and 20% fun. Sessions vary rep ranges, for example a Wednesday of 15–20-rep sets that drives less soreness, plus isometrics like holding a thigh-parallel squat for two minutes.

• Weight cuts are mostly water and need careful rehydration.
Roughly two-thirds to 70% of body weight is water. Fighters can cut 8–15 lb of water in a day, ideally with most of the drop done passively earlier in fight week, then rehydrate with about 110–125% of the fluid lost.

EXAMPLES

• The identical twins
Galpin studied identical twins, one untrained and one an endurance athlete with about 30 years of training journals. The untrained twin was roughly 50% slow, 30% 2A and 20% hybrid; the trained twin was about 95% pure slow twitch, showing how much training reshapes fibers.

• A world-record hurdler
An athlete who held world records in the 110 m and 60 m hurdles had about 24% pure 2X fibers, an extraordinary figure given how rare those fibers are.

• Octogenarian Olympic skiers
Galpin examined former world champions and Olympic cross-country skiers from the 1940s–50s who never stopped competing, now 85-plus, and saw them hop curbs for fun.

• A fighter's same-day rebound
A fighter Galpin worked with in Abu Dhabi weighed in at 136 lb and was about 152 lb within roughly five hours, illustrating how much water can be cut and restored.

• A finisher with breath holds
Galpin's conditioning finisher: 10 seconds all-out effort, then a breath hold to failure, then 30 seconds of nasal-only breathing for recovery, repeated for rounds.

• Muscle is ravenous for energy
Galpin explains that muscle contraction requires ATP even to release, and muscle protein is constantly broken down and resynthesized, with released amino acids often used elsewhere in the body. That turnover is one reason he says skimping on

protein makes no sense, especially with aging.

OTHER RELEVANT

- **Train speed and power, not just strength.**
  Short explosive drills early in a session protect fast fibers and foot speed, which are what keep older adults from falling.
- **Don't build muscle expecting a huge metabolic boost.**
  Muscle helps glucose control and function, but the resting calorie gain is small. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Plan with the 60/20/20 split.**
  Balance what you need now with long-term development and enjoyment so you keep showing up for years. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Use isometrics and varied rep ranges.**
  Longer holds and higher-rep days add stimulus with less soreness and joint stress. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Weight cuts are for athletes, done carefully.**
  If you must cut, front-load passive losses and rehydrate deliberately; most people should simply compete closer to their walking weight.

237 Optimizing life for maximum fulfillment | Bill Perkins

Guest: Bill Perkins
Date: 2023-01-09 · Duration: 1:58:06
URL: https://www.youtube.com/watch?v=eE8W1Lp_VRE

KEYPOINTS

• Money is only useful as a means to experiences, and its value is tied to time.
Perkins, a hedge-fund manager and energy trader and author of Die With Zero, frames every purchase in hours of life: a $10 shirt cost 'an hour and 15 minutes' of work. He asks people whether they'd rather be 20 with nothing or 90 with $100 billion; nearly everyone picks 20, revealing that health and time outrank money.

• Experiences have seasons; some expire.
Perkins' biggest regret is skipping a backpacking trip through Europe with his roommate Jason in his early 20s while he kept his head down as a clerk. Jason came back 'richer' with no real career cost. When Perkins later went, with money, he wouldn't stay in hostels or ride the trains, and the experience was good but 'not as rich' because its moment had passed.

• Solve for net fulfillment, not maximum wealth.
The book is essentially a life-cycle hypothesis plus what Perkins calls counterfactual regret minimization: plan to convert money into the highest-value experiences while you can still enjoy them, instead of autopiloting toward a bigger number. Attia pushes back that 22–24 is early to think this way, and they agree saving still matters.

• Use time buckets to plan.
Divide life into segments (20–25, 35–40, 50–60 and so on) and list the experiences you want in each across leisure, relationships and career. Some activities transfer to later decades, some get less enjoyable, some become impossible, so you can't push everything to the 80–86 bucket. Leave room for 20–30% discovery of things you didn't plan.

• Net worth should probably peak in your 50s.
Perkins estimates net worth should crest somewhere in the 50s, after which you deliberately spend down on experiences, gifts and giving rather than dying with a large surplus. Health, he notes, is the multiplier on every bucket.

• Fear is usually fear of judgment, not risk.
When people resist a bold change, Perkins breaks down what they actually fear; often they can survive the financial hit and are really afraid of what others will think. He separates real risk from imagined risk and sets explicit tolerances, like a physical risk threshold of about 1 in 10,000 unless the reward is extraordinary.

• Think in expected value.
Perkins, a trader and poker player, explains that a 50/50 bet paying 4-to-1 is a great bet even though you lose half the time. Casinos make money on edges as small as fractions of a percent; good traders are right perhaps 55–60% of the time.

• Give to people when it matters most.
Perkins criticizes the secret-millionaire story of a secretary who lived frugally and left about $10 million at death: the gift arrived too late to help her or the people she might have helped. He prefers giving to children around ages 25–33 rather than at 60-plus, and admires John Arnold for quitting full-time trading before 40 to focus on philanthropy.

• Countdown clocks break autopilot.
Perkins notes that people tend to say kids don't want to be with you at 13, forgetting how quickly that window closes. Perkins uses a 4,000-weeks calendar and 'death clock', and counts down to milestones like a daughter's 14th birthday, to make time concrete. Autopilot is how two years and 40 extra pounds slip by unnoticed.

• Many people have no buffer at all.
Attia recalls a 2008-era figure, from a friend involved in running the TARP program, that roughly 30% of Americans couldn't come up with $1,000 in an emergency. For a 40-year-old with $50,000 net worth, Perkins says the thinking still applies: map experiences to seasons and find lower-cost equivalents.

EXAMPLES

• The $30,000 safari
An African safari with kids priced at about $30,000. Perkins asks whether you'd rather die with $30,000 more or have that shared experience now; if a $30,000 trip is never realistic, find a cheaper experience that gives similar fulfillment.

• Reading his own book
After writing it, Perkins went through his will, made a list of 30–50 people and started giving them annual tax-free gifts now, rather than leaving bequests.

• The hospital bill vs. time
Perkins describes intensive hospital care for his father costing a huge sum per night, and notes that late-life spending buys little extra life compared with earlier spending on experiences.

• Counting reunions
At a wedding of about 117 guests, Perkins realized most pairs in the room would see each other perhaps 20 times, and fewer than 50 times, in their lives, so he began throwing parties to increase those numbers.

• A big 45th birthday
Perkins rented out a hotel for a large birthday celebration, a 'memory dividend' he still draws on, while recalling that his wedding years earlier cost under $20,000, an obscene sum to him then.

OTHER RELEVANT

• Price things in time.
Convert costs into hours of your life to see trade-offs clearly. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Build time buckets.**
  List the experiences you want per decade, especially those with physical or relational expiration dates, like time with young kids.
- **Interrogate your fear.**
  Ask what the real downside is and whether it's survivable; separate risk from fear of judgment. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Give while it helps.**
  Consider giving to children, family and charities when the money has the most utility, not at death. Perkins' own children's money sits in a trust set to release between about ages 25 and 33, which he considers the optimal window, and he argues charitable giving loses impact the longer it's deferred.
- **Protect health as the multiplier.**
  Every bucket depends on being able to do things; Attia ties this to training for later decades.

235 Training principles for mass & strength, changing views on nutrition, & creatine supplementation

Guest: Layne Norton
Date: 2022-12-19 · Duration: 3:13:41
URL: https://www.youtube.com/watch?v=EbykBDSAwzE

KEYPOINTS

• Strength and fitness are among the strongest predictors of mortality.

Attia lines up the hazard ratios for all-cause mortality. Hypertension adds about 20%, type 2 diabetes about 30% and smoking about 50%. Being weak rather than strong adds about 250%. Having a VO2 max in the bottom 25% versus the top 2.5% adds about 400%. Muscle mass also matters but is tightly linked to strength. Norton adds that lifting is the best thing for bone density, and that strength and balance help prevent the fall in the first place.

• Progressive overload is the core principle, and many rep ranges build muscle.

For a beginner, adding 5 lb a week to a squat (95, 100, 105 for the same reps) is progressive overload. Sets of 10–15 build lean mass and therefore strength. But strength is a specific skill, so low-rep, heavy practice is needed to express a true one-rep max. Ahead of his best squat of 668 lb, Norton practiced heavy singles, mostly around 90% and occasionally 95%.

• Use RPE, but learn what real failure feels like.

On the rating-of-perceived-exertion scale, RPE 10 means no reps left and RPE 9 means one left. Norton cites research in which beginners and intermediates misjudged their RPE by about five when researchers then pushed them to true failure. He has shifted toward more sets at RPE 6–7 rather than grinding at RPE 8–9, which he feels lowers injury risk while still adding volume as overload. Using variations of the competition lifts reduces the anxiety of being 'tested' against previous numbers.

• Super-slow training works, but it isn't magic.

Attia describes patients who will only do one weekly 20–30-minute super-slow session: about 8–10 machines, one set each to failure lasting roughly 90–105 seconds. Norton says there are 'many ways to skin a cat' for hypertrophy. He critiques a slow-rep study that used 30% of one-rep max for 10 reps, when a normal pace at that load allows 30–50 reps, so the comparison wasn't fair. Doing any training beats doing none.

• Testosterone matters even if relative gains look similar between sexes.

Some cite a study showing men and women adding about 10% lean mass to argue testosterone doesn't matter. Norton points out that 10% of 70 kg is 7 kg, while 10% of 50 kg is 5 kg, and the absolute loads differ hugely. Ray Williams, the first drug-tested man to squat over 1,000 lb raw, carried about 308 lb of lean mass. Norton calls his own view on testosterone thresholds speculation.

• Creatine monohydrate is the lowest-hanging supplement fruit.

Phosphocreatine donates phosphate to regenerate ATP. Creatine is also an osmolyte that pulls water into muscle, which may itself be anabolic. Norton takes 5 g daily even before meets. Loading (e.g., about 30 g a day for a week) saturates muscle faster but often causes GI bloating and nausea, and over the long run it doesn't matter. He hasn't seen clear evidence that more than about 5 g helps. The hair-loss worry traces to one 2009 study showing a DHT rise that has never been replicated.

• Norton changed his mind on LDL, BCAAs and fasting.

He once favored HDL/LDL ratios and particle size. Mendelian randomization data persuaded him that LDL is causal and an independent risk factor, and he now takes a low-dose statin. His LDL had stayed around 125–150 even with less saturated fat and 60–70 g of fiber a day. He dropped BCAA products because whey beats BCAAs even at matched doses. Grant Tinsley's studies showed no significant lean-mass difference with 16:8 fasting when people train within the eating window, though bodybuilders may still prefer frequent protein.

• Eat fiber from real food: about 15 g per 1,000 calories.

Norton gets about 60 g of fiber a day and says the evidence linking fiber and fruit and vegetable intake to lower heart disease and cancer risk is unusually consistent across meta-analyses. He cites a 2020 analysis showing that higher vegetable intake was linked to lower risk. Fiber bars count for something, but 40 g from three bars isn't equal to six to eight servings of produce. He notes the irony that his research was funded by egg, dairy and beef groups, yet he is defending plants against carnivore advocates.

• Tracking food intake reveals what you're really eating.

Restaurant fat can turn a 500-calorie dish into 1,500 calories. Clients who swear they eat 1,500 calories often discover, once they track, that it's about 2,800, which Norton calls 'freedom.' Weighing even a brownie (about 40 g) acts as a governor on extra servings.

EXAMPLES

• The Minnesota Coronary Experiment

A large controlled diet trial replaced saturated fat with omega-6-rich oils in an institutional setting. It finished in 1973, showed no benefit and went unpublished until 1989; Norton recalls the investigator saying they 'didn't like the way it turned out.' Chris Ramsden later reanalyzed the unpublished data. Norton says that, if the details hold, it is the most damning evidence that omega-6 oils lower lipids while raising events. Attia notes a 1960s cholesterol-lowering drug that increased events and was withdrawn. Both caution about how long the trial ran.

• Meet day

Norton chooses his opener carefully because a missed attempt can't be lowered. He uses visualization and breath work to push his heart rate to about 160–170 before a lift. At the 2015 Arnold Pro meet he aggravated his back a week out, and his final 661-lb squat rotated slightly.

• Bodybuilding prep

At his leanest he ate about 1,900 calories (about 260 g protein, about 100 g carbs and 30–40 g fat) 20 weeks into a diet. Going from about 15% to 7% on calipers was easy; below that was brutal. Avoiding fluid restriction and eating 300–400 g of

carbs on show day kept his muscles full, since muscle is about 70% water.

- **Bribing for breakfast protein**
  Attia now bribes his 14-year-old daughter to get at least 30 g of protein before school.

OTHER RELEVANT

- **Train strength and VO2 max as longevity priorities.**
  The hazard ratios dwarf many conditions people worry about more.
- **Overload gradually and sometimes test real failure.**
  Calibrate RPE with occasional sets to failure on safe exercises, and use more moderate-RPE volume to limit injury.
- **Take 5 g of creatine monohydrate daily.**
  Skip loading if it upsets your stomach. The hair-loss claim rests on a single unreplicated study.
- **Target about 15 g of fiber per 1,000 kcal from whole foods.**
  Use bars as a supplement, not a substitute for produce.
- **Track intake for a while.**
  A few weeks of logging recalibrates your sense of portions and calorie-dense restaurant food.

234 Chris Hemsworth on Limitless, longevity, and happiness

Guest: Chris Hemsworth
Date: 2022-12-12 · Duration: 1:16:17
URL: https://www.youtube.com/watch?v=n_jhqgWNKFA

KEYPOINTS

• Limitless grew into something more personal than planned.

Darren Aronofsky called Hemsworth about a six-episode docuseries on longevity. The core team met in New York around November 2019, and shooting began in January. Hemsworth had never hosted anything and worried about seeming genuine. Attia, the show's medical adviser, saw him give more of himself as trust grew. Hemsworth says the risks felt safer once he believed he wouldn't be exploited.

• A 3–4-day fast is a 'reboot,' but expect to feel rough.

Attia explains why the fast was four days: three to four days is roughly the point at which the body meaningfully changes how it handles the absence of nutrients. He normally wouldn't take a patient past three days, but production pushed it to four. Hemsworth also worked out daily and learned breath-holding and spearfishing while fasting. Attia warned there would be stretches of sluggish, grouchy mood.

• Ocean cold is a different stress from an ice bath.

In Norway the water was about 36°F. Their first swim lasted about four and a half minutes, longer than any ice bath Hemsworth had done, in snow and wind and while treading water, which removes the thin warm layer that forms around a still body in a tub. He says it was more a grit test than adaptation, and he relied on coach Ross Edgley's voice. For comparison, Attia has done long swims at about 49°F and calls even that a huge difference.

• Joy comes from contrast.

Attia describes the post-swim euphoria as a 'temporal juxtaposition' of being very low and then very high. We don't feel speed, only acceleration, and he argues emotions work the same way: constant bliss wouldn't feel like profound joy. Hemsworth still makes time for 30–60 seconds of cold water even on busy days.

• Lift heavy, start early, never stop.

Hemsworth seems genetically inclined to be muscular and explosive; he says he grew quickly once he started training while playing footy at 17. Attia tells patients that heavy loads recruit fast-twitch (type 2) fibers, which decline with age. The strength episode moved from dragging a car (Edgley had done a similar feat for about 20 hours) to a 100-ft rope climb from a cable car about 1,000 ft above the Blue Mountains, a better test of grip, strength and top-end fitness. Edgley's advice: be strong, not heavy.

• APOE4/E4 raises Alzheimer's risk sharply but isn't destiny.

Blood work from December 2019 showed Hemsworth carries two copies of APOE4. Attia puts the risk at roughly 8–10 times the general population. Only about 1% of people carry two copies, and about 20–25% carry at least one. Attia had seen only about three such patients, and two suspected it from family history. He told Hemsworth the gene is not deterministic, that earlier action means more risk reduction, and that it could be 'a blessing' as motivation. Attia calls the view that nothing can be done 'complete nonsense.'

• Sauna is a passive cardiovascular stressor with consistent, though not fully proven, data.

In a sauna at about 195°F, Hemsworth's pulse started around 64 bpm. Attia explains that the heart pumps harder to move blood to the skin for cooling, much like exercise. He notes the studies point strongly in the same direction even if the case isn't proven like some interventions. Hemsworth and his wife Elsa have a sauna and ice bath at home, which he calls the best recovery tool.

• Labeling arousal as excitement changes performance.

Hemsworth used to feel like throwing up before auditions and could barely think on set. He read about research in which performers had the same physical arousal (raised pulse, clammy hands, shortness of breath) whether they called it fear or excitement. He decided the feeling meant 'Spidey senses up.' He believes fear pushes and purpose pulls, and both are needed. Fear, he says, keeps him self-deprecating and humble.

EXAMPLES

• Climbing the rope

Hemsworth had never climbed a rope. He trained on a 10-ft rope at home, repeatedly going three-quarters of the way up and jumping off. For about two and a half weeks he stopped lifting and cut calories, dropping a couple of kilos. The real rope, three to four times longer than anything he'd trained on, took about a couple of minutes. His quads, especially his right leg, burned worse than his forearms, and afterward his fingers were locked into claws.

• Imagining his death

In the final episode, palliative-care physician BJ Miller had him live as an octogenarian for three days and picture his last moment. His mother had recently told him that, when she thought she was dying, she felt only gratitude. He realized he wasn't ready, and that the scene he pictured, family and friends in his living room, happens every other weekend.

• Getting Thor

He auditioned for Thor and got no callback, while his younger brother Liam made the final six. Joss Whedon and Drew Goddard, who were working with him on Cabin in the Woods, were baffled. Casting reopened and he auditioned again for Kenneth Branagh, this time without putting anyone on a pedestal or trying to please, and won the part.

• Rush

Ron Howard thought he wouldn't fit in a Formula 1 car. Hemsworth studied interviews with James Hunt, styled his hair like Hunt's, practiced the accent and won the role. Attia jokes that he has watched it so many times Hemsworth should be paid per viewing. Hemsworth hasn't watched it since the premiere.

OTHER RELEVANT

- **Learn your APOE genotype.**
  Attia wishes everyone knew it early, because it shapes prevention around exercise, sleep, metabolic health and more.
- **Use contrast and discomfort deliberately.**
  Short cold exposures, hard climbs and fasting can build resilience. Long fasts beyond about three days deserve medical oversight.
- **Relabel pre-performance nerves.**
  Treat a racing heart as readiness, not threat.
- **Curate your work.**
  Hemsworth wants more time to prepare and decompress between films, working with directors such as George Miller who stretch him, rather than taking roles just for the paycheck.
- **Notice what you already have.**
  The meaningful moments may already be here; change your attention, not just your circumstances.

232 Shoulder, elbow, wrist, and hand: diagnosis, treatment, and surgery of the upper extremities

Guest: Alton Barron
Date: 2022-11-28 · Duration: 4:33:07
URL: https://www.youtube.com/watch?v=CtGwx2VAH_E

KEYPOINTS

• The shoulder trades stability for mobility.
Alton Barron, an orthopedic surgeon specializing in the shoulder, elbow and hand (and the surgeon who operated on Attia), explains that the shoulder is a shallow ball-and-socket that relies on the labrum, capsule and rotator cuff for stability. That makes it the most mobile and among the least stable joints, which is why rotator cuff, labral and dislocation injuries are so common.

• History, mechanism and exam beat imaging alone.
Barron says if you compulsively take the history, mechanism of injury and symptoms and do a careful physical exam, you'll be about 95% accurate before the MRI. MRIs of people over 50 often show degenerative labral tearing that isn't the pain generator; he describes a woman in her early 60s told she needed surgery for such a tear, which is often the wrong call.

• Anatomy predisposes some people to injury.
The acromion comes in types: type 1 is flat (most people), while the hooked type 3 is far from rare (Barron estimated perhaps 30% for types 2–3) and predisposes to impingement mainly in overhead athletes and lifters. Spinal stenosis and other variants also change risk, so screening can be useful in contact sports.

• Frozen shoulder is common and often misread.
Adhesive capsulitis, which Barron sees two or three new cases of weekly in one office, shows as a stiff, tight capsule that blocks motion (for example external rotation stopping at about 30 degrees with pain). Its cause is unknown and multifactorial, worse with diabetes, and it can mimic or conflate other diagnoses. Neck problems can also refer pain to the shoulder, so the exam includes the cervical spine.

• Arthroscopy and better anchors transformed repair.
Barron started practicing in 1996, when most work was open surgery and early arthroscopic techniques were judged retrospectively, with high failure rates in some series. Modern repairs use heavy sutures and anchors into bone to reinforce healing, and age alone is not a barrier: he has repaired rotator cuffs in people in their 90s who healed fully.

• PRP and stem cells: plausible in places, oversold overall.
Barron uses PRP selectively in his Manhattan office for things like lateral epicondylitis and some tendon injuries, and thinks cells may help muscle tears, but says stem cells won't regrow a labrum. Many studies justifying these treatments are poorly designed, a lot of money is involved, and patients fly abroad (including Germany) for unproven injections.

• AC joint separations are graded by displacement.
Up to about 30% widening is grade 2; 100% or more is grade 3, with higher grades beyond. Many grade 3 injuries can be managed without surgery; a study of NFL athletes about 20 years ago supported this. Hockey players and quarterbacks hit by '300-pounders' are classic cases.

• Throwers' elbows depend on their shoulders.
Pitchers develop asymmetric shoulders, gaining roughly 45 degrees more external rotation on the throwing side; losing 10–15 degrees can add torque on the elbow. Tommy John (UCL) reconstruction revolutionized baseball, and throwers live with 15–20-degree elbow contractures and stay functional, since a 100-degree arc covers most daily needs.

• The hand is neurologically enormous.
More than half of higher cortical neurons (Barron says over 60%) map to the hand in the homunculus. Splinting a wrist in too much flexion or extension raises pressure on the median nerve and can cause acute carpal tunnel syndrome, so neutral positioning is safest. Hand fractures are finicky too: the average adult bone heals in about six weeks, but some wrist bones take 10–12 weeks.

• Thumb-base arthritis is extremely common.
Barron says about half of people will experience osteoarthritis of the thumb's basal joint in their lifetime, and perhaps a quarter of those (around 12.5% overall) may need surgery. Tennis elbow's sweet spot is ages 40–60, increasingly into the 70s as people stay active.

EXAMPLES

• Attia's shoulder
Attia describes a decade of shoulder pain and his own surgery with Barron, and the 'tissue work and training' that delayed it for years; archery practice of 100 shots the day before surgery illustrates how active he remained.

• Barron's father
Barron's father swam vigorously in Lake Travis at 94½ and died at 95 of pancreatic cancer; after a rotator cuff repair in his 90s you couldn't tell he'd ever torn it.

• The 97-year-old patient
Barron operated on both of a 97-year-old woman's shoulders back to back; she later greeted him on 57th Street saying she was doing great, which shows age alone isn't a contraindication.

• A musicians' foundation
Barron, who treats many musicians, co-founded a foundation to help uninsured musicians with Elvis Costello and Diana Krall, approved by the IRS in 2017, with a launch concert at Austin's Paramount Theater. A violinist might play 20,000 bow strokes in one Mozart concerto.

• Mom's wrist plate
Barron's mother broke her wrist at about 82 and got a titanium plate, part of his argument for fixing fractures aggressively in

active older adults.

OTHER RELEVANT

- **Get examined before you get scanned.**
  A careful history and exam should drive decisions; asymptomatic degenerative findings on MRI shouldn't automatically lead to surgery.
- **Protect external rotation and scapular mechanics.**
  Especially for overhead athletes, shoulder range and control protect the elbow. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Be skeptical of biologic injections.**
  PRP may help specific tendon problems; stem-cell claims for structural repair are largely unproven and expensive.
- **Splint in neutral.**
  After wrist injuries keep the wrist neutral and fingers moving to avoid nerve compression. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't let age stop treatment.**
  Active people in their 70s–90s can do well with repairs and fracture fixation. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

230 Cardiovascular disease in women: prevention, risk factors, lipids, and more

Guest: Erin Michos
Date: 2022-11-07 · Duration: 2:15:04
URL: https://www.youtube.com/watch?v=QykLgWm8h08

KEYPOINTS

• Heart disease mortality in younger women has stopped improving.
Michos, a Johns Hopkins preventive cardiologist, describes her European Heart Journal analysis of CDC WONDER data on US women under 65 from 1999 to 2019: cancer mortality kept declining, but since about 2010 progress on heart disease stalled and reversed. Worldwide, she cites roughly 18.5–19 million deaths a year from atherosclerotic cardiovascular disease versus about 10–11 million from cancer.

• Women increasingly don't know heart disease is their top killer.
In 2009, 65% of women surveyed knew heart disease was the leading cause of death in women; by 2019 only 44% did. Young patients fear breast cancer more, even though heart disease mortality is roughly 8–10 times higher. Clinicians also perceive women as lower risk than men with the same risk profile, leading to undertreatment.

• Ten-year risk scores fail younger people.
A 30-year-old with blood pressure of 160 has a 'low' 10-year risk simply because of age, yet a high lifetime risk. Michos and Attia note that at the bottom of the calculator's age range almost no input yields a high 10-year score, and that no trial enrolled people 25–45 long enough to show events prevented — yet no one doubts treating causal factors like hypertension or smoking early.

• Guidelines still lean on 10-year risk, with modifiers.
Under the 2019 ACC/AHA primary-prevention guidelines, below 5% 10-year risk lifestyle may suffice; above 20%, a high-intensity statin to cut LDL by 50% or more. Risk-enhancing factors and a coronary calcium score refine decisions, though a zero score is less reassuring under 40 because plaque takes time to calcify.

• Female-specific factors change risk.
Menarche before 11 or after 17, preeclampsia and gestational diabetes, and menopause before 45 (especially before 40) are associated with higher cardiovascular risk. PCOS is linked to about a 30–50% increased risk on average; insulin resistance appears in about 95% of obese and 75% of lean women with PCOS.

• Pregnancy dramatically raises lipids — by design.
Lipids climb and peak in the third trimester: total cholesterol up about 25–50%, triglycerides about 150–300%, LDL around 66% — normal physiology to supply the fetus. Across the menstrual cycle the swing is small, roughly 10–12 mg/dL in total cholesterol.

• Familial hypercholesterolemia is undertreated in women.
FH carries about a 20-fold increased risk and, in women, onset of disease roughly 20–30 years earlier; women with FH lose the usual female advantage, partly because they miss years of statin therapy over pregnancy concerns. Michos notes FH itself doesn't raise malformation or preeclampsia risk, and treatment in pregnancy is a shared decision.

• Statins work equally well in women.
A meta-analysis of over 18 randomized trials with more than 40,000 women showed similar relative benefit to men, scaling with each 1 mmol/L (39 mg/dL) LDL reduction. Yet in a survey representing 11 million US women with established disease, women were 45% less likely to be on statins.

• Much statin intolerance is nocebo.
Up to 30% of statin-treated patients report muscle symptoms, but blinded trials such as SAMSON suggest up to about 90% of those symptoms also occur on placebo. Michos often uses low doses of rosuvastatin (5–20 mg), notes CoQ10 lacks good evidence but is harmless if patients want it.

• Non-statin options fill the gap.
Ezetimibe adds roughly 18–21% LDL lowering; PCSK9 monoclonal antibodies lower LDL about 50–60% and Lp(a) about 25%, with outcome benefit in FOURIER and ODYSSEY; inclisiran, an siRNA, has lipid data from ORION trials. For very high-risk patients she believes optimal LDL may be around 30 or lower.

• Lp(a) is a risk enhancer even at low LDL.
Lp(a) has a variable number of kringle IV type 2 repeats (2 to over 40). In the Copenhagen General Population Study, Lp(a) above 50 mg/dL carried risk even with LDL below 70. Investigational drugs pelacarsen and olpasiran lower it 80–90%, but outcome data are pending.

• Hormone therapy is reasonable for symptomatic women near menopause.
For symptomatic women under 60 or within 10 years of menopause, Michos sees HRT as appropriate; she generally doesn't start it more than 10 years after menopause or over 65.

EXAMPLES

• The decade advantage
Attia frames it: a still-ovulating 40-year-old woman has roughly the cardiovascular risk of a 30-year-old man. Michos agrees on average, while noting people aren't averages.

• Pravastatin given too late
A trial giving pravastatin to women at risk of preeclampsia at 35 weeks showed no benefit — unsurprising, Michos says, since preeclampsia develops much earlier. A larger trial of about 1,500 high-risk women starts around 12 weeks.

• GLP-1 drugs for weight loss
Tirzepatide, a dual GIP/GLP-1 agonist, produced up to about 50 pounds of weight loss at the highest dose; semaglutide's STEP trials showed roughly 30 pounds, though they weren't compared head to head.

- **Women missing from trials**
  Her review of lipid-lowering trials from 1990–2018 found women were only about 29% of participants, and about 36% for newly approved cardiometabolic drugs through 2017; only about 10% of leadership roles in top-journal trials went to women.
- **Marathons in many states**
  Michos has run marathons in about 36 states with a goal of finishing rather than racing.

OTHER RELEVANT

- **Think in lifetime risk, not just 10-year risk.**
  Elevated blood pressure, LDL or apoB in your 30s matters even if your calculator score looks low.
- **Tell your doctor about pregnancy history.**
  Preeclampsia, gestational diabetes, PCOS and early menopause are risk enhancers that should shape prevention. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Screen for FH and Lp(a).**
  Very high LDL or a family history of early heart disease warrants evaluation; Lp(a) is worth measuring at least once.
- **Don't abandon statins on symptoms alone.**
  Discuss dose changes, alternative statins or non-statin drugs with your clinician, given how often symptoms are nocebo.

229 Understanding cardiovascular disease risk, cholesterol, and apoB

Guest: Allan Sniderman, Tom Dayspring
Date: 2022-10-31 · Duration: 1:18:53
URL: https://www.youtube.com/watch?v=UWQsbBZHHUU

KEYPOINTS

• This is a compilation on why ASCVD prevention must start early.
Attia assembles clips from earlier conversations, chiefly with Allan Sniderman and Tom Dayspring, with commentary in between, ordered as a primer on atherosclerotic cardiovascular disease, cholesterol and apoB. His premise: people under 30, 40 or even 50 think heart disease isn't their problem yet, and the data say otherwise.

• The first event is often the last.
Historically, more than half of first heart attacks were fatal, which is why a cardiologist friend once joked he saw fewer heart attacks than pathologists. Survival has improved, but sudden death remains a common first symptom, so waiting for symptoms is a poor strategy.

• Events cluster earlier than people assume.
In the data Attia shows, slightly over 50% of men who will have a cardiac event have it before 65, and almost 25% before 54. For women it's about one-third before 65; women carry the same disease burden but experience it about a decade later.

• Atherosclerosis starts in youth.
Autopsy work by Herbert Stary and colleagues, and studies of young soldiers and accident victims, showed atherosclerosis in people in their 20s and 30s. The disease gets a foothold over the first three decades, and lesions that can cause clinical events typically develop from the fourth decade onward.

• The 10-year risk model has two fatal flaws.
Sniderman credits 10-year risk calculators with a big step forward in the 1980s–90s, but under the 2019 ACC/AHA algorithms almost everyone is 'low risk' at 40, so treatment effectively starts at 55–60. First, because there are many more people under 60, the absolute number of events in 'low-risk' younger people is high even though the rate is low. Second, by 60 the disease has been progressing for decades.

• A population risk number isn't your risk.
A 4.1% 10-year estimate means about 4 of 100 similar people will have an event, but real risk within that group varies widely. Telling someone their risk is above 7.5% also implies 92.5% of the time nothing happens, a weak motivator. Sniderman prefers lifetime or 30-year risk: for a 30-year-old, the risk to 65 might be around 30%, a number people can act on, and you can show how much benefit is lost by starting at 45 or 55 rather than 35.

• There's no 'good' or 'bad' cholesterol, only lipoproteins.
Dayspring stresses that cholesterol is carried in lipoproteins, and the apoB-100 family (LDL, VLDL, IDL and Lp(a)) is atherogenic; apoB-48 on chylomicrons is set aside. Each atherogenic particle carries one apoB, so apoB counts the particles that enter the artery wall, in the presence of an injured endothelium.

• Standard lipid panels mislead.
An LDL-C of 140 mg/dL says little about particle number. Standard panels give several numbers, but treatment decisions are mostly based on LDL-C, so the others 'do nothing'. Attia is pessimistic that medical training will switch to apoB soon, even though the 2019 guidelines leaned toward it.

• Mendelian randomization makes apoB the causal metric.
Because genes are randomly allocated at conception, Mendelian randomization avoids much of the confounding that plagues 30-year observational studies. Studies in the last decade show apoB (and cholesterol) is causal while HDL is not, and that apoB outperforms LDL-C for risk.

• Lower apoB further and earlier.
Sniderman suggests at least a 50% reduction in higher-risk people. Attia argues physiologic levels are below about 50 mg/dL; PCSK9 inhibitors routinely reach 20–40. Halving plasma cholesterol barely changes total body cholesterol, so very low levels aren't dangerous, and children live safely around 40. Attia thinks apoB of 20–30 from your 20s could largely eliminate ASCVD and treats an apoB of 60 (about the 5th percentile) as a ceiling.

EXAMPLES

• The woman with an LDL of 220
One clip describes a patient with total cholesterol over 300, LDL-C around 220 and apoB about 170 mg/dL, the kind of case that would be flagged early with lifetime thinking but missed by 10-year calculators at a young age.

• A 40-year-old with a zero calcium score
Attia walks through a 40-year-old at the 50th percentile for apoB (the 20th percentile is about 80 mg/dL), not insulin resistant and with a calcium score of zero, ambivalent about therapy. He argues the zero score doesn't remove decades of future exposure.

• Two calculators, different answers
Attia notes one algorithm might say 10% and another 15–20% for the same person, both of which are meaningless to an individual who will either have an event or not.

• Hypertension's lesson
Sniderman contrasts decades of basic-science research on hypertension with the clinical reality that drugs are used simply because they work, and notes that risk factors track: someone in the high group at 35 has about a 95% chance of staying there.

• Plaque precedes events by decades
Sniderman explains that for someone who has a heart attack at 45 or 50, the disease didn't start two years earlier; it has been accumulating since early adulthood, which is the core argument for treating cumulative apoB exposure rather than waiting for risk scores to cross a threshold.

OTHER RELEVANT

- **Measure apoB, not just LDL-C.**
  Ask for apoB (and check Lp(a) once); it reflects particle number, the actual driver. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Think in 30-year or lifetime risk.**
  If you're 30–45, evaluate your exposure to age 65 and beyond rather than your 10-year estimate.
- **Start earlier and aim lower.**
  For people already tracking high in their late 30s or early 40s, lowering apoB toward the 5th–20th percentile is Attia's approach; discuss options and trade-offs with a clinician.
- **Don't be reassured by youth or a zero score.**
  Disease begins decades before events; prevention is cheapest and most effective early. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

228 Improving body composition, female-specific training principles, & overcoming an eating disorder

Guest: Holly Baxter
Date: 2022-10-24 · Duration: 2:32:07
URL: https://www.youtube.com/watch?v=kD3I7WchL9E

KEYPOINTS

• Baxter's path ran from sprinting to bodybuilding to recovery.
Holly Baxter, a coach and competitive bodybuilder who grew up in a small Australian town, was a sprinter (100 m, long jump, triple jump) and only began lifting around grade 11. She later worked with a coach linked to 2000 Olympic 400 m champion Cathy Freeman, and built a career in nutrition and resistance training, eventually spending about half her work week coaching in person.

• Her eating disorder began early and lasted a decade.
Baxter describes a childhood with a lot of hostility and confrontation, depression, two suicide attempts and hospitalization for much of grade 11. A brief period of anorexia became binge eating disorder and bulimia, a pattern that continued for about 10 years. She was fortunate to avoid esophageal erosion, though she never had blood work then to check electrolytes.

• Weekly therapy was the turning point.
Since 2016 she has consistently attended therapy nearly every week, missing maybe 20 weeks in total for travel. Consistency made her accountable and got her talking about past trauma and family communication styles she had never examined. Part of recovery was accepting a body weight over 70 kg (peaking around 75 kg) after years of fearing it; she now sits around 63 kg.

• Contest-lean women are not healthy.
At competition Baxter got to about 10–11% body fat. She lost her period for about five years, even after calories and body fat returned to normal, which she attributes to years of bingeing and purging. Among competitors she has coached, roughly half lose their cycles; Attia frames amenorrhea as the body signaling it isn't fit to reproduce.

• Building muscle is slow, even with excellent conditions.
Natural athletes gain on the order of a pound or so of lean mass per month at best in a dedicated phase. Baxter's best year was 13 lb of fat-free mass in 12 months, including about 6 kg in one late stretch, with training volume up about 50% in the first 12 weeks, 2–2.5 hours a day, five days a week, and 10,000 steps instead of cardio. You won't 'accidentally' get bulky.

• Beginners need little volume to start.
Baxter starts new clients with 30–40-minute sessions, three days a week, and perhaps one working set per exercise at RPE 6–7 (a set of 10 with 3–4 reps in reserve). Weekly volume starts around 10–15 sets per muscle group and can progress to roughly 30 in advanced lifters if they can execute.

• Compound lifts anchor the program, with lots of variation.
Every program includes a squat or hinge variation (heels-elevated, Smith machine, box squats, deadlift variants), adjusted to anatomy, since long femurs change squat mechanics; Baxter's low-bar squat went up about 50% for that reason. Exercise choice adapts to the equipment available.

• Nutrition is about half the outcome.
Protein targets for hypertrophy range from about 1.8 to 3 g per kg of lean body mass depending on preference. For a build phase, a 10–20% calorie surplus is enough; studies comparing 20%, 40% and 60% surpluses mostly show extra fat gain above about 20%.

• Cut slowly, then 'reverse diet'.
For a 140-lb woman wanting to lose 10 lb of fat, Baxter aims for around 0.5–1% of body weight per week, about 0.7–1.4 lb. After a cut, she adds calories back in small weekly increments (about 100 kcal) so maintenance is restored gradually, holds weight for a while, then cuts again if needed.

• Female programming leans toward higher reps, with exceptions.
Baxter defaults to the hypertrophy range (8–12 or 8–15) and some endurance work (15–20) for women, but says it's roughly a 50/50 split, and many women do well with heavy, low-rep work too. Her clientele has shifted to ages 35–65, where bone density and life constraints like raising kids reshape priorities.

EXAMPLES

• The pull-up gap
Baxter estimates about 90% of women can't do a single unassisted pull-up; her own last max-rep set was about 20 at body weight, and she sometimes adds load.

• From 20s to 90s
Starting Romanian deadlifts with 20–25-lb dumbbells, Baxter progressed to 90-lb dumbbells for sets of 12, which shows how fast novices can progress with consistent work.

• Rest by heart rate
Rather than a fixed rest timer, her rule of thumb: start the next set once heart rate is back below about 100 bpm.

• The 2,000-calorie client
For a weight-stable woman eating 2,000 kcal, Baxter would move to about 2,400 for a building phase, adjusting the surplus partly to the client's comfort with gaining some weight; when cutting, intake might come down to around 1,875, then return gradually.

• Her father's bones
Baxter's father has severe osteoporosis and arthritis and needs a double shoulder reconstruction, which motivates her focus on bone mineral density and longevity. Attia notes the message applies to both sexes but is especially important for women, who are sometimes more hesitant to lift heavy.

OTHER RELEVANT

- **Seek consistent therapy for disordered eating.**
  Baxter's recovery came from weekly, long-term work, not a quick fix. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Treat a lost period as a warning.**
  Amenorrhea during dieting or training signals inadequate energy and can persist for years. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Start with minimal effective volume.**
  Three short sessions and a few hard sets build habits and strength without burnout.
- **Eat enough protein, modest surplus.**
  Aim for about 1.8 g/kg of lean mass or more; keep surpluses near 10–20%.
- **Lift for bones as you age.**
  Resistance training matters especially for women in midlife for bone density and function. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

226 The science of happiness | Arthur Brooks, Ph.D.

Guest: Arthur Brooks
Date: 2022-10-10 · Duration: 1:47:49
URL: https://www.youtube.com/watch?v=dA5OmuP8vTQ

KEYPOINTS

• Fluid intelligence peaks early; crystallized intelligence rises later.
Drawing on Raymond Cattell's work, Brooks explains that fluid intelligence — raw processing speed, innovation, solving novel problems — peaks in the late 30s and declines through the 40s and 50s. Crystallized intelligence — pattern recognition, explaining, teaching, managing people — improves through the 40s, 50s and 60s and stays high into the 70s and 80s. That's why many classical musicians peak in their late 30s, and why he can no longer read his own mathematically dense academic papers from age 35.

• Thriving later means jumping to the 'second curve'.
Brooks argues the people who end up happy in later life deliberately move from fluid-intelligence work to crystallized-intelligence work — teaching, mentoring, synthesizing. His 2019 article on this became one of the 50 most-read pieces of that year across publications and grew into his book 'From Strength to Strength' (February 2022).

• Happiness has three 'macronutrients': enjoyment, satisfaction and purpose.
Parallel to Attia's healthspan framing, Brooks proposes a 'happiness span'. Without enjoyment, satisfaction and purpose in abundance and balance, you won't report being a happy person. He also stresses that unhappiness is a separate subject, not simply the absence of happiness.

• Satisfaction fades by design.
The elation of a job well done leaves quickly so you'll be ready for the next circumstance — just as your pulse returns to baseline 15–30 minutes after a treadmill session. An ancestor staring joyfully at berries while a sabre-toothed tiger crept up wouldn't survive. Homeostasis is why accomplishments never satisfy for long.

• Satisfaction = what you have ÷ what you want.
Rather than endlessly managing your 'haves', Brooks advises managing the denominator — your wants. Serious 'wants management' can be a game-changer for driven people.

• Use a 'reverse bucket list'.
His old bucket list made him feel like a loser for everything unfulfilled. Now he lists his worldly cravings and ambitions and makes a conscious, metacognitive commitment not to be attached to them — including his own opinions.

• Men especially lack real friends.
Happy people without spouses have very close lifelong friends — people who know your secrets and would take your 2 a.m. call. Successful men often have plenty of 'deal friends' but no real friends; when Brooks asks men to name two and when they last spoke, they struggle. Spouses are great, but even married people need friends.

• Loneliness and solitude are different.
Isolation is always bad, but solitude is needed at different levels for different people. You can be lonely inside a relationship — partners who are lonely while living together is a strong predictor of divorce. Longitudinal data, including the Harvard Study of Adult Development, show happy people in their 80s and 90s had cultivated strong relationships decades earlier.

• Money, power, pleasure and fame are the four idols.
Fame sounds unappealing to most, but the desire for admiration and prestige is the same idol. Success addiction and workaholism trade being happy for being special; Brooks calls the belief that the world would be better if everyone were success-addicted a fallacy of composition.

• Identify your 'death fear'.
Brooks says most people aren't afraid of dying itself but of the extinction of how they understand themselves — becoming irrelevant, being forgotten. For many of his Harvard students it's fear of failure. Fear, he argues, is the antithesis of love.

• Ancient Hindu stages map the second half of life.
The Vedic ashramas divide an ideal life into four 25-year quarters. The hardest transition — a 'second adolescence' — is around 50, entering vanaprastha (50–75), which requires wanting less and chipping away, followed by the final stage from 75. Brooks notes the odds of reaching 100 in the US are about one in 6,000, so the ages aren't dogma.

EXAMPLES

• French horn decline
Brooks went professional at 19 aiming to be a soloist, but by his mid-20s his technique was declining for unclear reasons. He finished a college degree by correspondence a month before turning 30 — partly in secret, because classical music is 'a cult' — left horn at 31 and earned his PhD at 34.

• The man on the plane
On a red-eye from LA to Dulles, Brooks overheard a famous, admired older man tell his wife he might as well be dead because no one cared about him anymore. Brooks realized he'd be that man in 30 years without a plan; he has never revealed the man's identity.

• Bach's second curve
Bach died surrounded by people who loved him because he dedicated his work to others rather than clinging to the ego of fame.

• Running a think tank
As CEO of the American Enterprise Institute for 10 years, Brooks managed about 300 employees, raised roughly $50 million a year and worked 80-hour weeks — 'like running for the Senate and never getting elected'.

• The five-years exercise

He asks both his ~27-year-old MBA students and peers his own age to imagine themselves five years older, as a way to reveal how they neglect relationships.

OTHER RELEVANT

- **Plan your second curve before you need it.**
  Shift deliberately toward teaching, mentoring and synthesis as fluid abilities decline.
- **Manage wants, not just haves.**
  Write a reverse bucket list and practise detaching from ambitions. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Audit your real friendships.**
  Name two people who'd take your 2 a.m. call and when you last spoke; schedule time with them.
- **Seek solitude, avoid isolation.**
  Distinguish chosen quiet from loneliness, including loneliness within a partnership. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Name your death fear.**
  Reflect on what you fear losing about your identity, and how it drives the four idols.

225 The comfort crisis, doing hard things, rucking, and more | Michael Easter, MA

Guest: Michael Easter
Date: 2022-10-03 · Duration: 2:04:03
URL: https://www.youtube.com/watch?v=OHdp75ezdyY

KEYPOINTS

• We're living in a 'comfort crisis'.
Michael Easter, a journalist and author of The Comfort Crisis, argues that modern life has engineered away nearly every discomfort humans evolved with (hunger, cold, boredom, physical effort, exposure to death) and that removing them all has costs to health and well-being. For 99.999% of our evolution, he notes, those discomforts were constant.

• Getting sober taught him the value of hard things.
Easter grew up with a single parent and a family history of alcoholism. He drank more than his peers without consequences until about 23–24, living alone in New York for grad school, when he realized that if he kept going he would die early, whether at 35, 55 or 75. He quit in December 2014 and got involved with people with similar struggles, as his mother suggested; the early 'white-knuckling' was the hardest thing he'd done.

• Boredom is a signal, and smartphones killed it.
Boredom is an evolutionary discomfort telling us the return on how we're spending time has worn thin, so go do something else. Easter traces external stimulation from 1920s radio to 1950s television to June 29, 2007, the iPhone's launch, which he calls the death of boredom. He cites data that Americans spend around 12 hours a day consuming media, and recommends letting boredom happen for creativity and reflection.

• Nature works best without a phone.
Easter's rule when he brings friends rucking or into the backcountry: no phone, no podcast, no music. Disconnection plus nature delivers benefits that screen-mediated outdoor time doesn't.

• Hunting changes how you think about food and death.
Hunting is 'extreme boredom and moments of pure panic', scouring thousands of acres, not action-packed. Killing your own food makes the cost of a meal, and the ease of modern food, viscerally clear. Attia recounts his daughter's first hunt; Easter describes an elk hunt at 11,000 feet that reshaped his thinking about life and death.

• Happiness can thrive without Western comforts.
In Bhutan, a country of roughly three million (with around 600,000 in the capital, Thimphu, by Easter's figures), GDP ranks low globally but happiness measures rank high; one researcher found about 92% of Bhutanese say they are happy. Death is woven into culture: people contemplate it several times a day, and clay tsa-tsas made with cremated ashes sit everywhere, sometimes 300 at a roadside bend.

• Perspective on deep time helps.
If Earth's history were one calendar year, all recorded human history fits into roughly the last 27–33 seconds before midnight on New Year's Eve. Easter says he'd rather be homeless today than king of France 500 years ago, a reminder of how much our comforts have improved life and of our responsibility to use them well.

• Misogi: challenges with a 50% chance of success.
Borrowed from a Japanese purification concept, a misogi is a once-a-year challenge you have about a 50% chance of finishing and that won't kill you. The point is to learn that you chronically undersell your capabilities and to carry that confidence into everyday life.

• Rucking is a near-perfect fitness tool.
Walking with weight on your back combines cardio and strength. Running loads joints with roughly eight times body weight per stride versus about three times for walking, so even adding 30% of your body weight while rucking stresses the knees less than running. Heavy rucking can push heart rate high; Attia saw 150s–160s on a hard ruck versus his usual 130s–140s.

• Load, packs and practice.
Attia and Easter ruck with about a third of their body weight as fast as they can walk, which is simply uncomfortable. But even 20 lb during phone calls 'sneaks in' steps with load. A hip belt helps shift weight off the shoulders for heavy packs over 100 lb.

EXAMPLES

• Boulder under the Santa Barbara Channel
One misogi: a group took turns diving, picking up an 85-lb boulder, walking about 10 yards underwater and surfacing, for roughly five miles.

• Backcountry hunters' body composition
A small study of hunters packing loads deep into the mountains over about 10 days found they lost around 14% of their body fat while keeping, and in some cases slightly gaining, muscle.

• The axis deer shot
Attia describes a 47-yard bow shot on an axis deer (about 150 lb) that hit the neck and spinal cord, so he had to run up and finish it with a knife, which made the reality of taking a life vivid.

• Attia's carry metric
For women, one of Attia's strength tests is carrying 75% of body weight for a minute, which is impressive given typical upper-body strength.

• The farm in Tuscany
Staying on a 400-acre Tuscan farm where the newest building was about 300 years old and the oldest church 500–600 years old gave Easter a sense of how small a single life is.

OTHER RELEVANT

- **Schedule a yearly misogi.**
  Pick a hard, safe challenge with roughly even odds of success. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Let yourself be bored.**
  Leave gaps without a phone; boredom is a cue to redirect and a source of ideas. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Start rucking.**
  Begin with a light load (even 20 lb), walk with good posture, use a pack with a hip belt as loads grow, and build toward a challenging but joint-friendly load; it preserves muscle while burning fat.
- **Go outside unplugged.**
  Get time in nature without devices, letting your attention wander rather than filling every minute with input.
- **Contemplate mortality.**
  Reflecting on death, as in Bhutan, can sharpen priorities and gratitude. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

224 Dietary protein: amount needed, ideal timing, quality, and more | Don Layman, Ph.D.

Guest: Don Layman
Date: 2022-09-26 · Duration: 2:14:12
URL: https://www.youtube.com/watch?v=BqmG2y4IeY8

KEYPOINTS

• Muscle is an organ of metabolism as well as movement

Don Layman, a professor emeritus of nutrition, grew up on a farm in the 1950s and has studied protein and muscle for decades. He sees muscle as doing two jobs. The first is mobility: most people who die after 65 die from some consequence of immobility, such as falls, fractures or hospitalization. The second is metabolism: skeletal muscle is the main site of insulin action and holds 75–80% of the body's glucose storage capacity. From that view, he says, you should plan a diet around muscle and around protein first.

• The RDA is a minimum to prevent deficiency, not an optimal intake

The 0.8 g/kg RDA comes from short nitrogen-balance studies, often seven days long, in college-age students. The method measures nitrogen and multiplies it by 6.25, assuming protein is 16% nitrogen, so it counts anything containing nitrogen. The estimated average need is then raised by two standard deviations to cover about 97.5% of people. Layman says every essential amino acid also has metabolic roles at intakes far above that minimum. Leucine activates mTOR, arginine supplies nitric oxide, lysine feeds carnitine, and cysteine is used to make glutathione.

• Protein quality varies widely

Animal proteins and most isolates, including soy isolate, are about 95% or more digestible, while raw plant sources may be only 60–70% available. On DIAAS, the digestibility-corrected quality score, Layman ranks whey isolate at about 100%, a ribeye at about 96%, soybeans at about 80% and shredded wheat at about 40%. A cereal label claiming 4 g of protein is still just nitrogen × 6.25. Of roughly 7,000 foods in the USDA database, about 4,000 have amino acid profiles and fewer than 300 have DIAAS scores. Layman is working on a simpler score based on three amino acids: leucine, lysine and methionine.

• At high enough intake, the protein source matters less

Layman's rule of thumb: at about 120 g of protein a day, the split between animal and plant probably doesn't matter, because you will cover your essential amino acids. At 50 g it matters enormously. So a plant-based eater aiming for about 125 g is probably fine, while a vegetarian eating 56 g is 'going to get in trouble'.

• Older muscle is less responsive, but more protein can make up for it

Muscle proteins turn over with half-lives of roughly 15–16 days. The body makes about 300 g of new protein a day while most Americans eat about 80 g (women about 70, men about 90), so most of it is recycled. With age, a given dose of protein triggers less synthesis than it does in a 16-year-old. Layman says raising intake from 0.8 to about 1.6 g/kg can bring a 65-year-old's muscle protein synthesis response up to that of a 20-year-old.

• Protein is an absolute need, so never set it as a percentage of calories

A 75-year-old woman eating 1,200 calories still needs about 100 g of protein, which is 35–40% of her calories. Setting fat at 30% and carbohydrates at 50% and leaving protein with the remainder gets it backwards. Layman says you should set protein first and build the rest of the diet around it.

• The first meal of the day matters most

After an overnight fast, protein synthesis is suppressed and muscle is catabolic until a meal provides about 3 g of leucine, which is roughly 30 g of high-quality protein. Layman advises 40–45 g at the first meal and again at the last meal, with smaller amounts between. In his study of people averaging 37 years old, 90 g split 30/30/30 beat 10/20/60. He now thinks the ideal might have been closer to 40/10/40.

• Big meals aren't wasted, but muscle has a ceiling per meal

You will digest and absorb 100 g of protein at a meal, despite the myth. However, muscle can use only about 25–60 g of it per meal depending on quality, and the liver uses the rest. Total daily protein still matters. A very large lifter needing 250 g would do better with four or five meals than two, but Layman says that's about total supply rather than the leucine–mTOR signal.

• Higher-protein diets help weight loss mostly by preserving lean mass

Layman's trials ran from 12 weeks to 16 months, the longest multicenter one with about 120 subjects. Calories were equal, and the higher-protein group lost about 8 lb more, roughly 6.5 lb of it fat. He estimates an energy advantage of about 170 calories a day, enough to explain the difference. For anyone over 40, losing lean mass during weight loss matters, and he says that's when protein becomes critical.

EXAMPLES

• Ruminants upcycle protein

For every 60 g of low-quality plant protein and nitrogen a ruminant eats, Layman says it can produce about 100 g of protein with a balanced amino acid profile. He uses this to argue that cattle play a role in producing quality protein.

• Peter's shoulder surgery

Unable to squat or deadlift after shoulder surgery, Peter lost 10 lb in three weeks, some of it water. Five months later he still hadn't fully regained his muscle mass, and he uses this to show how quickly muscle is lost and how hard it is to rebuild.

• Plant 'milk' and plant 'meat'

Layman points out that many nut milks have about 1 g of protein per 8 oz versus about 8 g in cow's milk, and he calls labelling them milk 'pure deception'. On plant-based meats like Beyond and Impossible he has limited knowledge. Lab-grown meat is described as unlikely to be feasible on energy, cost and sanitation grounds.

• Kids need small amounts

Children grow efficiently on snacks of 8–10 g of protein. A small child may need only about 40 g a day, so parents needn't push adult-sized portions.

- **Why industry funds this research**
  Layman explains that NIH has generally left applied food research, such as comparing whey and soy, to industry. That forces researchers to turn to dairy councils and other industry bodies for funding.

OTHER RELEVANT

- **Front-load protein**
  Make breakfast, or your first meal, 40–45 g of quality protein, and do the same with your last meal.
- **Count grams, not percentages**
  Set an absolute daily target (Layman cites about 1.6 g/kg for older adults) and build meals around it. This matters most when cutting calories.
- **Be skeptical of epidemiology on 'high' protein**
  Studies often call 1.2 g/kg 'high' and define low as under 0.8 g/kg or 10% of calories. 'High-protein' groups also often eat more calories overall, so protein is 'along for the ride'.
- **If plant-based, eat more total protein**
  Aim for about 125 g a day and choose higher-quality sources to cover leucine and lysine.

222 How nutrition impacts longevity | Matt Kaeberlein, Ph.D.

Guest: Matt Kaeberlein
Date: 2022-09-12 · Duration: 2:43:50
URL: https://www.youtube.com/watch?v=4sqyGwqyAao

KEYPOINTS

• Human nutrition science is structurally hard to do well.
Kaeberlein and Attia note that because people age so slowly, longitudinal studies of today's 70-year-olds rely on data and methods from 40 years ago; much nutritional epidemiology is decades old. Both have grown less dogmatic: healthy people eat very different diets, from protein-hungry ancestral patterns to ketogenic diets, often sharing little besides leafy vegetables.

• Calorie restriction is the oldest, most robust longevity intervention in animals.
Experiments date to the early-to-mid 1930s. In mice, CR extends lifespan substantially — the largest effect Kaeberlein has seen is about 65% restriction producing about a 65% lifespan increase in Weindruch and Walford's graded study. CR mice also have less age-related disease and preserved function in heart and immune system, which he finds more compelling than epigenetic clocks.

• CR has real costs to muscle and strength.
Calorie-restricted mice lose body weight and grip strength — normalized grip strength drops on the order of 30–35%. Attia argues few humans would view losing 30% of weight and 30% of strength as good; Kaeberlein agrees the human trade-off is uncertain.

• The monkey studies disagreed.
The Wisconsin rhesus study (2009) reported CR animals outlived controls with fewer age-related diseases; the NIA study (2012) found no lifespan difference. Wisconsin controls ate a diet with about 28.5% of calories from sucrose, a key reason for the divergence; a later reconciliation paper tried to explain it. The 30–40-year experiments can't realistically be repeated. Kaeberlein reads the overall monkey data as suggestive that CR improves health in primates, with the lifespan question unresolved.

• Much of the 'fasting' benefit may be calorie restriction — and vice versa.
Lab CR mice eat their ration quickly, so they also fast most of the day. Studies that fed mice continuously found about two-thirds of CR's benefit came from fewer calories and one-third from the fasting period. Kaeberlein's 2021 Science review argued much intermittent-fasting and time-restricted-feeding literature conflates the two.

• Starting CR late helps far less; rapamycin works late.
Most evidence suggests CR started past about 15 months in mice (like a 40–50-year-old human) yields little benefit. In a 2019 study of 800 female mice switched between diets, late CR had small effects. By contrast, the NIA Interventions Testing Program — rapamycin nominated by Dave Sharp — found robust lifespan extension starting at 20 months, about a 60–65-year-old human, published 2009.

• mTOR inhibition didn't cause the expected muscle loss.
Because mTOR drives muscle protein synthesis, researchers expected rapamycin and CR to accelerate sarcopenia. Lab animals didn't show that, though Kaeberlein cautions against extrapolating.

• Protein restriction extends lifespan in mice, but humans are another matter.
Restricting total protein or specific amino acids — methionine, tryptophan, branched-chain amino acids — extends mouse lifespan, possibly via different mechanisms, including FGF21 released on low-protein diets. Steve Simpson's nutritional-geometry work explored these ratios.

• Protein needs probably rise with age.
In the Levine/Longo epidemiological study, lower protein was associated with lower mortality before 65 but higher mortality after. Because death rates climb nonlinearly after 65, Attia's own modelling suggested high protein's net mortality benefit begins around 50. Attia targets about 1 g per pound of body weight — over twice the 0.8 g/kg RDA — in roughly four 40 g meals.

• IGF-1 is probably not very informative after about 50.
An IGF-1 receptor antibody in old mice (Nir Barzilai and Yousin Suh) gave roughly a 14–15% median lifespan extension. But Attia argues that a fit person with slightly higher IGF-1 and a younger immune system likely has lower total cancer risk; lowering IGF-1 from high levels may cut cancer risk without the reverse being symmetric.

• Function and exercise matter most.
So-so epidemiology suggests 30–50% of exercise's full benefit comes from going from nothing to about 15 MET-hours per week. Attia emphasizes that frailty dominates life after 75: living to 100 cancer-free is pointless if you're an invalid for 25 years.

EXAMPLES

• Intermittent ketogenic mice
One lifelong ketogenic diet study in mice showed no lifespan effect, but an intermittent version — keto every other day or every few days, normal diet otherwise — gave about a 15% increase.

• Organ shrinkage with fasting
Within 24 hours, fasted mice show dramatic reductions in organ size followed by rapid regrowth on refeeding — also seen in fasting-mimicking diet work.

• The 80/20 principle
Attia credits Tim Ferriss for the idea of getting 80% of results with 20% of effort — relevant to nutrition, where getting basics right matters more than fine-tuning.

• Whole foods vs. protein bars
Kaeberlein argues eating a simple whole food is inherently less risky than a protein bar with 14 ingredients, given how little is known.

• Reverse-feeding experiment

Attia asks whether anyone has fed CR and control mice at the same frequent intervals — every two hours — to remove the fasting component. Kaeberlein says at least one study did something similar, which is where the roughly two-thirds calories / one-third fasting split comes from; he stresses this is mouse data and human eating patterns differ.

OTHER RELEVANT

- **Don't rely on calorie restriction for longevity.**
  Mouse benefits are large when started young, but human costs in muscle and strength may outweigh gains, especially in midlife.
- **Prioritize adequate protein as you age.**
  Spread protein through the day; Attia's 1 g/lb target is his practice, not a universal prescription.
- **Be skeptical of fasting hype.**
  Benefits attributed to time-restricted eating may largely reflect eating fewer calories. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Build function now.**
  Even modest exercise captures a large share of the benefit; strength and fitness protect against late-life frailty.
- **Judge interventions by function, not just biomarkers.**
  Kaeberlein prefers evidence that a heart or immune system still works like a young one over shifts in epigenetic clocks or lab markers, which may not translate to outcomes.

221 Understanding sleep and how to improve it

Guest: Matthew Walker
Date: 2022-09-05 · Duration: 1:37:11
URL: https://www.youtube.com/watch?v=APEwc0HjAqg

KEYPOINTS

• Modern society has cut sleep sharply in an evolutionary blink.
Walker argues evolution spent millions of years establishing an eight-hour night of sleep, and in about 70 years we've lopped off roughly 20–25% of it. He compares it to deciding to lower everyone's oxygen saturation by 20–25% for a century — no one would think that a good idea. Sleep deprivation likely degrades health faster than not eating or not exercising; Guinness stopped accepting sleep-deprivation record attempts.

• Sleep cycles every 90 minutes, but the mix changes across the night.
You descend from stage 1 through stages 2, 3 and 4 (deep, slow-wave sleep), rise back after about 70 minutes, then enter REM — repeating roughly every 90 minutes. Early cycles are dominated by deep non-REM sleep; later cycles by REM. Sleep is scored in 30-second epochs, using criteria in place for 60–70 years.

• Cutting sleep short disproportionately costs REM.
Someone sleeping six hours instead of eight loses 25% of total sleep but may lose up to 70% of their REM, because REM concentrates in the final hours. Waking at 5:30 to 'get a jump start' has a steeper price than it seems.

• Brainwaves slow dramatically as sleep deepens.
Awake, brain activity oscillates around 50–60 times per second; relaxing in bed, it drops toward 10 cycles per second; theta around 6–7. Stage 2 features sleep spindles of 10–15 cycles per second. Deep sleep's slow, high-amplitude waves looked so coma-like that it had a bad reputation for 20–30 years.

• Chronotype is largely genetic and shifts with age.
About 25–30% of people are morning types, 25–30% evening types, the rest in between; companies like 23andMe estimate it from genes. Teenagers' chronotype moves later, so a 15-year-old in bed at 10:30 for a 5:30 bus can't fall asleep — biology, not laziness. It drifts back in adulthood and earlier again in old age, hence Florida's early-bird dinner specials.

• Sleep efficiency means you need more time in bed than sleep.
A healthy person in their 40s has about 90% sleep efficiency. To get eight hours (480 minutes) of actual sleep, they need roughly 8 hours and 50 minutes in bed. Walker's 7–9 hour recommendation refers to sleep, not time in bed.

• Counterintuitively, insomnia is treated by restricting time in bed.
Compressing the sleep window builds sleep pressure and re-teaches the brain that bed is for sleep. Don't lie awake: after about 20 minutes, get up and return only when sleepy, to avoid a learned association between bed and wakefulness.

• Naps are a double-edged sword.
For people sleeping well, naps can be fine — hunter-gatherer tribes often nap in summer afternoons and sleep around 8:30–9 p.m. But for insomniacs, a late-afternoon nap releases sleep pressure needed at night.

• Cool room, warm bath.
Current data suggest about 65–67°F is optimal. A hot bath or shower helps not because you're toasty but because blood rushes to the skin and core temperature then plummets. A smart thermostat can warm the room in the final 15–20 minutes before waking.

• Walker has softened on blue light.
His book cited a Harvard study in which an hour of iPad reading delayed melatonin, reduced REM and impaired sleep for days. Work by Michael Gradisar at Flinders University changed his mind: he's less convinced device harm comes from blue light, though he believes it has some effect; engagement and displaced sleep matter too.

• Coffee's benefits may come from antioxidants, not caffeine.
A 2017 review found decaffeinated coffee — same antioxidants, no caffeine — shares many health associations. For Americans eating poor diets, morning coffee may be a main antioxidant source. Walker still advises avoiding caffeine in the afternoon.

• Sleeping pills carry real risk; CBT-I is first line.
The FDA updated mortality warnings on sleeping pills. Dan Kripke's research found even three to 18 pills per year associated with statistically significant mortality increases. In 2016 the American College of Physicians said pills shouldn't be first line for insomnia; cognitive behavioural therapy for insomnia (CBT-I) should.

EXAMPLES

• Attia's residency sleep
During surgical residency, averaging about 114 hours a week at the hospital, Attia calculated he slept about 28 hours a week — none one night, eight another — and believed for years that sleep was optional.

• Survival without food vs. sleep
One person survived 382 days without food; even a lean person could last about 30 days. The last credible sleep-deprivation record attempt reached roughly 24 days, debatably.

• Phone-first mornings
Walker warns that checking your phone on waking floods you with anxiety. His rule: delay it, and try to push to 10 minutes after you sit down.

• Three-minute meditation
He argues three minutes daily beats 20 minutes once a week — consistency over dose.

• Sleep tracking blind spots
Walker notes that sleep quality is hard to sense because you are non-conscious during it, and current wrist-worn trackers

cannot reliably measure some of the metrics that matter, such as the depth of deep sleep. He treats them as rough guides rather than definitive scores.

OTHER RELEVANT

- **Protect the end of the night.**
  Waking early to gain time disproportionately sacrifices REM sleep.
- **Budget time in bed for sleep efficiency.**
  Plan roughly 8 hours 50 minutes in bed for eight hours' sleep.
- **Build a wind-down routine.**
  Sleep is like landing a plane: spend 15–30 minutes on stretching, meditation, and putting devices away.
- **Try CBT-I before pills.**
  Work with a therapist; use pills only as a short-term, last resort with your doctor.
- **Respect your chronotype.**
  Schedule demanding tasks around your biology where possible, and don't blame teenagers for late body clocks.
- **Keep the bedroom cool, not you.**
  Fall asleep more easily in a room that is too cold than too hot; warm up in bed or with a bath beforehand so core temperature can drop, and avoid alcohol in the evening and caffeine in the afternoon.

220 Ketamine: Benefits, risks, and promising therapeutic potential | Celia Morgan, Ph.D.

Guest: Celia Morgan
Date: 2022-08-29 · Duration: 1:42:40
URL: https://www.youtube.com/watch?v=fNFnr8UTGI4

KEYPOINTS

• Ketamine began as a safer replacement for PCP

Celia Morgan, a psychopharmacologist who has studied ketamine for nearly 20 years, explains that Parke-Davis synthesized it in the 1960s as an anaesthetic to replace phencyclidine (PCP, 'angel dust'). Both act on the NMDA receptor, but ketamine is about 10 times less potent and lacks PCP's long-lasting psychosis-like effects. Edward Domino coined the term 'dissociative anaesthetic' for the class, which some also extend to nitrous oxide. Ketamine remains a valuable anaesthetic, especially where respiratory depression is a concern.

• Its effects change with dose

At low doses, ketamine has stimulant properties. Higher doses bring perceptual distortions, a sense of floating or melting and dissociation. Morgan notes that people at higher doses are especially vulnerable to accidents because they are partly but not completely detached from reality. Like LSD, it has no practical lethal dose in the usual sense because it doesn't suppress breathing, but behaviour under its influence can be dangerous.

• Heavy recreational use causes serious bladder damage

Ketamine is directly toxic to the lining of the bladder. Morgan has worked with heavy users, including 16-year-old girls, who needed their bladders removed (cystectomy). This harm appears mainly at very high, repeated doses. She has seen people functioning on several grams a day, doses that 'would floor an elephant'. It became a recreational epidemic in the UK in the 1990s and early 2000s, partly because it was cheap and gave strong escapism.

• Regulation came late

Morgan says the US scheduled ketamine (now Schedule III) around 1997, and the UK followed in 2006. In 2003 Putin banned it in Russia even for human medical use. After Brigitte Bardot petitioned him on behalf of animals, the ban was lifted for veterinary use but kept for humans, which Morgan calls 'horrendous' given how good an anaesthetic it is.

• A single low-dose infusion can lift treatment-resistant depression within hours

Robert Berman's group at Yale published an early study in 2000 using a single infusion of 0.5 mg/kg over 40 minutes in treatment-resistant depression. For an 80 kg person that is 40 mg, compared with perhaps 100–200 mg for a recreational 'blast off'. Early studies such as Carlos Zarate's at NIMH reported response rates around 75%. As with most new treatments, rates have fallen as more studies have come out. Morgan's rough estimate is that 50–60% of patients may not respond, and she says better real-world data are needed. Benefits often last about two days to a week.

• How it works is still debated

One theory is that ketamine blocks NMDA receptors on glutamatergic neurons directly, triggering a downstream cascade. Another is that it blocks NMDA receptors on GABAergic interneurons, releasing the brakes on glutamate. It may be both. Either way, it increases synaptic plasticity in the prefrontal cortex, growing new synapses and dendrites, and this correlates with the antidepressant effect. In animals, the plasticity window starts about four hours after a dose and peaks around 24 hours.

• Time therapy for when the brain is most plastic

As a psychologist, Morgan's interest is in pairing ketamine with psychological therapy delivered in that window, so people can learn new patterns while the brain is most able to change. Her group is using EEG to chart when that window occurs in humans. She worries about frequent low or daily 'maintenance' dosing given what she has seen in addicted users, and says an international registry of real-world patients would help define safe dosing.

• Ketamine plus therapy showed promise for alcohol dependence

Morgan's trial gave three infusions of 0.8 mg/kg, one to two weeks apart. The dose was higher than for depression because of cross-tolerance with alcohol. The trial had four arms of 24 patients each (96 in total), and patients received about 11 hours of support over six months. In the group that got ketamine plus relapse-prevention therapy, the abstinence rate at six months was about 86%. The group that got placebo plus education still reached about 68%, which she partly credits to a supportive team and trial effects. A 280-patient phase 3 trial funded by the UK government is under way in NHS settings.

EXAMPLES

• Evgeny Krupitsky's Russian studies

Starting in the 1980s, Russian psychiatrist Evgeny Krupitsky gave inpatients with alcoholism or heroin addiction ketamine with psychotherapy, using intramuscular doses of about 1–2 mg/kg. Morgan recalls roughly 40% less relapse at 12 months in groups of about 100. She considers the work important but 'dodgy' by modern ethics and trial standards.

• John Lilly and Marcia Moore

Neuroscientist John Lilly, who invented flotation tanks and inspired the film Altered States, became so addicted that he described being on an almost round-the-clock ketamine drip. Marcia Moore, whose husband was an anaesthetist, also experimented heavily with it and froze to death after taking it outdoors.

• Ketamine in the UK clinic

Morgan says no ketamine product is licensed for depression in the UK because the national regulator hasn't recommended Spravato (intranasal esketamine). About five NHS centres prescribe IV ketamine off-label for treatment-resistant depression, and private clinics are emerging. She is involved with one of them.

• Why heavy users keep going

In interviews with about 120 users, reasons included cheapness, escapism and, for 'psychonauts', the pursuit of insights. Tolerance builds quickly, so people take more and more.

• Blood pressure on the drip

During infusions, blood pressure typically rises only modestly, by about 10 points. An anaesthetist is present, and one trial infusion was stopped when blood pressure went above about 180.

OTHER RELEVANT

- **Treat ketamine as medicine in a supervised setting**
  Morgan advises against self-experimentation. If someone does use it outside medical care, start with a very small dose. Doses of 100–200 mg are high.
- **Pair it with therapy rather than relying on the drug alone**
  The best results in her research come from combining ketamine with structured psychological work in the days after dosing.
- **Don't expect it to work for everyone**
  Perhaps half of people with treatment-resistant depression don't respond. Benefits may last days, so plans for maintenance need careful monitoring.
- **Watch for warning signs of misuse**
  Frequent use, rising doses and urinary symptoms are red flags. Heavy use can permanently damage the bladder.

219 Dialectical behavior therapy (DBT): skills for overcoming depression & emotional dysregulation

Guest: Shireen Rizvi
Date: 2022-08-22 · Duration: 2:36:04
URL: https://www.youtube.com/watch?v=qA2sgsxImM8

KEYPOINTS

• DBT grew out of CBT's failures with chronically suicidal patients.
Rizvi, director of the DBT clinic at Rutgers and a former student of Marsha Linehan, explains that Linehan began in the 1970s trying to apply standard cognitive behavioural therapy to people who were chronically suicidal. CBT's heavy emphasis on change left these patients feeling invalidated — as if their suffering were being dismissed — and many dropped out.

• The core dialectic is acceptance and change.
Linehan's insight was to balance change-oriented behavioural strategies with acceptance strategies drawn from Zen practice. 'Dialectical' means holding two seemingly opposite truths and finding a synthesis rather than a mushy compromise.

• Psychotherapy trials often exclude the hardest patients.
Rizvi explains the standard randomized trial — say, 12 weeks of CBT versus nothing or treatment as usual — used narrow inclusion criteria, often excluding suicidal or complex patients. CBT works well for many, but not for everyone, and evidence often doesn't generalize to those excluded.

• Linehan was, in effect, her own index case.
Linehan was hospitalized in her late teens or early 20s, received a lot of treatment, and only went public about her struggles in a New York Times piece around 2010–2011. Attia compares her synthesis to Bruce Lee's Jeet Kune Do, built from over 30 martial arts by keeping what was useful and discarding what wasn't.

• Borderline personality disorder is fundamentally emotion dysregulation.
People experience intense, uncontrollable, rapidly shifting emotions — affective lability — that drive behavioural dysregulation such as substance use, reckless spending, impulsive sex and driving. Chronic self-injury or suicide attempts appear in more than 75% — in some studies 90–95% — of people meeting criteria. Rizvi believes men are underdiagnosed and must be more severe to receive the diagnosis.

• 'Wise mind' synthesizes emotion mind and reasonable mind.
Conflict often arises when one partner is in emotion mind and the other in reasonable mind. Wise mind asks what is valid in each and seeks a synthesis.

• Radical acceptance reduces suffering without condoning.
Rumination — 'if only I'd left 15 minutes early' — adds suffering to pain. Accepting that nothing can change the present moment can bring distress from 100 down to around 50; if a problem recurs, change strategies address prevention later.

• DBT teaches skills in several domains.
Mindfulness (capacity to be aware of the present), interpersonal effectiveness, emotion regulation and distress tolerance are the core four; a fifth set of self-management skills was in the 1993 manual and now appears as 'walking the middle path', developed for adolescents and families by Jill Rathus and Alec Miller.

• Chain analysis and vulnerability factors reveal what drives problem behaviour.
A chain analysis maps the events, thoughts and feelings leading to a target behaviour like exploding in anger. Vulnerability factors — poor sleep, an overloaded schedule, physical pain — make negative emotions more likely, and treating them can make life run more smoothly.

• Opposite action changes unwanted emotions.
Simple in concept, hard to execute: act opposite to the urge. If anxiety urges avoidance, approach; and do it all the way — a fake smile doesn't work.

• DBT skills help people without a diagnosis.
Attia, who meets no DSM-5 criteria, credits DBT with transforming his anger. Rizvi wonders whether low-dose interventions like skills videos might help many people before they need intensive therapy, though evidence is still emerging.

• Distress tolerance is about surviving the moment, not solving it.
When distress is at 90 on a 0–100 scale, Rizvi says, people are not taking in information or learning much, so the first goal is to bring arousal down. Skills such as mindfulness and acceptance make an unchangeable moment more bearable; problem-solving and prevention come later, once the person can think clearly. This is why DBT separates crisis skills from change skills.

EXAMPLES

• DEAR MAN with a 13-year-old
DEAR MAN — Describe, Express, Assert, Reinforce; stay Mindful, Appear confident, Negotiate — is for asking for something or saying no. Attia role-plays asking his 13-year-old daughter to postpone getting a third ear piercing; Rizvi advises keeping it short.

• Attia's anger homework
Attia spent about three months filling out worksheets for every episode of anger — around 16 a day — realizing he didn't want his kids seeing him angry all the time.

• Accepting grief
Attia describes a close friend whose daughter drowned a year earlier, exploring how radical acceptance applies to unchangeable tragedy.

• Surgery and pain
After shoulder surgery with six trocar sites, Attia used acceptance to avoid escalating frustration, while trying to wean off pain medication; Rizvi notes chronic-pain patients are often told nothing can be done or that it's in their head.

- **Missing a flight**
  Rizvi uses a missed-flight scenario: mindfulness can lower distress in the car, even if it rises again at the airport.

OTHER RELEVANT

- **Use DEAR MAN for hard asks.**
  Script a short request, reinforce why it benefits the other person, and be willing to negotiate.
- **Address vulnerability factors first.**
  Sleep, pain and overcommitment raise emotional reactivity; fixing them can prevent blowups. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Practise opposite action fully.**
  Act against avoidance or anger urges wholeheartedly, not half-heartedly. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Find a properly trained therapist.**
  Many clinicians claim DBT without fidelity; Linehan's DBT-Linehan Board of Certification lists certified clinicians.
- **Start small with self-directed skills.**
  Rizvi suggests that people without a diagnosis can benefit from exposure to DBT skills through books, workbooks and videos. Pick one or two skills — such as noticing vulnerability factors or practising opposite action — and use them deliberately in daily life before deciding whether formal treatment is needed.

217 Exercise, VO2 max, and longevity | Mike Joyner, M.D.

Guest: Mike Joyner
Date: 2022-08-08 · Duration: 2:12:19
URL: https://www.youtube.com/watch?v=hN12iDSlFEc

KEYPOINTS

• The roughly 50% mortality benefit of activity has held up for 70 years.

Joyner, a Mayo Clinic anesthesiologist and exercise physiologist, begins with post-war London. Bus conductors climbing the stairs all day had far less cardiovascular disease than the seated drivers, and active and sedentary telephone workers showed similar gaps. He calls the roughly 50% risk reduction 'incredibly consistent' across later studies, including Harvard alumni and Swedish finishers of the 90-km Vasaloppet ski race compared with matched controls. NCI data showed about four to six extra years of life expectancy with substantial activity.

• More fitness keeps helping, with no clear plateau.

Peak capacity is measured in METs; one MET is about 3.5 mL O2/kg/min, and running a 10-minute mile is about 10 METs. Researchers once thought the benefit plateaued at 10–12 METs. A Henry Ford group in Detroit found it keeps rising to 15–16. In the study Attia highlights, the bottom 25% for VO2 max had a hazard ratio of about 5.04 versus the top 2.5%, and the third quartile was still at about 2.75. Joyner once suggested that, apart from cancer screening, people reaching 12–14 METs might safely ignore much else.

• Joyner sees no meaningful J-curve, though lifelong hard training may raise AFib risk.

He calls the real-world Vasaloppet data dispositive. Lifelong heavy trainers seem to have more atrial fibrillation than healthy people active at about 50–70 MET-hours a week. But they show no excess of fatal ventricular arrhythmias, their AFib risk is probably still lower than that of sedentary, hypertensive, obese or diabetic people, and AFib is treatable. The biggest gain comes from the first 10–15 minutes a day of activity, which improves muscle insulin sensitivity and buffers against weight gain.

• Inactivity is devastating, and decline with age is steep.

In 1966 NASA had five college-age men spend three weeks on bed rest at UT Southwestern, prompted by astronauts returning atrophied. Thirty years later Ben Levine and the late Jere Mitchell re-tested them: three weeks of bed rest had caused losses comparable to 30 years of aging. Joyner says around the mid-70s the limit shifts from heart and lungs to muscle strength. He cites the claim that about 70% of 70-year-olds can't get up off the floor.

• Build a high VO2 max early, because you lose about 10% per decade.

VO2 max typically falls about 10% per decade (estimates range from 9% to 12%). Trained people may hold steady until their late 30s or early 40s. An elite group retested in their late 40s and 50s showed that the third who kept training hard had minimal losses. Starting from 60 rather than 35 mL/kg/min means that at 60 or 70 you can out-perform an untrained 30-year-old. Attia's 'Centenarian Olympics' asks you to reverse-engineer what you want to do at 85.

• Fitness improves the autonomic nervous system, measurable by heart-rate recovery.

Fast heart-rate recovery after a maximal test reflects strong vagal tone. The vagus nerve also drives heart-rate variability and suppresses abnormal beats. Blood pressure normally rises sharply during a VO2 max test, from about 115/75 to 160/95 or more. Cardiac output (heart rate × stroke volume) can climb from about 5 to 15–20 L/min, and 30–40 L/min in elite athletes. Joyner suggests worrying less about HRV and more about whether you're doing 30, 60, 100 or 180 minutes a week.

• Elite endurance training has converged on a mostly easy, some hard model.

Across running, cycling and swimming, roughly 60–70% of training is easy to moderate, 20–30% is harder and about 10% is very hard. Joyner says Kipchoge likely runs 14–18 hours a week at 7,000–8,000 ft, with perhaps 10 miles a week faster than race pace. Joyner notes the top performers of the late 1960s and early 1970s had VO2 max values in the high 70s, not 90. Since then the gains have come mainly from better races and longer careers.

• You can out-exercise a bad diet only up to a point.

Lumberjacks ate 5,000–6,000 calories a day and the Old Order Amish stay lean through manual labor. Joyner says that in a modern high-calorie, low-activity world that's the caveat. Body temperature rises only a degree or two even as metabolism climbs 10–20-fold, an example of homeostasis.

EXAMPLES

• Joyner's weekly routine

Joyner is 63, with past bests of about 30:40 for 10K and 2:25 for the marathon. He warms up for 10–15 minutes, then does a 22-minute circuit of squat thrusts, jump rope and whole-body exercises. Then he does 8 three-minute bike 'ladders' climbing from 100 W to 350 W in 30-second steps. Easy days are 30–40 minutes of light cycling and rowing. He averaged 316 W for an hour and does something hard about 120–130 times a year, never going more than a week without intensity.

• His VO2 max then and now

As a young athlete weighing about 75–80 kg, he had a VO2 max of about 5.4 L/min, around 70 mL/kg/min. He now weighs about 95 kg after deliberately gaining weight.

• Phelps's 75s

Joyner watched a teenage Michael Phelps train at North Baltimore Aquatic Club during his Hopkins years. Coach Bob Bowman had him swim lots of 75s rather than full 200 flys, with perfect form, so his stroke count didn't change across laps even in the brutal 200 butterfly.

• Clarence DeMar

Born around 1888–1890, DeMar won the Boston Marathon seven times, took bronze in the 1924 Olympic marathon and trained all his life. He died of stomach cancer at about 70.

• Running the US convalescent plasma program

In April 2020 Joyner became principal investigator of a program planned for 5,000 patients that grew to more than 100,000. They found that high-antibody plasma given early helped. He now focuses on immunosuppressed patients who can't clear

COVID; one-time doses are about 200–400 mL.

OTHER RELEVANT

- **Avoid inactivity of every kind.**
  Walking the dog, gardening and taking the stairs all count, and even 10–15 minutes a day captures the biggest early benefit.
- **Train VO2 max hard in midlife.**
  Intervals such as 4-minute efforts, or one-mile repeats with jogs, plus mostly easy volume, raise the baseline you'll age from.
- **Use a hard-easy pattern, and build older beginners up slowly.**
  Joyner credits the hard-easy idea to Stan James and Bill Bowerman. People in their 60s–70s may need three to six months of pre-training before hard intervals.
- **Hold form and tempo during hard efforts.**
  When it burns, the goal is not losing technique or rhythm.
- **Treat hip fractures as a key risk.**
  Attia notes that one-year mortality after a hip or femur fracture in people 65+ ranges from about 25% to 60% across studies, often cited around 40–50%.

216 - Metabolomics, NAD+, and cancer metabolism | Josh Rabinowitz, M.D., Ph.D.

Guest: Josh Rabinowitz
Date: 2022-08-01 · Duration: 2:27:10
URL: https://www.youtube.com/watch?v=_kezGvY5bN8

KEYPOINTS

• Metabolism went from unfashionable to central.
Josh Rabinowitz, an MD-PhD who runs a metabolomics lab at Princeton, recalls a mentor saying that in the late 1990s metabolism researchers felt like the bottom 10th percentile because nobody found it interesting. Tools for measuring hundreds of metabolites and their fluxes have since made it a frontier in diabetes, aging and cancer.

• Concentrations hide flux.
Metabolomics measures levels; fluxomics measures how fast molecules are made and used. Attia's fasting glucose of 89 mg/dL represents only about 4–5 grams of glucose in the blood, roughly 20 calories and a few minutes of fuel, yet it stays in a tight 80–100 range overnight because production and consumption match. A static reading of 180 vs. 90 says little about which flux went wrong.

• Homeostasis is extraordinarily tight.
Attia uses pH as an example: the scale runs 0–14, but humans live at about 7.4 and can barely survive outside about 7.0–7.7, a narrow window on a logarithmic scale. Glucose is similar: Attia has seen his own range from about 50 to 240–250 mg/dL, a 5x span, while lactate ranges 60-fold.

• Glucose and fat compete for oxidation (the Randle hypothesis).
Rabinowitz thinks much of what sets blood glucose is competition between glucose and fat. In diabetes, underlying problems in fat handling mean more glucose is needed either to induce enough insulin to suppress lipolysis or to outcompete fat for burning in tissues, with ectopic fat in liver and muscle as part of the problem.

• Lactate is a fuel, not just waste.
Back to yeast, cells run glycolysis whenever needed and 'spit out' redox-balanced waste (lactate in humans, ethanol in yeast), then pick it up and reuse it in the TCA cycle. Attia has measured his lactate from about 0.3 mmol at rest to 20 mmol after an all-out two-minute effort. Rabinowitz's work helped establish lactate as a major circulating fuel.

• Fasting lactate may flag metabolic dysfunction.
Attia observes that insulin-resistant people often have fasting lactate approaching 2 mmol with no activity, while healthy people sit below about 0.5. Rabinowitz agrees the correlation is interesting and plausibly reflects impaired mitochondrial oxidation, though causation isn't settled.

• Metformin inhibits complex I, but that may not be the whole story.
It's not disputed that metformin inhibits complex I of the electron transport chain, where NADH is offloaded to make NAD+. The open question is whether that's the main effect at clinical doses of around two grams a day; 'five people who study metformin will tell you five different things.'

• NAD declines only modestly with age.
NAD+ levels fall perhaps 10–20% with aging, a percent change rather than a fold change, compared with much larger swings when tissues are stressed. NADH carries electrons for energy production, while NADPH supports biosynthesis and antioxidant defense.

• NAD supplements: plausible, unproven.
Oral NAD is broken down in the gut, and NR (nicotinamide riboside) largely enters the body as nicotinic acid or nicotinamide. People don't flush on NR or NMN at 500 mg–1 g because that doesn't produce enough niacin to cross the threshold of a few grams. Rabinowitz isn't convinced that boosting NAD by 20% in a 50-year-old helps, and says proper trials are needed; IV NAD has little supporting evidence.

• Cancer may become a chronic disease through metabolism plus immunity.
Rabinowitz admits he once doubted immunotherapy's promise. He now favors a 'stalemate' strategy that combines multiple modes of action, including metabolic and nucleic-acid targets, rather than hitting hard on one lever. Pancreatic cancer, his main focus, is the fourth leading cause of cancer death, with even stage 1 disease about 80–85% fatal.

EXAMPLES

• Ketogenic diet plus chemotherapy
In animal models, chemotherapy lowers tumor glucose, and adding a ketogenic diet that reduces insulin and glucose makes a powerful combination.

• SGLT2 inhibitor trial
Because patients can't be asked to give up the joy of food, Rabinowitz's group is starting a trial combining an SGLT2 inhibitor with a low-carbohydrate (not fully ketogenic) diet to induce ketosis while allowing some normal eating.

• Cahill's starvation studies
George Cahill's work showed that after 40 days of starvation people still had about 3 mmol of glucose, with ketones supplying up to about 60% of fuel.

• The Women's Health Initiative digression
Attia argues the WHI was misinterpreted: estrogen alone trended toward lower breast cancer risk (hazard ratio about 0.8), while estrogen plus MPA showed a barely significant hazard ratio of about 1.24, an absolute increase of about one in a thousand. He predicts a generation of women will be seen as having been harmed by fear of hormone therapy, though he grants a possible slight cardiovascular risk.

• Attia's insulin suppression test

During an insulin suppression test with Gerald Reaven at Stanford, Attia's glucose fell dangerously low ('I almost died') and, once corrected, rebounded to about 240 mg/dL. It's his illustration of how wide glucose swings can be even in a healthy person, and how hard the body works to restore the set point.

OTHER RELEVANT

- **Watch flux, not just levels.**
  A single glucose or lactate number is a snapshot; patterns across fasting, meals and exercise matter. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Consider fasting lactate as a clue.**
  High resting lactate may hint at poor metabolic health, an observation rather than a validated test. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Be skeptical of NAD hype.**
  Precursors are fairly safe, but benefits in humans remain unproven; IV NAD has little support. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Read relative risks with absolute numbers.**
  The WHI shows how a 25% relative increase can mean about one extra case per thousand women.

215 - The gut-brain connection | Michael Gershon, M.D.

Guest: Michael Gershon
Date: 2022-07-25 · Duration: 2:12:52
URL: https://www.youtube.com/watch?v=qqc0iEIPp8w

KEYPOINTS

• The gut has its own nervous system: a 'second brain'

Michael Gershon, a Columbia anatomist and cell biologist who has studied the gut for about 60 years and wrote The Second Brain, explains that the enteric nervous system can run the bowel on its own. When surgeons cut the vagus nerves to treat peptic ulcers, once thought to be psychogenic, the gut kept working. It didn't cure ulcers either, because most are caused by the infection Helicobacter pylori. Peter says this was one of the episodes where he learned the most.

• A gut with no outside connections still produces a coordinated reflex

In a very chilly English laboratory at the turn of the 20th century, Bayliss and Starling cut all the nerves to an animal's intestine and raised the pressure inside it. The gut still contracted above the bolus and relaxed below it, a pattern they called 'the law of the intestine'. Seventeen years later, during the First World War, the German scientist Trendelenburg, kept out of the army by tuberculosis, strung a loop of guinea pig intestine on a J-shaped tube in vitro, blew into it, and found the gut 'blew back' in the same coordinated wave, with no brain or spinal cord at all.

• Rapid cell turnover helps explain why colon cancer is common and small-bowel cancer rare

The cells lining the gut turn over very rapidly. Gershon links the colon's susceptibility to cancer to the especially frequent turnover of its surface cells. The small intestine absorbs most nutrients and water. The colon mainly conserves sodium (absorbing sodium and secreting potassium) and recovers the final roughly 100 mL a day of fluid. Cholera shows what happens when secretion overwhelms absorption: Gershon says about 3 million people still die from it every year.

• Gut and brain communicate both ways

The gut signals the brain through nerves (including stretch and nutrient sensors) and through hormones from enteroendocrine cells, such as cholecystokinin. Some of these are transported across the blood–brain barrier, while glucose is sensed directly in the brain. Most gut hormones reduce appetite. Ghrelin promotes it. Butterflies and stress diarrhoea are this system at work, and Gershon notes that you don't want to stop and defecate when fleeing a foxhole.

• Gastric bypass works partly by triggering the gut's emergency satiety signals

Normally, the stomach only lets sub-millimetre particles into the small intestine, because larger loads set off a 'don't do this' alarm. Bypass reroutes food so it reaches the intestine directly. Gershon says this activates that emergency satiety response over and over, which may help explain the rapid, near-universal benefits for obesity and type 2 diabetes.

• Most of the body's serotonin is made in the gut

Gershon did his senior thesis on serotonin at Cornell in 1958. Enterochromaffin cells make about 95% of the body's serotonin, and about 80% of the gut's endocrine cells produce it. It also acts as a neurotransmitter in enteric nerves, a growth factor for gut neurons and a trigger of inflammation. SSRIs therefore affect the gut. They cause nausea by amplifying serotonin signals to the brain, speed transit at first and later can cause chronic constipation as receptors desensitize. Gershon adds that depression is potentially lethal, so these risks are often worth taking.

• Leaky gut is real but usually overused as a term

The lining has to keep the gut's contents out while letting material move into the gut, which can be dangerous. Gershon says the most common cause of genuine leakiness is allergy, meaning immune hypersensitivity that opens the tight junctions between cells. Severe cases can lose so much protein (exudative enteropathy) that serum albumin falls and the body swells with oedema.

• Shingles can infect gut neurons

Gershon and his wife, the virologist Anne Gershon, found that the varicella-zoster virus, which causes chickenpox and shingles, can lie dormant in enteric neurons and reactivate as 'shingles of the gut'. About 15% of shingles sufferers develop postherpetic neuralgia, pain that can persist for years. He calls the newer shingles vaccine, about 97% effective, remarkable, and Peter got his before 50.

EXAMPLES

• A serotonin-transporter mouse and autism

A mouse carrying a serotonin-transporter mutation, called G56A, which is found in about 2% of people with autism spectrum disorder, shows avoidance of other mice, repetitive behaviours, slow gut transit and fewer enteric neurons. Gershon stresses that it is one of many genes linked to autism, not the cause. He also notes the field is fraught because of Andrew Wakefield's discredited claims linking vaccines, gut disease and autism.

• Fecal transplants for C. difficile

Antibiotics wipe out competitors and let C. difficile take over, producing a toxin that causes massive diarrhoea. Oral vancomycin is first-line treatment. For the roughly 25% who don't respond or relapse, a fecal transplant by enema or capsule is life-saving and approved. Donor stool is carefully screened because the gut harbours perhaps 500 potentially lethal species.

• Lean and fat microbes in mice

Colonizing germ-free mice with microbes from a lean strain produces lean mice, and microbes from a fat-prone strain produce fatter ones. Antibiotics have been used in farming for about 60 years because they make animals grow faster.

• Swallowed safety pins

Children swallow paper clips, coins and even open safety pins, and the gut almost always passes them. Gershon marvels that an open pin is propelled sharp end trailing, so it almost never gets stuck.

OTHER RELEVANT

• Be skeptical of home microbiome kits

Most gut organisms can't be cultured. After a decade of patients insisting on these tests, Peter is still looking for a case where

one mattered. Gershon's exception is stool DNA cancer testing such as Cologuard, which detects about 90% of GI cancers. That makes it a useful option where colonoscopy is inaccessible, but missing 10% is too much to treat it as a replacement.

- **Eat a balanced diet with plenty of fibre**

  Gershon favours balance over restrictive diets. Indigestible fibre from foods like lettuce and celery feeds gut bacteria, which turn it into short-chain fatty acids.

- **Consider probiotics around antibiotics, with modest expectations**

  Gershon admits he knows little about which probiotics work. Some evidence supports taking Saccharomyces alongside antibiotics, and others favour Lactobacillus or Bifidobacteria. A probiotic must survive the trip and actually do something, and the market is full of charlatans.

- **Get the shingles vaccine**

  Given how often the virus reactivates with age and how painful nerve damage can be, Gershon strongly endorses vaccination.

213 Liquid biopsies and cancer detection | Max Diehn, M.D. Ph.D.

Guest: Max Diehn
Date: 2022-07-11 · Duration: 2:26:07
URL: https://www.youtube.com/watch?v=rOU3rEHlhDo

KEYPOINTS

• Liquid biopsies began with a clinical frustration.
Diehn, a Stanford radiation oncologist, treats many early-stage lung cancers that haven't spread; targeted high-dose radiation cures most, but about 20–25% recur. Imaging can't tell after treatment who still harbours microscopic disease, and by the time a tumour is large on a scan — at 10×10×10 cm the tumour burden itself is fatal — options are worse. He wanted a blood test that could see cancer earlier.

• Older blood markers are limited by normal-tissue production.
PSA, CEA and CA 19-9 have long been used, but normal cells make them too — normal prostate cells make prostate-specific antigen — so they lack specificity for screening.

• Sensitivity and specificity must be read together, with prevalence.
Sensitivity is how many people with cancer test positive; a mammogram might be about 85% sensitive, missing 15 of 100 cancers. Calling everyone positive yields 100% sensitivity but useless specificity. Attia stresses that in a low-prevalence population, positive predictive value can be modest even for a test that sounds great.

• Low-dose CT is a proven lung-cancer screen.
Early chest X-ray studies showed no benefit, but the landmark National Lung Screening Trial randomized high-risk smokers to low-dose CT or chest X-ray and found about a 20% relative reduction in lung-cancer deaths. With a single-digit absolute benefit (say 5%), the number needed to screen is around 20. False positives were a concern in the original protocol; modern protocols reduce them. Radiation is low relative to the regulatory 50 mSv annual limit.

• The field moved from circulating tumour cells to cell-free DNA.
Early-2000s work focused on intact tumour cells in blood, filtered using markers like CD45 (a pan-white-cell marker). Attention shifted to cell-free DNA: double-stranded fragments of about 170 bases. Healthy people have roughly 1–5 ng/mL in plasma, so 20 mL of blood yields about 10 mL of plasma and 10–50 ng of DNA.

• Tumour DNA is a tiny fraction of the signal in early cancer.
In early-stage patients circulating tumour DNA is often well below 0.01% — sometimes 0.001% — of cell-free DNA. About 99.9% of fragments map to normal germline sequence.

• Tracking many mutations at once multiplies sensitivity.
If a patient's tumour has been sequenced, looking for 10 of its mutations instead of one raises sensitivity about tenfold, since you don't need to see all of them. Prior methods bottomed out near 0.01% (one in 10,000); Diehn's lab tackled this from around 2014, and newer methods go further.

• Filtering out white-blood-cell mutations is essential.
About 80–90% of cell-free DNA comes from white blood cells. With age, leukocytes acquire mutations through clonal hematopoiesis, which then appear in plasma. Diehn's team sequences both cell-free and leukocyte DNA to subtract them. Cancer-derived fragments are also a few bases shorter on average.

• Minimal residual disease detection is the near-term win.
After treatment, ultra-sensitive tests can detect microscopic residual disease with a very high positive predictive value: detectable ctDNA means the cancer will very likely return. This is easier than screening because the tumour's mutations are already known.

• Pan-cancer screening is far harder.
Without a known tumour, tests like Grail's look at methylation patterns of cell-free DNA. Specificity is above 99%, but presented stage I lung-cancer sensitivity is about 5% or less — and stage I is exactly where blood tests matter, since larger tumours show on CT.

• Diehn's target for a breakthrough.
He argues 50–75% sensitivity for true stage I cancers while keeping specificity above 99% would be a big step. Dropping specificity to 80% inflates sensitivity by luck — a trade some groups make.

• Cell-free RNA could add tissue-of-origin information.
Diehn says cell-free RNA exists in plasma and is a much more nascent field than cell-free DNA. Because RNA reflects which genes are active, it could in principle reveal what tissue a signal comes from and add information beyond mutations or methylation. His long-term vision is a single blood draw that detects cancer and points to where it is.

EXAMPLES

• The 50/99.5 thought experiment
Attia models a test with 50% sensitivity and 99.5% specificity at 1% prevalence: a negative result moves you from about 99% to roughly 99.5% confidence of no cancer, while a positive carries about a 40% chance of truly being cancer. Patients must understand both.

• Biased sensitivity
Including one stage I and 999 stage IV patients can make any test look highly sensitive; unbiased reporting by stage matters.

• Attia's own blood
Attia notes his small red cells (MCV in the 50s–60s) to illustrate individual variation in blood measures.

• Funding liquid-biopsy research
When Diehn began around 2012, grant reviewers were skeptical; liquid-biopsy proposals now score well and submissions have grown dramatically.

- **Liquid biopsy vs. tissue biopsy**
  In patients with known advanced cancer, blood-based mutation testing shows high agreement — in the high 80s percent — with tissue biopsy, and can sometimes find mutations a biopsy misses because a needle samples only one part of a tumour.

OTHER RELEVANT

- **Ask about low-dose CT if you've smoked.**
  Eligibility depends on pack-years; screening those unlikely to get lung cancer produces mostly false positives. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Interpret multi-cancer blood tests carefully.**
  A negative result doesn't rule out early cancer given low stage I sensitivity; discuss predictive values with your doctor.
- **Ask about ctDNA monitoring after treatment.**
  Residual-disease testing may flag recurrence earlier, though whether acting on it improves outcomes is still being studied.
- **Treat biomarkers as one input.**
  Combine blood tests with imaging and risk factors rather than relying on any single test.
- **Smoking history drives lung risk non-linearly.**
  Risk rises with pack-years and some studies suggest it plateaus around 20–30 pack-years; screening is targeted at people above a meaningful risk threshold so benefits outweigh false positives.

212 - The Neuroscience of Obesity | Peter Attia, M.D. & Stephan Guyenet, Ph.D.

Guest: Stephan Guyenet
Date: 2022-06-27 · Duration: 2:48:44
URL: https://www.youtube.com/watch?v=9G3iLbQCIHI

KEYPOINTS

• Obesity rose slowly for decades, then took off around 1980

Stephan Guyenet, a neuroscientist and author of The Hungry Brain, says the earliest useful US data come from Civil War veterans measured around 1890–1900, when only a small fraction had a BMI over 30. Representative national sampling began in the 1960s, when about 12% of adults were obese. That rose to about 15% by the late 1970s and early 1980s and is about 43% today. Guyenet thinks the lifetime risk of obesity is well over 50% for US adults. Type 2 diabetes prevalence has risen roughly five-fold over the past 50 years.

• The 'obesity paradox' is mostly an artifact of illness causing weight loss

Studies associated with Katherine Flegal found that the lowest mortality in meta-analyses of millions of people often fell in the overweight range. Yet excess fat drives diabetes, cardiovascular disease and some cancers. Guyenet says later research suggests the paradox comes mainly from reverse causation. Poorly controlled diabetes, kidney failure, COPD and cognitive decline all cause weight loss, which makes leanness look worse than it is.

• The hypothalamus regulates body fat like a thermostat

Guyenet calls this regulatory system the 'lipostat'. The first clue came in 1840, when the Viennese physician Bernhard Mohr described a woman with rapid, extreme obesity who turned out at autopsy to have a tumour in her hypothalamus. Hypothalamic obesity from tumours or brain damage still occurs.

• Leptin defends against starvation more than against weight gain

Leptin was discovered in 1994 by teams led by Jeffrey Friedman and Rudy Leibel as the missing gene in the extremely obese ob/ob mouse. Cutting calories by about 25% for a couple of days drops leptin far more than fat mass changes, and the brain reads that as a threat. Leptin resistance means higher leptin levels don't produce the expected reduction in appetite. The system is quite happy to let us gain weight. What it is built to prevent is starving.

• Body weight is highly heritable, and the genes act mostly in the brain

Guyenet cites a meta-analysis of twin studies estimating BMI heritability at about 75%. Studies of about 800,000 people have found about 900 variants, each of small effect, and they are disproportionately expressed in the brain. Our genes haven't changed in 100 years, so the susceptibility was always there. What changed is the environment, which now matches it.

• Highly rewarding foods recalibrate the brain's reward system

In Michael Krashes's mouse study, mice normally ate unrefined pellets. Once given calorie-dense, refined, high-fat pellets, their reward circuits devalued the old food, so it no longer satisfied or motivated them. Guyenet thinks the same happens to people raised around modern food. Gut neuropod cells, discovered around 2018, sense glucose, amino acids and fatty acids and signal directly to vagal neurons, which helps explain how strongly this learning is hardwired.

• The carbohydrate–insulin model versus energy balance

The modern carbohydrate–insulin model, set out in a recent review led by David Ludwig, is far more complex than earlier versions. Guyenet and Kevin Hall represent the energy-balance view, which nearly all researchers studying body-fat regulation accept. A key piece of evidence is John Speakman's study of 29 diets in five mouse strains. Replacing carbohydrate with fat made mice fatter until fat reached about 60% of calories, and beyond that they got slimmer again. The combination of fat and carbohydrate seems most fattening, which is why both low-fat and low-carb diets can work.

• Work with the non-conscious brain, not against it

Rather than relying on constant willpower, Guyenet suggests sending the brain signals that point toward slimming. Shape your food environment: keep tempting food out of sight and add effort barriers, since peeling an orange in another room beats grabbing chips. Choose foods that satisfy on fewer calories, and avoid liquid calories, which bypass the feedback system.

• Medication is now a reasonable option for people with obesity

For a BMI of about 30–35 or higher with impaired quality of life or health concerns, Guyenet thinks medical treatment is worth considering and recommends seeing an obesity medicine specialist. He calls semaglutide, as far as can be told, very safe, with about 18% weight loss, more than diet and lifestyle typically achieve. Like lifestyle change, it has to be maintained. He says we are entering an era of drugs designed from mechanism rather than found by accident.

EXAMPLES

• Two people at 160 lb

Peter imagines siblings at 160 lb: one has always been that weight, while the other got there by losing 40 lb. They look identical. Peter asks whether weight gain ratchets the body's set point upward permanently and whether there are life stages when it is most vulnerable. Guyenet says he honestly doesn't know, only that most people can gain weight at almost any age.

• Carnivore and LDL

Guyenet says there are no randomized trials of the carnivore diet, only anecdotes and a survey of about 2,000 dieters recruited from social-media groups, in which David Ludwig was involved. The survey showed a mean LDL rise of about 30–40 mg/dL. Peter cites Paul Saladino's publicly shared LDL-C of 533 mg/dL as an extreme case. He worries about people who see apoB jump from the 50th to above the 99th percentile and dig in rather than asking what it means.

• Peter's daughter and junk food

When his daughter, now 13, was a baby, Peter and his wife carefully kept her away from junk food. He uses this to argue that some foods are instantly rewarding, with no acquired taste needed.

• Red Pen Reviews

Guyenet runs a 501(c)(3) nonprofit that reviews popular nutrition books, at about 40–100 hours per book, with random citation checks. It has published 14 reviews since 2019. Peter says he has accepted that about 5% of his own book will turn out

to be wrong and plans a public page to collect corrections.

OTHER RELEVANT

- **Engineer your environment**
  Reduce cues and easy access to highly rewarding foods so you aren't fighting urges all day.
- **Favour satiating, less energy-dense foods**
  Calories needed to feel satisfied vary widely between foods. Whole foods, protein and fibre generally fill you up on fewer calories.
- **Don't drink your calories**
  Liquid calories slip past the satiety signals that regulate intake.
- **Talk to a specialist if obesity is affecting your health**
  GLP-1 drugs such as semaglutide are now effective tools, but plan on long-term use.

210 - Lp(a) and its impact on heart disease | Benoît Arsenault, Ph.D.& Peter Attia, M.D.

Guest: Benoît Arsenault
Date: 2022-06-13 · Duration: 2:24:36
URL: https://www.youtube.com/watch?v=4H0mVPKsGG8

KEYPOINTS

• Genetics resurrected Lp(a) as a cardiovascular risk factor.
Lp(a) was discovered in 1963 by Swedish scientist Kåre Berg. Interest faded when studies in the 1990s and early 2000s came back negative — partly because assays were unreliable — and PubMed activity dipped. Three genetic studies published in 2009, including Robert Clarke's PROCARDIS work with about 3,000 cases and 3,000 controls, identified variants in the LPA gene linked to heart disease, and Mendelian randomization established Lp(a) as causal.

• Lp(a) is an LDL-like particle with an extra protein attached.
Every LDL carries exactly one apoB-100. Lp(a) adds apolipoprotein(a), which binds apoB — Arsenault says good evidence suggests this happens inside liver cells. Apo(a) contains kringle domains; kringle IV has 10 subtypes, and the type 2 subunit varies in copy number from one to as many as 40 repeats. Smaller isoforms are associated with higher Lp(a) levels.

• Measurement units and assays matter.
Old assays overestimated large isoforms and underestimated small ones; newer antibodies bind other regions and count particles better. Lp(a) can be reported in mg/dL or nmol/L; 50 mg/dL corresponds to roughly 125 nmol/L, so a patient tested both ways may think their level 'doubled' when it didn't.

• Lp(a) is largely genetic and stable, so measure it at least once.
Most guidelines suggest measuring once in a lifetime because levels are remarkably stable. More than 2,000 variants in the LPA region are associated with high levels, so a parent and child can both have high Lp(a) for different genetic reasons. Attia notes an apoB test costs about $14 — and the same logic applies to Lp(a).

• Risk rises with concentration.
At highish levels — around 50 mg/dL or 125 nmol/L — risk may be increased 50% to 100%; at very high levels it climbs further. Roughly 20% of people (depending on ethnicity, at least 15%) have levels above 50 mg/dL. Attia admits he had been telling patients 10%, understating it.

• Oxidized phospholipids make Lp(a) especially harmful.
Lp(a) carries far more oxidized phospholipids than LDL, affecting endothelial cells, smooth muscle cells, macrophages and aortic valve cells. Its sequence similarity to plasminogen may also impair clot breakdown, though Arsenault considers oxidized phospholipids the key.

• Aortic valve stenosis has the strongest link.
Comparing top versus bottom quintile, aortic valve stenosis shows the biggest relative risk, followed by peripheral artery disease and heart attack, then ischemic stroke. Arsenault's group studied Lp(a) particles from valve-stenosis patients, about 20 per study arm, to explore mechanisms.

• Statins don't lower Lp(a), and why.
Statins raise LDL receptor density, but Lp(a) levels are determined mainly by production rate, not clearance. Unexpectedly, PCSK9 increases apo(a) production in liver cells; PCSK9 inhibitors reduce Lp(a) production and lower it on average about 25–30%, with enormous variability.

• The PCSK9 story is a triumph of genetics.
PCSK9 was discovered in 2003 by Nabil Seidah in Montreal and Catherine Boileau in France, studying a family with familial hypercholesterolemia without an LDL-receptor mutation — gain-of-function in PCSK9. In 2006 Helen Hobbs's group at UT Southwestern showed loss-of-function variants caused lifelong lower LDL and less heart disease. People with no functional PCSK9 have LDL around 10–20 mg/dL with no apparent harm to reproduction, hormones or other disease risk.

• Niacin lowers Lp(a) but hasn't proved outcome benefit.
Niacin reduces Lp(a) on average about 20–30%. Large trials of HDL-modifying drugs, such as one of about 30,000 patients, illustrate why large outcome trials are needed in this field.

• Antisense drugs could transform treatment.
Ionis's antisense oligonucleotide (pelacarsen) showed in phase 2 data published in 2020 that monthly dosing brought about 90% of patients below 50 mg/dL. An outcomes trial in about 8,000 patients with established cardiovascular disease was expected to read out around 2025.

EXAMPLES

• High Lp(a), zero calcium
Attia describes a patient with Lp(a) of 690 nmol/L and LDL particle number around 1,800 nmol/L who had a zero calcium score — though in their 40s.

• Modest Lp(a), devastating disease
Conversely, he's seen patients with modest Lp(a) — 125–150 nmol/L — with six-vessel disease and calcium scores of 2,000, underscoring variable expression.

• FOURIER's underwhelming headline
Evolocumab's FOURIER trial showed only about a 15% relative risk reduction, disappointing many, but over just 2.2 years in patients already on maximal statins, with LDL lowered to about 30 mg/dL.

• EPIC-Norfolk
Arsenault analysed Lp(a) in about 18,000 people in the EPIC-Norfolk cohort, finding residual risk even when other factors were well controlled.

- **A residual-risk trial design problem**

  Arsenault notes most PCSK9 and statin trials were not built around high Lp(a). To test whether lowering Lp(a) itself reduces events, you would have to recruit only people with high levels — excluding about 80% of a typical trial population — which is exactly what the antisense outcome trials are now doing, using longer treatment periods to compensate for smaller enrolment.

OTHER RELEVANT

- **Get Lp(a) measured once.**

  There's at least a 10–20% chance yours is elevated; ask your physician to check it. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Know your units.**

  Compare like with like — mg/dL versus nmol/L — before concluding your level changed. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **With high Lp(a), lower apoB aggressively.**

  Attia takes a two-pronged approach: target apoB around 30–40 mg/dL, near childhood levels, and use a PCSK9 inhibitor if it achieves around a 30% Lp(a) reduction, until antisense therapies arrive.

- **Screen for valve and vascular disease.**

  Elevated Lp(a) warrants attention to aortic valve health and peripheral arteries, not just coronaries. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Tell relatives if yours is high.**

  Because Lp(a) is strongly inherited, a high result is a reason for first-degree relatives, including children, to be tested too.

209 Medical mistakes, patient safety, and the RaDonda Vaught case | The Peter Attia Drive Podcast

Guest: Marty Makary
Date: 2022-06-06 · Duration: 1:45:47
URL: https://www.youtube.com/watch?v=_eaVpetraXs

KEYPOINTS

• Patient safety has moved from blaming individuals to fixing systems.

Makary, a Johns Hopkins surgeon and public-health professor, says the field used to ask who messed up. It now asks how the hospital could be designed differently, for example by moving the NICU closer to labor and delivery, or holding an elevator for the trauma team. He traces early catalysts to the 1984 Libby Zion case, which led New York to limit exhausted residents and eventually to the 80-hour work week. The Institute of Medicine's 1999 report estimated 44,000–98,000 US deaths a year from medical care itself.

• Medical error may be the third leading cause of death, though the estimate is debated.

Makary's Hopkins review pooled existing studies and found a median of about 250,000 deaths a year. That would rank behind heart disease and cancer, ahead of stroke. One co-author argued the true number is higher because charts miss many errors. Attia pushes back that the studies counted any error that hastened a death, including in patients 'at the edge of the cliff.' Makary concedes it isn't perfect. A survey found a third of doctors believed it, a third didn't and a third weren't sure. As Don Berwick put it, whether it's third or ninth, it's a major problem.

• Standardized protocols can nearly eliminate certain harms.

In 2006 Peter Pronovost's ICU checklist for central lines covered full barrier precautions, avoiding the femoral vein and similar steps. Spread across dozens of hospitals, it cut median central-line infections from roughly 3–5% to just under 0.5%. Makary notes this happened fast, compared with the usual 17-year lag between evidence and practice. Ultrasound-guided placement later made line insertion safer still.

• Payment and checklists changed hospital behavior.

In 2008 Medicare stopped paying for 'never events' such as retained sponges or instruments; until then hospitals were paid for the second operation. Other insurers followed. In 2009 a surgical safety checklist inspired by the Apgar score, which Makary helped study, was shown to cut adverse events. It now hangs in most operating rooms worldwide.

• Errors are common, and most doctors have made one.

A 2014 Mayo Clinic survey of 6,500 doctors found that 10.5% reported a major medical error in the previous three months. Makary calls over-prescribing opioids a form of medical error and says he 'gave opioids out like candy.' He cites more than 100,000 recent opioid deaths in 12 months, though most now involve fentanyl rather than prescriptions. Sending a narcotic-naive patient home with 30 pills, when best practice is 10 or fewer, is an error Hopkins only recently began measuring.

• Honesty, more than error itself, drives malpractice claims.

Makary says people are hungry for honesty and remarkably forgiving when doctors are candid. Alert fatigue in electronic records (overriding five or six warnings for one order) and the loss of familiar paper charts create new failure modes.

• The RaDonda Vaught prosecution undid decades of 'just culture.'

On Christmas Eve 2017, Vaught, a 36-year-old Vanderbilt nurse hired in 2015, was taking 75-year-old Charlene Murphy, who was recovering from a subdural hematoma and nearly ready to go home, for a final scan. She typed 'VE' into an automated cabinet meant to dispense Versed. Vecuronium, a powerful paralytic, came up, and she overrode an alert. Nurses there said overriding alerts was routine. Murphy died. Makary says Vanderbilt listed the death as the brain bleed, didn't report it to state officials or CMS as required, and settled with the family under a gag. It became public through a Medicare report about a year later.

• A criminal conviction for an honest mistake chills error reporting.

Vaught was arrested in February 2019 for reckless homicide and abuse of an impaired adult. In March 2022 she was convicted of criminally negligent homicide and impaired-adult abuse, with prosecutors citing 10 mistakes in a 'Swiss cheese' failure. She received three years' probation with judicial diversion, meaning her record can be expunged. Makary says her arrest 'undid 23 years' of the just-culture doctrine, which treats honest mistakes as system problems and reserves punishment for reckless or malicious acts.

EXAMPLES

• 1,000 times the Ativan

During training, Attia saw a physician order 1 gram of Ativan instead of 1 mg for a patient who couldn't sleep. Typical doses run about 0.5–2 mg. The nurse, the pharmacy and the pharmacist all passed it along. The pharmacist even sent 20–30 mg while promising the remaining 970 mg later, and the nurse gave it, a textbook stack of failures.

• A transplant without a cross-match

In a heart transplant case, the donor match wasn't verified. An OR nurse sensed something was wrong but didn't speak up. The heart failed, a second heart was given and the young patient still died, which Attia notes cost two other people the hearts. The case helped make speaking up in the OR a hard science.

• The wrong-patient CT

Makary once had a CT done on the wrong patient with a similar name. The patient was already angry about a pancreatic leak. Makary apologized and told him exactly what happened; the man never sued, and they remain friends.

• Aviation as the benchmark

Apart from the 2009 Buffalo crash that killed about 50 people and a 2018 death after a passenger was partially pulled through a window, US airlines carried about 6 billion passengers from 2009 to 2018 without a fatality.

• 'I am RaDonda'

Hundreds of nurses rallied outside her trial with signs. Every doctor and nurse Makary spoke with said, in effect, 'that could

have been me.' The Tennessee Department of Health also refused to postpone its licensing hearing until after the criminal trial.

OTHER RELEVANT

- **Advocate in the hospital.**
  Ask what each medication is and why. Hopkins now asks nurses to explain every drug. Call patient relations, available 24/7, if you see a concern or error.
- **Ask about alternatives and question opioid quantities.**
  Most minor procedures shouldn't send a narcotic-naive adult home with more than about 10 pills.
- **Speak up, and make it safe for others to.**
  Makary warns that if you mock a nurse once for raising a concern, they may never raise one again.
- **Push for systemic fixes.**
  Makary's priorities for halving error deaths include payment reform that rewards safety, adopting tools like second-read software for imaging, and research funding for patient safety, which he calls a blind spot.

208 - Tragedy, grief, healing, and finding happiness | Kelsey Chittick

Guest: Kelsey Chittick
Date: 2022-05-23 · Duration: 2:11:50
URL: https://www.youtube.com/watch?v=zCp101ucrsM

KEYPOINTS

• Nate Chittick lived to the extreme, in good ways and bad

Kelsey Chittick met Nate in the summer of 1998, when she was a swimmer at UNC Chapel Hill. He was a poor kid from Allentown, Pennsylvania, who made everyone he talked to feel like the most important person in the room. He wasn't a first-round prospect, but he hustled his way into the NFL as a center and won a Super Bowl with the St. Louis Rams. They got engaged at the top of the World Trade Center in July 2001 and married in 2002. Kelsey says he was extreme in every way, good and bad.

• Leaving the NFL in your mid-20s is a brutal transition

Nate retired around 2004, before their son was born. Kelsey describes the drop from signing autographs as a Super Bowl champion to an ordinary job that might pay in a year what he used to earn in a week. Peter points out that the median NFL player's career looks nothing like Tom Brady's. Nate went back to school and was offered $50,000 a year. He eventually found purpose in serving others, but Kelsey says many former players 'fall off a cliff' after football.

• His weight became a lifelong fight

To play on the line, Nate bulked up to about 300 lb. He felt good at 235 and loved himself around 260, which Kelsey thought was still too heavy. In 21 years together, she never slept beside him without a sleep apnea mask. His weight was a recurring fight between them, and she later said she had been 'mean' about it before learning how sick he really was.

• She had premonitions for years

From about 2014–15, Kelsey dreaded leaving the family whenever she travelled and sometimes woke up screaming that Nate was gone. In November 2017, Nate encouraged her to go to a spiritual retreat in Jamaica. They texted lovingly for four days because she was too frugal to buy a calling plan. While she was there, he collapsed and died at age 40 while playing basketball with children during a toddler session at a trampoline park. Paramedics worked on him for 50 minutes. He died on 11/11, at about 11, which she takes as one of his 'nods' to her.

• Her North Star: the kids lost their dad but would not lose her

On the flight home, Kelsey decided her children, then 9 and 12, had lost their father but were not going to lose her. As a child, she had watched friends lose a parent and then lose the surviving parent to unending grief. She told her children they were not victims. They had had the best father for 9 and 12 years, and they would figure out a great life together.

• The autopsy found heart disease and stage 2–3 CTE

The cause of death was left ventricular cardiomyopathy, an enlarged heart; she says it fit, because he had a really big heart. The LA County coroner's brain exam found nothing, so she sent the brain to Boston University. She admits she partly hoped for compensation and wanted to know whether to let her son play football. Dr. Ann McKee told her Nate had stage two, almost stage three CTE, with lesions throughout his brain, and that it would have been a very hard life. Kelsey says this lets her feel grateful that she didn't have to watch him slowly deteriorate.

• Grief and happiness can coexist

Kelsey rejects the idea of moving neatly from one stage of grief to the next. She misses Nate terribly and is happier than she has ever been. She now has a very different relationship with death, and her household openly accepts it. She suggests modern comfort has made us less used to pain than people 10,000 years ago, who regularly recovered from terrible losses.

• Children grieve differently

Kelsey believes children are wired to move on faster, especially around 12, when friends become their whole world. Her daughter didn't want to draw her father dying, and needed to forget for a while to integrate what she had seen. Her son needed someone to talk to who 'didn't have a dog in the fight'. The family uses dark humour about how absurd Nate's death was.

EXAMPLES

• Jeff Saturday's start

Jeff Saturday, later one of the NFL's greatest centers, was Nate's freshman roommate. When they met, Nate was sobbing and hugging his parents, and Jeff wondered why he was rooming with 'this baby'. They became best friends. Jeff was overlooked in the draft before building an exceptional career.

• A plant-medicine ceremony

Kelsey grew up spiritually open but was an uptight, anxious non-drinker who judged drug users, partly because of addiction in her family. About a year after Nate's death she joined a shaman-led group ceremony with 'level 10' anxiety. In it she felt rage at Nate: 'you left me at 40 with a 9- and 12-year-old, I told you to lose weight'. Then she sensed him explaining that football was the easiest way to get people to listen to him so he could share about love. Her son, now 16, later photographed her notes.

• Rationing grief

Peter asks whether she limited how much time she spent watching old videos of Nate. Kelsey says grief groups discuss this a lot. Borrowing from Buddhist practice, she sets times to feel her emotions rather than either suppressing them or letting them flood her all day.

• Ric Elias's two minutes

Peter compares Kelsey's story to his friend Ric Elias, who was on the 2009 Hudson River landing and spent about two minutes certain he would die. That near miss changed how he lived.

OTHER RELEVANT

• Practice radical acceptance

Kelsey first met the idea in Tara Brach's work through her mother. Acceptance means not labelling what happened as good or

bad, and it brought her peace.

- **Make meditation non-negotiable**
  She calls herself 'militant' about daily meditation and wishes children learned this kind of mental distancing throughout school.
- **Tell children the truth and give them stability**
  Children need honesty, a steady parent and someone neutral to talk to. Don't expect them to grieve on an adult schedule.
- **Take health warnings seriously in former athletes**
  Weight gain, sleep apnea and a history of head trauma deserve proactive medical attention rather than arguments.

206 - Exercising for longevity: strength, stability, zone 2, zone 5, and more | Peter Attia, M.D.

Date: 2022-05-09 · Duration: 1:14:09
URL: https://www.youtube.com/watch?v=BSAX0KSNS_E

KEYPOINTS

• Training for longevity is different from training for performance.

Attia says performance goals such as a sub-2:40 Chicago Marathon, a sub-10-hour Ironman or a deadlift of 3.5 times body weight demand energy systems that aren't co-linear with longevity and can be 'orthogonal' to it. Longevity training rests on stability and strength, a large base of low-end aerobic work in zone 2 and brief bursts of zone 5. 'Life is zone one, zone two and zone five,' he says.

• Work backward from age 100 with a 'Centenarian Decathlon.'

Instead of planning year by year from 25, Attia projects his kids' ages forward and estimates he'd have great-grandchildren aged about 1 to 8 when he turns 100. He listed 18 things he wants to do with them. Examples: drop into a squat and pick up a 30-lb child (approximated by a goblet squat), lift 30 lb overhead like a carry-on bag, and climb three flights of stairs carrying 10 lb of groceries in each hand. Because of age-related decline, each must be done at a much higher level at 80, 60 and today.

• Today's centenarians mostly got there through genes, not habits.

Attia makes what he calls an extreme claim: almost every current centenarian made it because of exceptional genes. On average they didn't live better than their peers, and many smoked. He doubts many could do his 18 events. People hoping to 'hack' their way to 100 will have to be far more deliberate.

• Muscle and strength decline compounds, so being average at 50 isn't enough.

Estimates of muscle loss range from about 0.3% to 1–2% a year after 50, or roughly 35–40% between ages 20 and 80. Strength losses may be greater, around 2–3% a year and up to 4% in some studies. 'If you have the aspiration of kicking ass when you're 85, you can't afford to be average when you're 50.'

• Strength predicts mortality independently of muscle size.

Attia reviews a study of men and women averaging about 54 years old, followed for five to six years. In men, each 0.2-unit drop in quad strength normalized to CT muscle area, or each 0.34-unit drop normalized to DEXA, was linked to about 26% and 39% higher all-cause mortality. Grip strength normalized to arm lean mass showed about a 23% increase. Results in women were significant but with wider confidence intervals.

• Stability is usually the first thing to fail.

Dynamic neuromuscular stabilization (DNS) is based on 13–14 innate movements that babies master by about 18 months, which then deteriorate, especially once children start sitting in school. Attia's advice to a 25-year-old: build static stability, then dynamic stability, and integrate both into strength work. The core includes the diaphragm, obliques, transversalis fascia and pelvic floor. He admits he has always squatted and deadlifted without fully engaging his pelvic floor and now sees the damage it caused.

• Zone 2 should be steady, measured and frequent.

Attia does zone 2 four times a week for about 45 minutes, checking lactate every session. He knows his zone 2 wattage and expected heart rate. If heart rate runs high, he may be ill or dehydrated, so he lowers the power. He likes erg mode on a bike, which holds about 200 W regardless of cadence, so he can listen to audiobooks. A treadmill at a known incline works too. He prefers rowing for zone 5, not zone 2. Interactions with Iñigo San-Millán convinced him that zone 2 had been a glaring gap in his training.

• VO2 max is the size of your aerobic engine, and 'all-out' is limited to about 10 seconds.

A.V. Hill first described VO2 max in the 1920s. Attia once measured about 5.1–5.2 L/min, around 70 mL/kg/min at his heavier weight. A huge rower might hit 7 L/min while using less oxygen per kilogram. A riding partner who tested at 55–60 mL/kg/min always beat him, showing that VO2 max alone doesn't predict speed. Citing Alex Hutchinson's Endure, Attia says a true all-out effort lasts only about 10 seconds; even Usain Bolt slows in the second half of a 200 m.

EXAMPLES

• Breathing squats in high school

Attia took his 10-rep max and did 20 reps, taking three slow 10-second breaths (five seconds in, five out) between reps. The set lasted about 10 minutes, and he says only one other experience has matched the discomfort. Over a year he added more than 100 lb to his squat, but he doesn't recommend it.

• Deadlifts as an audit

Attia deadlifts two or three times a week, with both trap bar and straight bar, but rarely heavy, usually stopping around 350–375 lb. He films every rep for his coach, Beth Lewis, and treats the lift as an audit that everything is working perfectly.

• His Zone 5 sessions

On a StairMaster he alternates three minutes at zone 2 with one minute at his VO2 max (VO2 max ÷ 3.5 = METs) for 20–30 minutes, usually after a zone 2 session. On the bike he does four minutes at about 125% of FTP followed by four minutes of recovery.

• Tabata or Irisawa?

The 20-second-on/10-second-off protocol is named for Tabata, who wrote the paper, but Attia says Irisawa developed it. His problem with the standard 20/10 version is that people consciously or unconsciously pace themselves to finish it. He compares it with a 10-on/20-off variant on an air bike.

• His weekly structure

Tuesday, Thursday and Sunday are 45-minute zone 2 sessions. Saturday is zone 2 followed by about 30 minutes of zone 5, or a long, harder ride. He lifts Monday, Wednesday, Friday and Sunday, always after cardio, because he believes the reverse order erodes strength gains.

OTHER RELEVANT

- **Write your own centenarian list.**
  Pick concrete activities for your 90s and train well above that level now.
- **Prioritize stability before load.**
  Explore DNS, PRI or Pilates, and film your lifts.
- **Do zone 2 about 3–4 times a week for 45 minutes or more, plus some zone 5.**
  Use steady power or pace, and adjust if heart rate drifts high.
- **Treat strength as a vital sign.**
  Measure grip and leg strength, and don't accept average for your age.

205 - Energy balance, nutrition, & building muscle | Layne Norton, Ph.D. (Pt.2)

Guest: Layne Norton
Date: 2022-05-02 · Duration: 3:17:33
URL: https://www.youtube.com/watch?v=R-Ltg1dl2jM

KEYPOINTS

• Energy balance governs weight, but it isn't linear arithmetic.
Norton rejects the idea that burning 2,500 and eating 2,000 calories guarantees a pound lost per week indefinitely. Water, glycogen, gut contents and adaptive changes in expenditure distort the scale: a 200-lb person can read 196 or 204 on any day. He tells clients to treat it like the stock market and watch the trend.

• Not all calories you eat are absorbed or retained.
About 5–10% of energy is lost in faeces. The thermic effect differs by macronutrient: from 100 calories of fat you net about 97–100, from carbohydrate about 90–95, and from protein only about 70–80. Even celery has calories; there's no 'energy-negative' food.

• Resting metabolism is the biggest slice of expenditure.
For most people BMR is about 50–70% of total daily energy expenditure — about 55–60% for Norton. Indirect calorimetry estimates expenditure via the Weir equation, heavily weighted to oxygen consumption. Attia's measured BMR sits consistently around 1,900–1,950 calories.

• NEAT varies hugely and adapts.
Non-exercise activity thermogenesis explains much of why some people resist weight gain. In Levine's 1995 overfeeding study, people were fed about 1,000 calories above measured needs; one participant barely gained weight because spontaneous activity rose to compensate. After losing 10% of body weight, NEAT can fall by up to about 500 calories a day.

• Fitness trackers badly overestimate exercise burn.
A 2018 study of about 20 devices found they overestimate exercise energy expenditure by 28–93%, so a reported 500 calories might really be 260–400. Calorie intake is also routinely underestimated: 50 versus 20 grams of oil on a salad is invisible but adds hundreds of calories.

• Weight-reduced bodies fight back.
Formerly obese, weight-reduced people have lower BMR than never-obese people of the same size. Norton cites John Speakman's work on set-point ideas: evolution penalized getting too lean more than getting too fat, since famine was a real threat until the early 1900s.

• Habits matter more than the 'X's and O's'.
A systematic review of people who maintained weight loss found no single superior diet; consistent behaviours and habits mattered most. Many people do well Monday to Friday, then add pancakes, alcohol and poor choices on weekends.

• Ketogenic diets don't meaningfully raise expenditure.
The rigorous inpatient study run by Kevin Hall with Rudy Leibel, Eric Ravussin, Steve Smith and others found only a small increase on low-carb — about 57 kcal/day, near the detection limit — not the 250–500 promised. Above about 65–70% of VO2 max, ketogenic diets appear to impair performance.

• Protein needs for muscle are higher than the RDA, and the mTOR fears are misplaced.
Norton suggests about 1.6–2.4 g/kg of lean body weight to maximize muscle protein synthesis. He argues cancer-linked mTOR signalling stems from chronic, dysregulated insulin signalling in insulin resistance — not pulsatile rises after protein meals — and that 'high protein' in cancer meta-analyses often means just over 70 g/day or 1.2 g/kg.

• Train close to failure, not always to it.
Most sets for advanced lifters should be around RPE 7–8, a few at 9, rarely 10. Hypertrophy close to failure is similar to absolute failure, but failure creates disproportionate fatigue. A 6–15 rep range lets you accumulate volume efficiently.

• Muscle gain is slow even when done right.
Net muscle protein accretion is perhaps 5–10 grams a day at most; since muscle is about 70% water, that's roughly 26 lb of muscle per year as a theoretical ceiling, and much less in practice.

• Fat loss can be done in sprints.
Rather than one long diet, Norton cut back to his old 205-lb weight class over about a year using short fat-loss sprints — two or three weeks of an aggressive 750–1,000-calorie deficit — followed by breaks. For gaining, trained people put on lean and fat mass roughly 50/50 or 40/60, which is why he keeps surpluses small.

EXAMPLES

• The 50-year-old woman
A hypothetical 135-lb (about 60 kg) woman in menopause at 30–35% body fat eats only 50–60 g of protein a day. Norton would raise it to around 100–120 g, spread across meals, and aim for about 10 lb more muscle in two years — noting most people eat 65% of their protein at dinner.

• The trained 50-year-old man
For a 175–180-lb man in the low 20s body fat, Norton says 180–200 g of protein daily has no downside, with a slight surplus of 100–200 calories to gain muscle.

• Doubly labelled water vs. tracking
Norton's own tracked intake implied about 4,400 calories of expenditure; doubly labelled water measured about 4,200.

• Squatting to failure
Norton once squatted 480 lb for 14 reps, grinding the last so hard he couldn't rack the bar, and couldn't have managed another rep after 15 minutes' rest — fatigue far beyond the extra stimulus.

• Contest prep

He gets from about 14–15% to about 7% body fat, and the final push to very low levels takes 12–16 weeks because lean mass must be preserved; adipose tissue itself is about 13% lean tissue.

OTHER RELEVANT

- **Track trends, not daily weigh-ins.**
  Average weight over weeks before adjusting intake. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Distrust tracker calorie numbers.**
  Don't eat back exercise calories based on a watch.
- **Prioritize protein and strength as you age.**
  Falls and frailty drive mortality after about 70–75; muscle and adequate protein protect against them.
- **Avoid proprietary blends.**
  Choose third-party-tested protein powders; 'nitrogen spiking' with cheap amino acids or creatine can inflate protein claims. Take creatine — about 5 g a day — on its own.
- **Watch weekends and alcohol.**
  Weekend eating can erase a weekday deficit. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

204 - Centenarians, metformin, and longevity | Nir Barzilai, M.D.

Guest: Nir Barzilai
Date: 2022-04-25 · Duration: 2:48:00
URL: https://www.youtube.com/watch?v=Hbguf9GCdwI

KEYPOINTS

• Genes matter more the further out you go.
Nir Barzilai, an endocrinologist at Albert Einstein College of Medicine who studies centenarians, says twin studies put lifespan heritability low (around 20%), but for reaching 90 or 100 versus 70 or 80, genes play a much larger role. His cohort, begun in 1998, is mainly Ashkenazi Jews, chosen because a population bottleneck and isolation made their gene pool homogeneous and easier to study.

• Centenarians often carry 'bad' genes plus protective ones.
Among roughly 15,000 variants studied, 44 centenarians carried variants that by textbook standards should have made them demented at 70 and dead at 80, including Alzheimer's and Parkinson's risk genes. Barzilai's interpretation: protective variants buffer the damage. With some 80,000 rare genotypes in the population and perhaps '50 ways' to longevity, you need very large cohorts.

• Reduced growth hormone/IGF-1 signaling is a major longevity theme.
About 60% of his centenarians have variants that impair the GH/IGF-1 pathway (including FOXO3A-related genes); in one genotype, people reach normal height after puberty but keep low IGF-1 for life (about 12% of centenarians). Using UK Biobank data on about 440,000 people, they found high IGF-1 in younger people predicted outcomes differently, an example of how the 'right' level may depend on age.

• Growth hormone is a poor anti-aging drug.
Barzilai and Attia agree that GH is unlikely to be geroprotective; people taking it often also take metformin and exercise, so observational benefits are confounded.

• APOE2, CETP and TSH variants show up repeatedly.
APOE2, as allele frequency or homozygosity, is the most validated longevity genotype. CETP variants giving HDL as high as 130–140 mg/dL were an early finding. Centenarians also tend to have higher TSH (mild hypothyroid tendency), and Barzilai explains the thyroid feedback loop for listeners. Lp(a) is a counterexample: high levels in about 10% of the population cause damage that dwarfs other effects.

• Centenarians get sick later and die quickly.
Their 'superpower' is delaying disease by roughly 20–25 years. In controls aged 60–80, only about 10% are disease-free at 80, while about 30% of centenarians past 100 have no disease and take no treatment. A centenarian might have a first heart attack at 101 and die six months later, a compression of morbidity rather than a long decline.

• Metformin has an unusual track record.
Used since the 1950s–60s and approved in the US only around 1993, metformin in diabetics is associated with lower mortality than other drugs, and in the Diabetes Prevention Program both metformin and lifestyle prevented diabetes in roughly 30% of participants, a trial stopped early. Attia notes the healthy-user bias: compliant patients are healthier.

• TAME aims to make aging an FDA indication.
The Targeting Aging with Metformin trial plans about 3,000–3,500 non-diabetic participants aged 65–79 across 14 US centers (about 250 each), looking at a composite of age-related diseases. Using a multi-morbidity endpoint means 20–50 times fewer people are needed than a single-disease trial (versus about 12,000), making it much cheaper; the effects in prior studies are consistently 20–30%.

• Biomarkers of aging are the goal.
Barzilai wants tests to tell a 50-year-old whether they're biologically 40 or 60, for example to decide on screening. His group measured 5,000 proteins in 1,000 people to see what changes between 65 and 95, and TAME samples could validate such markers. Volatile metrics like fasting glucose (95 vs. 105 depending on last night's meal) are poor biomarkers.

• Metformin may blunt exercise gains.
Attia, who stopped taking metformin, notes it's a weak mitochondrial inhibitor and that studies show blunted improvements in cardiorespiratory fitness; it may be net positive for some people but not for those who exercise a lot. Barzilai thinks most benefit appears in people recruited above about 50, and that senolytics probably shouldn't be used before 70–80.

EXAMPLES

• The lactate check
In a 1987 study, Barzilai saw lactate rise from below one to above one mmol in everyone who took metformin, consistent with its mitochondrial effect.

• A $2.8 million gift
The American Federation for Aging Research received a single $2.8 million donation to recruit 10,000 centenarians plus offspring and controls, which Barzilai calls a bargain for finding rare protective genotypes.

• The 115-year ceiling
Barzilai puts the human species' lifespan at about 115 years (with outliers like 122), and jokes that if asked when we'll live to 150, the answer is 'in 150 years', because even starting now the experiment takes that long.

• Two VO2 maxes, neither disabled
Attia contrasts people at 30 vs. 50 mL/kg/min VO2 max: neither is 'disabled', but the gap determines what life feels like at 85. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Biblical ages
Asked about the long lifespans in scripture, Barzilai mentions an effort to assess whether any age claims from about 2,000

years ago in biblical stories have validity.

OTHER RELEVANT

- **Know your APOE and Lp(a).**
  These genes shape risk; most people lack centenarian genes and must delay disease through behavior and medicine. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't take GH for longevity.**
  Despite its popularity in anti-aging clinics, the evidence points the other way; lower IGF-1 signaling characterizes many centenarians. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Weigh metformin carefully.**
  Its benefits may be real for some, especially people with metabolic disease, but it could blunt training adaptations in active people; TAME is meant to settle this.
- **Aim to compress morbidity.**
  The goal is decades of healthspan, not merely more years. Centenarians show it's possible to push the onset of heart disease, cancer and dementia back by two decades; for everyone else, exercise, lipid control and metabolic health are the tools for chasing the same pattern.

202 - Peter on nutrition, disease prevention, and more — looking back on the last 100 episodes

Date: 2022-04-11 · Duration: 1:57:38
URL: https://www.youtube.com/watch?v=LkUPHBhM8Ow

KEYPOINTS

• Strong convictions, loosely held.
Looking back on episodes 100–200, Attia describes holding firm positions while staying ready to change them when evidence shifts. The episode is a tour of where his thinking evolved: cancer, apoB, Alzheimer's genetics, fasting, protein, exercise, NAD, psychedelics and sleep, ending with a long primer on Formula 1.

• His book has been a six-year project.
Begun in 2016, the manuscript had ballooned; his editor hoped for about 80,000 words, and Attia and co-writer Bill Gifford aimed to converge on around 120,000, still thick but manageable.

• Immunotherapy works for a minority, so far.
Checkpoint inhibitors and IL-2 produce durable responses in perhaps 10–20% of people with metastatic melanoma or renal cell cancer. Of cancer deaths, leukemias and lymphomas account for about 20% and solid organ cancers about 80%, so the big task is getting immune-based therapy to work across the solid tumors that make up the rest.

• GI cancers make a strong case for aggressive screening.
Of roughly 600,000 US cancer deaths, about 170,000 are in the digestive system, from mouth to anus. Colonoscopy timing and frequency matter: guidelines say 45–50, Attia had his first at 40–41 and was scheduled for another at 49. Pancreatic cancer lacks good screening, so he uses tools like diffusion-weighted MRI and liquid biopsies, which are imperfect.

• ApoB should be lowered early and far.
Attia argues infantile apoB levels of 30–40 mg/dL are not harmful, and that lowering apoB to 20–30 in everyone from their 20s might nearly eliminate ASCVD. Practically, anyone in their late 30s or early 40s above the 20th percentile should be treated. He uses 60 mg/dL (about the 5th percentile) as a ceiling.

• APOE4 risk is real but modifiable.
Attia's rough figures: E2/E4 is a wash or slight increase; E3/E4 confers about a 2–3-fold risk of Alzheimer's; E4/E4 about 8–12-fold (maybe 8–10). At the individual level many E4 carriers never develop disease, and other genes modify that risk.

• Time-restricted eating mostly works by eating less.
Attia now thinks the benefit of TRE comes largely from calorie reduction, not timing: 3,000 calories over 12 hours vs. 6 hours likely differ little. It can be problematic when people lose lean mass along with fat, so the scale improves while body composition worsens.

• Most people under-eat protein.
Attia calls the RDA of about 0.8 g/kg 'out to lunch': for an 80-kg (about 175-lb) person that's around 65 g a day. He believes the RDA reflects the minimum to avoid deficiency, not what's optimal for building and keeping muscle, especially with age.

• Exercise is the most potent longevity tool.
Moving from the bottom 25th percentile of cardiorespiratory fitness to the next quartile (low, below average, above average, high, elite) brings large mortality reductions, and the gains continue up the scale. Strength matters even more than muscle mass, though mass is a good proxy.

• He's uninspired by NAD precursors and wary of psychedelic hype.
Attia sees little evidence that NR or NMN extend healthspan. On psychedelics, he thinks they're a powerful therapeutic tool in the right setting but worries about treating them as a cure-all, given how often he hears people raving about a shaman in Peru.

• Trazodone has become his favored sleep aid.
An old antidepressant (a serotonin antagonist and reuptake inhibitor), trazodone caused too much drowsiness at 250–300 mg. At 25–100 mg nightly off-label, Attia says it helps more than 80% of the people who try it and, crucially, preserves sleep architecture, unlike drugs such as Ambien that just render you unconscious. He's also less worried about blue light than the stimulation of what you do on screens.

EXAMPLES

• A new patient at the 99.9th percentile
Attia cites Framingham Offspring apoB percentiles (5th about 62, 10th about 70, 20th about 78, 50th about 97, 80th about 118, 95th about 140) and a new patient whose apoB was around 171, past the 99.9th percentile.

• The 'I lost 5 pounds' trap
A typical 5'11" person who goes from 180 to 175 lb on fasting feels great, but DEXA shows visceral fat unchanged and lean mass down; only the crude scale number improved. A 300-lb person losing 70% fat and 30% lean is still net better off.

• Grip weakness after surgery
Two days after shoulder surgery, Attia noticed his right grip was weaker because he couldn't recruit the full shoulder and scapular musculature, an illustration of how connected the kinetic chain is.

• Senna's qualifying record
In the F1 section, Attia praises Ayrton Senna's more than 60 pole positions in 161 races and recalls mid-1980s McLarens boosted to as much as 1,400–1,600 horsepower in qualifying versus about 800 in races.

• F1 tires and pit stops
Each tire change costs a guaranteed 25–26 seconds; with 10 teams and 20 drivers, strategy around soft and medium compounds and qualifying (Q1 cuts five, Q2 sets 11–15, Q3 decides the top 10) often decides races.

OTHER RELEVANT

- **Screen GI cancers aggressively.**
  Consider colonoscopy earlier and more often than minimum guidelines, discussed with your doctor. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Eat more protein than the RDA.**
  Aim well above 0.8 g/kg, especially during weight loss, to protect lean mass. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Check body composition, not just weight.**
  Use DEXA or similar to make sure fat, not muscle, is what you're losing.
- **Treat sleep drugs by their effect on architecture.**
  If a sleep aid is needed, ask a clinician about options that preserve deep and REM sleep.
- **Climb the fitness percentiles.**
  Every step up in VO2 max and strength pays off. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

201 - Deep dive back into Zone 2 Training | Iñigo San-Millán, Ph.D. & Peter Attia, M.D.

Guest: Iñigo San-Millán
Date: 2022-03-28 · Duration: 3:15:41
URL: https://www.youtube.com/watch?v=-6PDBVRkCKc

KEYPOINTS

• Zone 2 is the intensity that maximally stimulates type 1 fibers and their mitochondria.

San-Millán defines zone 2 as the point of highest fat oxidation: mainly type 1 fibers are recruited, fat is mobilized from adipose tissue and burned in mitochondria, and pyruvate and lactate are oxidized rather than piling up. Glycolytic flux isn't very high. Training here builds mitochondrial function, fat oxidation and lactate clearance through MCT1 transporters.

• Blood lactate of about 2 mmol/L is a practical upper boundary.

Once lactate passes about 2 mmol/L, a person is leaving zone 2 for zone 3. Indirect calorimetry measures oxygen consumed and CO2 produced to estimate fat versus carbohydrate use, and the 'FatMax' point usually lines up with this lactate marker. San-Millán has used this method for about 16–17 years and has validated it against muscle biopsies that test how fatty acids, pyruvate and glutamine are oxidized. Someone with metabolic syndrome may leave zone 2 almost immediately, already outside it by about 100 W.

• Lactate is a key fuel and signal, not waste.

When glycolysis runs fast, converting pyruvate to lactate regenerates the NAD that glycolysis needs. Lactate is then exported or shuttled into mitochondria via MCT1 and burned, a concept San-Millán credits to George Brooks, whom he thinks may someday win a Nobel. Problems arise from the hydrogen ions that accompany lactate, which acidify muscle, and from poor clearance.

• Dose matters: aim for three to four sessions a week of about 60–90 minutes.

In San-Millán's lab data, one day a week leads to deterioration over time, especially with age. Two days may maintain fitness but won't be enough for a beginner. Three days produce clear gains, four is ideal, and five or six is better still if you have the time. Sessions of about one to one and a half hours are on target, though beginners should build from 20–40 minutes. He notes that people who only do high-intensity work, and bodybuilders, often have very poor mitochondrial function.

• Muscle is where type 2 diabetes starts, and contraction offers a second route for glucose.

About 80% of carbohydrate is oxidized in skeletal muscle. With insulin resistance, GLUT4 transporters can't move to the cell surface. Muscle contraction moves them in an insulin-independent way, and the fittest athletes need almost no insulin for this. That, San-Millán argues, makes zone 2 exercise a direct therapy for dysglycemia.

• Metrics for the Tour de France: watts per kilo at a given lactate.

Discussing Tadej Poga Ö , whom Attia says may become the greatest Tour rider ever, San-Millán explains that FTP alone isn't enough. A plot of watts per kilogram against lactate production is among the best predictors, and it guides race strategy alongside overnight heart rate, HRV and how the rider felt. Attia notes that decisive climbs once required about 6 W/kg clean versus about 7.1 W/kg in the EPO era. The race is decided by minutes over roughly 100 hours, at a few strategic moments.

• Mitochondrial dysfunction may explain some long COVID.

San-Millán's study with National Jewish Health tested long-COVID patients, including previously healthy athletes who had run marathons but now struggled on stairs. Their fat oxidation and lactate profiles were significantly worse than those of people with type 2 diabetes and metabolic syndrome. He hypothesizes that the virus hijacks mitochondria, as other viruses do.

• Lactate may act as an 'oncometabolite.'

Warburg noted in 1923 that cancer cells have high glycolytic flux, and what struck him was the lactate. San-Millán's group, with a first paper published and six or seven more in progress, found that lactate regulates the expression of key breast-cancer genes and is seeing the same in lung cancer. If cells can't clear lactate, it may drive growth and proliferation.

• Supplements and drugs that touch metabolism are unresolved.

Attia asks whether metformin's raised lactate reflects real mitochondrial impairment or a drug artifact, which matters if metformin is used as a geroprotector. San-Millán says much more research is needed. On NAD, levels fall with age, but he cautions against simply supplementing, noting that many metabolites decline and raising one may not help. Both raise the possibility that boosting NAD could be harmful in someone with an existing cancer.

EXAMPLES

• Attia's VO2 max test in ketosis

About 10 years ago, after three years on a ketogenic diet, Attia was tested 6–12 months into a return to cycling. At failure he was burning almost no fat and just under 6 g of glucose per minute, about 24 kcal/min. Another athlete in ketosis for seven years, with a 20-minute FTP of about 412 W, showed similar data. San-Millán says very low-carb athletes often top out at about 2–3 mmol/L lactate and that rapid shifts in apparent fat oxidation after diet changes can be gas-exchange artifacts.

• ICU patients and glutamine

Critically ill patients show extreme hyperglycemia even without glycogen stores, probably from muscle protein breakdown releasing glutamine. San-Millán notes that glutamine has been shown to improve survival in these patients.

• Overworked, not overtrained

Attia trains about 10 hours a week, cardio and strength combined, yet has bad days when he's overworked. San-Millán says that even at five to seven hours a week, work stress can leave you drained, with a heart rate that won't rise. His fix is to take a day off completely and sleep more.

• Individualizing zones

After a metabolic test, San-Millán converts the zones into watts, speed or heart rate. These usually correlate well, so people without power meters can use heart rate or pace when running or walking.

OTHER RELEVANT

- **Train zone 2 at least three, ideally four, times a week for about an hour or more.**
  Keep lactate at or below about 2 mmol/L, or use a matched heart rate or power.
- **Don't rely only on HIIT or lifting.**
  San-Millán sees poor mitochondrial function in people who skip aerobic base work.
- **Use exercise as a glucose-lowering tool.**
  Muscle contraction moves glucose into cells without insulin, which especially matters with insulin resistance.
- **Be cautious with metabolic supplements.**
  Evidence on NAD boosters and on metformin for longevity remains incomplete.

199 - Running, overcoming challenges, and finding success | Ryan Hall

Guest: Ryan Hall
Date: 2022-03-14 · Duration: 2:58:57
URL: https://www.youtube.com/watch?v=0gOHy74y1hE

KEYPOINTS

• Hall grew up living high and training low before it was fashionable.
In Big Bear, his father started a cross-country and track team just so he could run, driving down to sea level about twice a week for hard interval sessions before returning to altitude. Later, at about 7,000 ft, Hall could run 12–15 miles at 4:48 per mile — about marathon pace — yet gained less at sea level (4:40–4:42) than less-acclimatized runners like his wife Sara.

• Marathoners need real speed.
Hall ran 50 seconds for 400 m in high school, but argues that top-end speed limited his 5,000 m potential, since elite men close the final lap in about 52. As a coach he wants athletes who can run 49 seconds for 400 m. His half-marathon pace of 4:33 per mile is 34 seconds per 200 m — speed Attia notes few people could hold for even half a mile.

• Power and strength matter for runners — he wishes he'd lifted better.
Hall did 50-metre hill sprints twice a week during marathon training, but in hindsight didn't use his weight-room time well. Attia cites a strength coach who reportedly took an elite runner's deadlift from about 1.3 times bodyweight toward 2.7–3 times, and notes ground-contact times around 0.2–0.25 seconds reflect power.

• Progressive overload has many levers.
Overload can mean more weight, sets or reps, or less rest. Hall has become fascinated with blood-flow-restriction training, using a fraction of the normal load — useful for injured runners.

• The record half marathon came out of nowhere.
In 2007 he ran 59:43, obliterating the American half-marathon record by over a minute — despite having spent ages 13–23 focused on speed and the 5K, where his best was about 13:16. Middle miles at 4:32 and 4:28 'scared' him. He was suddenly 'America's great hope' for the 2008 Olympic marathon.

• Beijing taught pacing lessons.
Expecting a slow, hot race, he started tentatively and had to work from about 60th to finish 10th.

• Boston 2011 was his best day.
After a poor half marathon a month before, he floated through easy runs and ran 2:04:58 for fourth — at the time the fastest by an American — while the top two ran about 2:03, almost a minute under the then world record. The halfway split of 61:52 was so fast the organizer radioed that the clocks were wrong.

• Dropping too low in weight backfired.
At 5'10", Hall's best racing weight was about 137 lb; below that he got worse, and he once hit 127. Between races he regained 10–12 lb to about 150, then reduced gradually over six months. Before London 2012, he did a one-week fast and dropped to 130 instead of rebounding, starting training depleted. His brothers walk around at 165–170, suggesting his natural weight.

• Elite endurance training wasn't optimal for health.
His testosterone was clinically low every time he tested — around 150. Attia notes his own was in the low 200s through surgical residency.

• Identity outside performance sustained him.
At Stanford, injured and not improving, Hall saw himself as a failure every morning. His faith reframed it: God sees him the way a parent sees a child, with love unrelated to performance. Being a better teammate became a focus too.

• Plantar fasciitis and a worn body ended his career.
Plantar fasciitis began before the 2012 trials, persisted until his 2016 retirement, and he felt his body was saying it had been pounded with 100-mile weeks for 20 years.

• Elite marathon pace is almost unimaginably fast.
Attia points out that a 4:42–4:48 mile pace is something almost no recreational runner could hold for 800 metres, let alone 26.2 miles. Hall predicts an official sub-two-hour marathon within our lifetime, noting a woman had just run about 62:50 for the half, and says that at any level, signing up for a race lets you share the experience with tens of thousands of others.

EXAMPLES

• Gaining 25 lb of muscle
After retiring, Hall went from 167 to 192 lb over nine months while doing zero cardio — no running, biking or swimming.

• Grand Canyon water carries
He carried two water containers weighing about 62–65 lb each up a 6.3-mile, roughly 7% grade trail out of the Grand Canyon, and trained with 20-minute carries every other day, 30 seconds on, 30 off.

• Seven marathons, seven continents, seven days
Hall ran seven consecutive marathons on seven continents without specific training, getting better during the challenge before crashing at the end.

• Marathon fuelling
Bottles plus gels at 15K and 30K, the latter caffeinated; Hall says he is '100% faster' with caffeine. Attia mentions research on acetaminophen lowering core temperature, which Hall never tried.

• A resting heart rate of 27
At his fittest, Hall's resting heart rate was about 27 and his marathon heart rate around 167.

• Workouts at Mammoth

Main sets like 10×1 km or 6×1 mile at altitude around 4:30 pace (roughly 4:20 at sea level), with 90 seconds to two minutes of walk-jog recovery, plus an easy 30–35-minute afternoon run.

OTHER RELEVANT

- **Train speed and power even for endurance.**
  Include sprints, strides and strength work; aerobic base alone limits performance.
- **Don't chase weight below your natural set point.**
  Hall's performance and motivation fell when he went too lean. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Separate worth from results.**
  An identity rooted in faith, family or values buffers the inevitable failures.
- **Vary your overload.**
  Adjust sets, reps, rest or use tools like blood-flow restriction rather than only adding weight.
- **Respect accumulated wear.**
  Hall says that if he could do it again he would have listened to his body sooner; after two decades of 100-mile weeks, persistent injuries like plantar fasciitis were a signal to change course rather than run through.

198 - Eye health—everything you need to know | Steven Dell, M.D.

Guest: Steven Dell
Date: 2022-07 · Duration: 2:49:17
URL: https://www.youtube.com/watch?v=1SavpBUUy2Q

KEYPOINTS

• Eye surgery is microsurgery at an extreme scale.
Steven Dell, an ophthalmologist and refractive and cataract surgeon, describes sutures as fine as 11-0 (cardiac surgeons use 7-0 or 8-0 for coronary arteries); as a trainee he practiced tying 11-0 every night on call. Each surgical field's 'bread and butter' changes by era; when he trained, it was cataract surgery and diabetic retinal disease.

• The eye handles a staggering range of light.
Humans can function from dim light to around 200,000 lux, many orders of magnitude. Eye color variation mirrors skin pigmentation: darker eyes cluster near the equator, where visible, UV and infrared light are more damaging to the retina.

• 20/20 is average, not the limit.
20/20 means seeing at 20 feet what a 'normal' person sees at 20 feet; 20/10 is better. Some athletes Dell has treated were 20/20 and wanted 20/15 or 20/10, which modern laser vision correction can achieve, though most of their medical screening had never checked vision at all. The theoretical limit, set by photoreceptor spacing, is somewhere around 20/8.

• Astigmatism is extremely common.
Astigmatism means the eye's focusing power differs by meridian; Dell estimates that more than 60% of people with glasses have a significant amount. The cornea is about 500–550 microns thick, roughly a credit card.

• Myopia is an epidemic driven by indoor near work.
Up to 90% of the population in some Southeast Asian cities is now nearsighted, too fast to be evolutionary. The eye adapts within a lifetime. Staying inside in dim light doing near tasks raises myopia risk about 16-fold compared with kids who go outside, and brightness matters: noon outdoor time beat 8 a.m. outdoor time, likely through light-driven retinal dopamine release.

• Prescriptions should stabilize in your early 20s.
The eye typically stops changing around ages 23–24. Afterward, worsening prescriptions usually signal cataract formation, which begins affecting the lens's light-bending power in the 50s–70s. Dell rarely sees patients in their 70s without some cataract.

• Cataract surgery and lens implants have transformed outcomes.
Modern cataract surgery with implanted lenses, developed from the 1980s, both removes the cloudy lens and can correct refractive error. Dell has worked since the mid-2000s on implant designs that could restore focusing ('zoom'). New eye drops such as a pupil-shrinking drug that works in about 15 minutes (expected commercially in early 2022) can temporarily improve near vision.

• PRK, LASIK and SMILE trade off differently.
First laser treatments were in 1989, with FDA approval of PRK and LASIK around 1995–96. PRK removes the roughly 50-micron epithelium and reshapes the surface, with slower recovery. LASIK cuts a roughly 100-micron flap (about 20% of the cornea) and is like opening a book to page 100 and removing pages 100–110; it carries lower infection risk but introduces flap risks. SMILE extracts tissue through a tiny keyhole. Thin corneas or strong prescriptions may favor PRK.

• Dry eye follows laser surgery and is common generally.
Both PRK and LASIK cause temporary dry eye in most patients, usually resolving in about 60–90 days, sometimes longer. GLA (from black currant seed, borage or evening primrose oil) may help. The NEI's DREAM trial of 3 g/day of EPA and DHA found no superiority over olive oil, though Dell notes criticisms of its design.

• Glaucoma is many diseases with one endpoint.
Glaucoma is probably about 100 different diseases sharing a final common pathway of pressure-related damage to the optic nerve. Pressure is measured by indenting the anesthetized cornea with a known force. Management has improved greatly, including minimally invasive glaucoma surgery (MIGS).

• The eye is a window into metabolic disease.
Diabetes is largely a microvascular disease, and the retina lets clinicians watch it directly; leaking vessels are an early sign of retinopathy. Dell and Attia reject binary HbA1c thresholds (5.6 normal, 6.0 prediabetic, 6.5 diabetic): risk is a continuum, and damage visible in the eye is probably also in the kidneys and toes.

EXAMPLES

• Recess outdoors halves myopia
In a trial of 7–11-year-olds, half spent 80 minutes of recess outside and half stayed indoors; the outdoor group had about half the incidence of nearsightedness, even without instructions to look at distant objects.

• Attia's 20/15 experiment
Attia once tried a stronger-than-normal prescription to reach 20/15; Dell explains that over-correction rarely gives superhuman performance.

• Pharaohs and hot pokers
Ancient cataract treatment involved pushing the lens out of the visual axis with a sharp instrument. Attia argues it would be better to be in the bottom 10% economically today than the top 10% 5,000 years ago.

• Pilots and athletes
Professions requiring 20/20 uncorrected vision, like pilots, rely on laser correction; lasers today typically get people to 20/20 or better.

• Stable prescriptions
Attia notes his own prescription has been stable for 15–20 years, which Dell says is exactly what to expect after the early 20s until cataracts begin to change the lens.

OTHER RELEVANT

- **Get kids outside, especially midday.**
  Aim for daily outdoor recess and play; bright outdoor time is the most powerful myopia prevention; limit long near-work sessions in dim rooms.
- **Wear sunglasses in intense light.**
  Light is valuable for circadian rhythm, but protecting eyes from UV and glare is reasonable. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Manage blue light at night, not by day.**
  Daytime blue light supports wakefulness and may prevent myopia; bright screens at 10–11 p.m. hurt sleep.
- **Treat diabetes and get eye exams.**
  Regular dilated exams catch silent problems like glaucoma and early retinopathy. Retinal changes show microvascular damage early; good glucose control protects vision.
- **Ask about options before refractive surgery.**
  Corneal thickness, prescription and lifestyle decide between PRK, LASIK and SMILE. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

197 - The science of obesity & how to improve nutritional epidemiology | David Allison, Ph.D

Guest: David Allison
Date: 2022-02-28 · Duration: 2:21:41
URL: https://www.youtube.com/watch?v=49-CvqNQ7qU

KEYPOINTS

• Obesity rose slowly for centuries before the field woke up in the early 1990s

David Allison, a statistician, obesity researcher and dean at Indiana University, notes that obesity rates in Western industrialized countries have climbed fairly steadily since at least the 1700s. Robert Fogel, who won a Nobel Prize for this work, traced it in historical records such as British naval recruits. The 'wake-up moment' came in the early 1990s with NHANES III. Before that, obesity research was seen as niche, and treating extreme cases was often disdained even by doctors.

• Body weight is strongly heritable, as was clear long ago

Allison says the genetic component could have been seen in Charles Davenport's 1923 family data for the Carnegie Institution, though Davenport is now viewed as a racist. Twin and adoption studies from the 1980s, notably by Stunkard, Sørensen and colleagues using Nordic registries, made it undeniable. The BMI similarity of identical twins is about the same whether they are raised together or apart.

• Bariatric surgery probably extends life

Bjorn Torp's mentor laughed at the idea that it needed proving, saying everybody knew surgery helped. But Allison insists you have to do the experiment. Lars Sjöström's Swedish Obese Subjects study was controlled though not randomized. Across studies, all-cause mortality reductions vary widely but are usually on the order of 50%, sometimes more. Peter and Allison both suspect the benefit is larger in people who start with type 2 diabetes.

• The 'obesity paradox' depends on age, era and confounding

The BMI with the lowest mortality (the 'nadir') rises with age: very roughly near 20 at age 20, and in the low 30s by 70–80. The nadir also shifts with calendar time. In both Denmark and the US, obesity looked less deadly in 1990s data than in 1970s data, a finding Allison's NIH grant is investigating. Much of the paradox stems from illness causing weight loss and smoking keeping people thin. A famous 1987 JAMA paper by JoAnn Manson and colleagues argued that analyses should include only never-smokers. A 1995 New England Journal paper from the same group added more exclusions, including people with variable weight, but even these didn't fully flatten the left side of the curve.

• BMI is crude but useful at population scale

The index is old; Ancel Keys rediscovered it and named it in the 1960s–70s. For a sense of scale: Kate Moss at her peak was about 16–17, the underweight cutoff is 18.5, obesity starts at 30, and a top sumo wrestler is around 43–44. Allison compares BMI to an ordinary car, fine for daily driving but not precise enough for the Indy 500. For individuals, Peter prefers DEXA, which also shows visceral fat and bone density. The usual cutoffs fit adult white women well but fit other groups less reliably.

• Losing weight is easy compared with keeping it off

Allison sees no single explanation for why maintenance is so hard. He rejects the popular belief that there is a diet that, eaten correctly, would let anyone maintain a healthy weight without counting calories or feeling hungry or deprived. Advocates disagree about which diet that is, whether low-carb, low-fat or not eating at night. He knows of no evidence that such a diet exists.

• Observational data can point in exactly the wrong direction

In one of Allison's mouse studies, genetically identical C57BL/6J mice in identical housing were randomly assigned to eat less, a medium amount or as much as they wanted. Those forced to eat more lived shorter lives, consistent with decades of calorie-restriction research. But within the free-feeding group, the mice that chose to eat more lived longer. The observational association was the exact opposite of the causal effect, even with every usual confounder controlled. Allison calls the defence that 'it's just confounding' an admission of the problem.

• Childhood-obesity science is often analysed badly

Cluster-randomized trials assign whole schools, classrooms or families to a treatment. That's fine with enough clusters, but the analysis must account for clustering and nesting. Allison says many studies don't, and he calls that 'science gone wrong in the worst sense'. He believes some researchers are obfuscating null results while the field repeats hackneyed advice.

• Separate honest mistakes from bad science

Allison distinguishes normative errors, where good methods give a wrong answer at the edge of knowledge, from non-normative errors, which are avoidable. A normative example is Galileo's lantern experiment, which wrongly concluded light travels instantaneously. A non-normative one: early-20th-century norms for the size of children's thymus glands came from cadavers of poor, undernourished children. Normal thymuses in better-fed children then looked enlarged and were irradiated to 'prevent' sudden infant death, causing many thyroid cancers.

EXAMPLES

• What Allison would fund with $10 million

He would not build farmers' markets in schoolyards. Instead, he would split the money into four pots: bariatric surgery (both providing and studying it), drugs, general early-childhood education and security to reduce disparities, and basic science, including senolytics and work on aging.

• Indirect interventions that worked

In the Abecedarian study, a general early-education programme with no weight-loss goal was followed up 30 years later, and in a paper in Science the women had less obesity. In Moving to Opportunity, randomly assigned housing vouchers to move to less poor neighbourhoods led to less obesity and diabetes years later.

• A surgery memory

Peter recalls an open Roux-en-Y gastric bypass in a 400 lb man during his training about 25 years earlier. The patient developed an anastomotic leak and died of sepsis about 40 days later, never leaving the hospital. Today the operation is far safer.

- **Parachute trials**
  People often say no randomized trial of parachutes is needed. Allison notes that Andrew Leigh's book Randomistas shows such trials have actually been done, and he warns that the line is too often used to excuse weak observational studies.

OTHER RELEVANT

- **Ask simple questions about any health claim**
  Was it studied in humans? Was it randomized? Did it measure the outcome being claimed, for long enough? Was the result significant and big enough to matter, and at a dose you'd realistically take?
- **Be wary of hazard ratios around 1.16**
  Small relative risks from observational diet studies, such as bacon and cancer, are often presented as if they proved causation.
- **Use better tools than BMI for yourself**
  DEXA or other body-composition measures give a truer picture than BMI for an individual.
- **Keep science and advocacy separate**
  Allison argues that blurring the two erodes public trust. Say when a recommendation reflects judgement rather than proof.

Freedom, PTSD, war, and life through an evolutionary lens | Sebastian Junger & Peter Attia (Ep. 195)

Guest: Sebastian Junger
Date: 2022-02-14 · Duration: 3:18:49
URL: https://www.youtube.com/watch?v=uaYKdPEktA0

KEYPOINTS

• His family history taught him about fascism early.
Sebastian Junger, a journalist, war reporter and author (The Perfect Storm, War, Tribe, Freedom), describes his father's family fleeing Franco's Spain in 1936 and then the Nazis in France; his father was Jewish and a physicist. When Junger turned 18 in 1980 and refused to register for Selective Service, his pacifist father surprisingly told him to sign, because some wars, like the fight against fascism, must be fought.

• Tree work and running shaped him before writing.
Junger ran a 4:12 mile and a 2:21 marathon, and spent years as a climbing arborist, topping 100-foot white pines between houses, work he loved for its danger and craft. A chainsaw injury and Achilles problems pushed him toward writing; living in Gloucester, Massachusetts, when the 1991 storm hit led to The Perfect Storm.

• War reporting took him into Afghanistan for decades.
His first war assignment was Afghanistan in summer 1996 as the Taliban took over, after the Soviets left in 1989. He was with Ahmad Shah Massoud in fall 2000 as he held the northeast; Massoud was assassinated two days before 9/11, which Junger sees as part of the same strategy. He entered Kabul behind Northern Alliance fighters in November 2001.

• By 2005 the 'easy win' was slipping.
Junger argues the early war was underfunded and undermanned, and the US failed to follow through for the many Afghans who welcomed it; by 2005 the Taliban insurgency was gaining traction and US casualties climbed. He also discusses the 2021 withdrawal and the collapse of the Afghan government.

• Restrepo documented one platoon for a year.
With his friend Tim Hetherington, Junger embedded with a platoon in the Korengal Valley, producing the book War and the film Restrepo. The soldiers, mostly 19–21 and childless, carried enormous loads (sometimes 160 lb on overnight patrols). Many joined after 9/11 out of duty, as an earlier generation responded to Pearl Harbor.

• PTSD is common at first; most people recover.
Junger had an unexplained panic reaction about 10 years after his war reporting, which he later understood as PTSD. He cites about 80% of people being fully recovered a year after trauma, which doesn't mean unchanged. Hetherington's death in 2011 sent him into his first truly dangerous depression.

• Humans evolved in small, interdependent groups.
For about 90% of our past, humans lived in groups of 30–50 people who couldn't survive alone, so loyalty and shared risk were essential. Junger argues modern isolation is a mismatch; soldiers describe combat units as the closest they've ever felt, and some miss war for that reason.

• Community heals trauma, and crises can unite.
Junger points out that depression and suicide dropped in London during the Blitz and in the US after 9/11, because shared crisis creates a call to action and belonging. In April 2020 he wondered whether the pandemic would do the same; instead division grew.

• He doesn't own a smartphone.
Junger deliberately avoids one, accepting that he can't email on the go, because he values attention and presence. He and Attia discuss parenting through an evolutionary lens, including letting young children sleep in the family bed, as was normal 10,000 years ago.

• A near-death experience shook an atheist.
In June 2020 a pancreaticoduodenal artery aneurysm, after months of ignored upper-abdominal pain, ruptured; his blood pressure fell to about 60/40. As doctors placed a line in his neck, he felt a black pit opening beneath him and saw his dead father, though he's an atheist and his father was a physicist. He says the aftermath was more traumatizing than combat.

• Freedom is about small groups resisting power.
His book Freedom grew from walking hundreds of miles along railroad lines with friends, carrying 60–70 lb and covering 10–20 miles a day. He explores how outnumbered groups resist, such as Montenegrins facing a 12-to-1 Ottoman invasion in the early 1600s, and why movements need leaders but also lateral networks.

EXAMPLES

• The 9/11 firefighter
Junger recounts a fireman friend whose brothers died on 9/11; one's last call came from an emergency phone on the 30th floor of a tower.

• Open schoolhouses in the 1930s
Junger notes that schoolhouses in the American West and Midwest were left unlocked for migrant families on the move, an example of community obligation at a larger scale.

• Waking up after nearly dying
Junger woke not knowing he'd nearly died until an experienced nurse told him; only later did the psychological impact hit.

• Women in resistance movements
He cites the observation that 'it takes one cop to handle 10 men but 10 cops to handle one woman', and points to the 1912–14 textile strikes and Algerian resistance to the French as examples of women's lateral networks.

• A teenage loss

Junger tells of a boy of 15 or 16 killed when a driver ran an intersection as his older brother drove him home from school, illustrating the unbearable pain of losing a child.

OTHER RELEVANT

- **Seek belonging, not just support.**
  Being part of a group that needs you can protect mental health and help people recover from trauma. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Know that recovery is the norm.**
  Most people heal from trauma within a year; persistent dysfunction deserves professional help. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Guard your attention.**
  Consider how much your phone costs you in presence, and whether constant reachability is worth it. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't ignore recurring pain.**
  Junger's months of untreated, searing abdominal pain, which he dismissed because he could bear it, nearly killed him.

How Fructose Drives Metabolic Disease | Rick Johnson, M.D.

Guest: Rick Johnson
Date: 2022-02-07 · Duration: 2:23:39
URL: https://www.youtube.com/watch?v=V02z9mqTWzg

KEYPOINTS

• Fructose is metabolized in a uniquely ATP-depleting way.
The first enzyme, fructokinase (ketohexokinase, KHK), phosphorylates fructose to fructose-1-phosphate as soon as it sees it, with no negative feedback. At high concentrations this rapidly drains ATP in the cell; Johnson says alcohol is the only other common nutrient that does something similar. Glucose metabolism, by contrast, is tightly regulated.

• ATP depletion produces uric acid, which harms mitochondria.
Falling ATP leaves AMP, broken down via AMP deaminase stepwise to uric acid. Inside the cell, uric acid causes mitochondrial oxidative stress, inhibits aconitase in the Krebs cycle, and shifts metabolism toward fat production and storage. Johnson frames this as an ancient survival mechanism to store fat before scarcity.

• The body makes its own fructose.
Johnson originally assumed a low-fructose diet would solve the problem, but the polyol pathway, via aldose reductase, converts glucose into fructose in the liver. High glucose, high salt concentration and raised blood osmolality all activate it. He guesses endogenous production may add roughly 25–50% on top of dietary intake for someone eating a lot of sugar — explicitly a guess.

• Mice lacking fructokinase are protected even from glucose.
Wild-type C57 mice given about 10% glucose in drinking water first eat less chow, then over about a month develop leptin resistance, eat more, and become fat and insulin resistant with active polyol pathways. Mice with fructokinase knocked out given the same glucose stay leaner — evidence that fructose made from glucose drives much of the harm.

• In calorie-matched studies, sugar still caused more harm.
In pair-feeding studies — 40% sugar versus starch with identical food — sugar-fed animals developed more fatty liver and metabolic features. Four months is about 15% of a mouse's two-and-a-half-year life, roughly 15 human years.

• Small daily surpluses add up.
Attia notes that if fructose drives about 300 extra calories of intake a day while reducing expenditure by only 25, the appetite effect matters far more — about a pound every 12 days from intake versus months from expenditure.

• Americans eat a lot of fructose.
About 15–20% of calories come from sugar, which is half fructose, so about 10–15% of the diet is fructose. It's not hard to eat 75–100 g a day (400 calories, around 15% of intake). About 10% of ingested fructose is excreted in urine.

• Vulnerability rises with age and menopause.
Johnson gives several reasons: younger people have healthier mitochondria; with obesity and fatty liver, fructose absorption increases; and the polyol pathway turns on more over time. In a study of children, lean kids absorbed about 70% of a fructose dose, while obese children with biopsy-proven fatty liver absorbed 100%.

• Lowering uric acid lowered blood pressure in teens.
In Dan Feig's JAMA trial, adolescents aged 14–15 with newly diagnosed hypertension were randomized to allopurinol or placebo; about 90% normalized blood pressure when uric acid was lowered. Another study gave 200 g of fructose a day to men with or without allopurinol.

• Blood pressure thresholds are debated.
Most of the world defines hypertension as 140/90; the US recently moved to 130/80. Johnson views 140/90 as the point for active management and says 135/85 carries little kidney risk and can be fixed with diet and exercise. Attia pushes back: if a 40-year-old should reach 100 with a GFR still around 40, standards should aim nearer 120/80 — just as lifelong apoB matters even when five-year trials can't show it.

• Salt and vasopressin link to obesity, not just blood pressure.
Raised salt concentration activates fructose production and raises vasopressin, a water-conserving hormone. Fat oxidation generates water, so animals store fat partly as a water source; vasopressin is high while animals like the fat-tailed dwarf lemur store fat. Johnson cites human data linking high-salt diets to obesity risk.

EXAMPLES

• Fruit vs. juice vs. dried fruit
An orange contains about 6 g of fructose; most fruits have 3–10 g, with mangoes, apples, pears and plums higher. Whole fruit comes with fibre, water and vitamin C and is hard to overeat — it's hard to eat more than two apples, but easy to eat 10 apples' worth of apple chips.

• Soft drinks vs. sports drinks
Soft drinks are about 11% sugar — 6% fructose, 5% glucose — which Johnson calls 'bad stuff'. Some sports drinks contain only 2–4% fructose with 4–6% glucose; during exercise, about 5–6% glucose and 1–3% fructose appears optimal.

• Attia's glucose monitor question
Attia asks how high glucose rises in the portal vein when a CGM shows 90 rising to 150 mg/dL; Johnson says that hasn't been measured, though portal levels are higher.

• The obesity paradox
With chronic illness, a BMI of 27 may do better than 20, and in old age 28 may do better than 24 — Johnson attributes this partly to the protective value of some fat stores.

• Calorie-restricted animals
Animals kept at 70% of normal intake have minimal fat stores.

OTHER RELEVANT

- **Cut sugary drinks first.**
  Liquid fructose delivers large, fast doses that overwhelm regulation. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prefer whole fruit over juice and dried fruit.**
  Fibre and volume limit dose. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch salt as well as sugar.**
  High salt may activate internal fructose production and raise blood pressure.
- **Aim lower than 'normal' blood pressure.**
  Discuss targets nearer 120/80 with your doctor, starting with diet, salt reduction and exercise.
- **Ask about uric acid.**
  It's an inexpensive marker that may flag fructose-driven metabolic stress; treatment decisions belong with your clinician.
- **Treat exercise-time sugar differently.**
  Johnson notes the context matters: during exercise, modest glucose-dominant drinks are used for fuel, whereas the same sugars at rest in a sedentary person feed the fat-storage pathway.

COVID Part 2: Masks, long COVID, boosters, mandates, treatments, and more

Guest: Marty Makary, Zubin Damania and Monica Gandhi
Date: 2022-01-24 · Duration: 2:53:03
URL: https://www.youtube.com/watch?v=jAjKQY0_BQA

KEYPOINTS

• Omicron hospitalization data in early 2022 looked far milder than earlier waves.

Recorded January 17, 2022, the panel led with a Kaiser Southern California preprint: about 52,000 documented Omicron cases, none requiring mechanical ventilation. Makary argued that with four or five community infections for every documented one, that represents roughly a quarter million infections. Omicron was then 98.3% of US cases per the CDC, up from 73% in mid-December, so older severity data no longer described the dominant variant.

• A large share of 'COVID hospitalizations' were incidental.

Hospitals reported that many admitted patients tested positive but were there for something else—about 53% at one system and 65% at Jackson Memorial in Florida. The panel's rule of thumb was 50–60% incidental, higher in highly vaccinated regions, which matters for interpreting dashboards and for whether hospital strain reflects COVID illness.

• Population immunity, not only the variant, explains much of the mildness.

Gandhi described the debate since South African scientists first flagged Omicron. A serology study found about 79% of South African adults had antibodies despite only around 25% vaccination; one analysis estimated vaccination alone carried a hazard ratio of 0.24 for severe outcomes. Her view: T-cell and B-cell immunity from prior infection and vaccines blunts severe disease even when antibodies wane.

• T cells and B cells give durable, broad protection.

Gandhi cited SARS-1 survivors with strong T-cell responses 17 years later, and elderly survivors of the 1918 influenza whose B cells could still make antibodies against that strain about 90 years on. Because Omicron's mutations cluster in the spike (about 32 of roughly 50 total), immunity to the whole virus—from infection or an inactivated vaccine like Covaxin—may help against future variants.

• Myocarditis risk tracks dose and spacing.

Moderna's dose is 100 micrograms versus Pfizer's 30, which likely explains its higher myocarditis signal and why several countries avoid it in younger men. A Canadian study found higher risk after the second dose with Moderna and with shorter dose intervals, supporting Canada's 8-week spacing. An Alabama study of 175 people over 80 found immune response about 3.5 times greater when doses were spaced three months rather than three weeks.

• Boosters matter most for the old and sick.

Per a CDC analysis discussed, the risk of a severe outcome after even two doses was tiny across the population, with a vanishingly small chance of death,while risk concentrated in people over 75 with multiple (often four) comorbidities. The panel argued booster messaging should focus there rather than on blanket mandates.

• Public risk perception was wildly distorted.

Attia recounted a parent who estimated his unvaccinated, healthy son in his late 30s had a 50% chance of hospitalization or death; the actual data suggested a risk on the order of 0.001. Makary showed that for 5–14-year-olds, suicide risk was about 6.5 times and homicide about 5 times that of COVID, and for 15–24-year-olds car crashes, suicide, homicide and overdoses together were roughly 9–10 times greater.

• Mask quality matters; cloth masks are largely obsolete.

Gandhi said cloth masks may once have reduced severity (possibly via humidified air) but vaccination now does that far better. The panel favored offering high-filtration masks—N95, KN95, KF94, FFP2—to those who want protection. A National Academy of Sciences study found 20-minute transmission risk of about 10.4% with surgical masks, 4.2% with an N95 lacking a nosepiece, and 0.14% with a well-sealed N95.

• One-way masking protects the wearer, which undercuts mandates.

Because a well-fitted N95 protects the person wearing it, the panel argued high-risk people can protect themselves without population mandates. Attia noted he wants his 87-year-old father, on chemotherapy, in an N95—an individual choice rather than a rule for everyone.

• Vaccination appears to reduce long COVID.

Gandhi, whose institution UCSF runs a post-acute COVID study, said long-term symptoms follow many severe viral infections. Three studies, including one from Israel published that morning, suggested vaccinated people had fewer long-COVID symptoms, and mild breakthrough infections in the vaccinated rarely produced lasting symptoms.

• Early treatments were underused.

Makary said a repurposed antidepressant, fluvoxamine, reduced mortality by 91% among compliant high-risk patients in a trial, yet official bodies said evidence was insufficient. He added that concentrated convalescent plasma reduced hospitalizations by about 50% and that many physicians knew little about either, along with the new oral antivirals.

• Polarization and tribalism hardened positions.

The group argued mandates and moralizing hardened the unvaccinated minority (about 15% of Americans over 5), and that dismissing natural immunity backfired. Attia joked about his brother being treated as a 'filthy person' for catching COVID in early 2020. They urged humility and fact-based discussion over fear-based modeling.

EXAMPLES

• The '300,000 deaths' forecast

Attia criticized a projection of 50,000–300,000 additional US deaths by March 2022 as fear-based; he called 300,000 deaths in roughly 40 days very unlikely.

• Sweden's long game

Once called a cautionary tale, Sweden later showed relatively favorable excess mortality, never focused on masks, and

achieved strong vaccine uptake in 2021.

- **US excess deaths in 2020**
  Makary cited about 477,000 excess deaths from March to December 2020, roughly 385,000 attributed to COVID, leaving tens of thousands unexplained and possibly due to missed care, overdoses and other indirect effects.
- **Quebec's unvaccinated tax**
  The panel pointed to Quebec's plan to tax the unvaccinated and to children barred from organized sports; Attia argued consistency would mean taxing people with BMI over 25 or high-risk hobbies.
- **The Robert Malone interview**
  Damania went point by point through Malone's Joe Rogan appearance, calling 'mass formation psychosis' a garbage term while acknowledging some valid concerns, and argued censorship made skeptics dig in.
- **NIH research priorities**
  Makary contrasted 254 NIH-funded studies on COVID health disparities with very few on how the virus spreads and just one grant on masks.

OTHER RELEVANT

- **Read hospitalization numbers critically.**
  Ask whether patients are admitted for COVID or merely with it, and which variant dominates.
- **Match precautions to personal risk.**
  Older people with multiple comorbidities benefit most from boosters, high-filtration masks and fast access to treatment; healthy young people face very low risk.
- **Upgrade the mask if you mask.**
  A well-sealed N95 or equivalent beats surgical and cloth masks by a wide margin.
- **Know the treatment options early.**
  Ask a physician about antivirals, monoclonal antibodies or other evidence-backed options before illness worsens, rather than relying only on vitamins.
- **Plan an exit for every intervention.**
  Attia argued any measure, like an investment or war, needs a defined end point; the panel expected mask mandates could ease within months as immunity rose.

191 - Revolutionizing our understanding of mental illness with optogenetics

Guest: Karl Deisseroth
Date: 2022-01-17 · Duration: 2:42:06
URL: https://www.youtube.com/watch?v=anKrNnJDBZk

KEYPOINTS

• A psychiatry rotation changed his career.
Karl Deisseroth, a Stanford psychiatrist and bioengineer and Attia's former medical school classmate (he was in the highly selective MD-PhD Medical Scientist Training Program), planned on neurosurgery until a rotation on a locked psychiatric unit, with patients who were a danger to themselves or others, convinced him psychiatry was where the greatest need and mystery lay. He trained before 80-hour week limits, with a young son born in 1996.

• Psychiatry in 2004 lacked causal tools.
When he set up his lab in 2004, treatments like drugs, electroconvulsive therapy and vagus nerve stimulation worked for some patients but without precise understanding. The brain has about 90 billion neurons, each forming 10,000–100,000 synapses, and earlier tools (lesions, electrodes, drugs) couldn't control specific cell types with precise timing.

• Optogenetics borrows light-sensitive proteins from microbes.
Microbial opsins were discovered in 1971 by Dieter Oesterhelt and Walther Stoeckenius at UCSF; these single-component proteins pump or pass ions when light hits them. In principle someone could have put them into neurons in the late 1980s or 1990s, but the currents were thought far too small: neurons need about 100–200 picoamps to fire. Deisseroth's lab published its paper in summer 2005, and several other papers followed within six months.

• Viruses made targeting specific cells possible.
The opsin gene (such as channelrhodopsin) is packaged into a virus that delivers it, paired with cell-type-specific genetic elements, into neurons; it can even be given systemically in some settings, though focal injection is cheaper. Deisseroth says the method wasn't really 'solved' until about 2009, after years of work on light delivery, viral vectors and generalizable targeting.

• Optogenetics established causality for dopamine and reward.
In 2009, his group selectively fired dopamine neurons, not nearby GABA or serotonin cells, and showed it was sufficient to drive preference. With typical rewards like sugar water or social contact, animals prefer the stimulated side about 70–30 or 80–20; dopamine stimulation produced similar effects.

• Anxiety's components can be split apart.
In 2013, his lab found separate, nearby cell populations controlling distinct features of anxiety: breathing changes, risk-avoidance behavior (like avoiding exposed spaces) and the negative internal state. Too little anxiety is also dangerous, as people who don't perceive threat take extreme risks.

• Anxiety links autism and depression.
Deisseroth emphasizes that anxiety can be crushing and becomes pathological when it exceeds the normal range; it's a common thread in autism spectrum disorders, depression and other conditions. Optogenetics has been used to study social behavior and states like parenting (work at Harvard in 2018 used the same tools).

• Depression involves discounting effort.
Where a manic person thinks anything's possible, a depressed person thinks nothing is, devaluing effort and leading to hopelessness and sometimes suicidality. Anhedonia, the absence of pleasure, is so central that major depressive disorder can be diagnosed without depressed mood. In fish and mice, 'giving up' can be adaptive in truly hopeless situations, which suggests depression is a misfiring of a useful circuit.

• Severe psychiatric illnesses are highly heritable.
Genetic contributions run about 50% for depression and up to 50–80% for schizophrenia, autism and bipolar disorder. Hypomania may be unusually prevalent in North America, possibly because of who emigrated. Early-life trauma has clear, lasting psychiatric effects, including on personality disorders like borderline, seen in animals too.

• Optogenetics is a discovery tool first.
Deisseroth stresses that the immediate value of optogenetics is in identifying which cells and projections cause which behaviors, insights that can then guide treatments using other methods, such as drugs, brain stimulation or psychedelic-assisted therapy (ketamine, psilocybin, LSD and MDMA are all of interest to him and Attia). Psychiatrists grasped its importance quickly because they knew better than anyone how much specificity their field lacked.

• Projections uses patient stories to explain the science.
Deisseroth wrote Projections from about 2017 to 2020, blending clinical stories with circuit science and working with language in ways atypical for a scientist. He received the Lasker Award for optogenetics. Self-harm ranks among the 10 leading causes of death, and higher if overdoses are included, which is why the stakes are so high.

EXAMPLES

• Alexander's mania after 9/11
A patient with no personal or family psychiatric history, sailing in the Mediterranean with his wife on 9/11, became fully manic a couple of weeks after returning home, a case Deisseroth uses to show how stress can unmask latent vulnerability.

• The close call in 2005
Deisseroth's 2005 paper beat several competing groups by months; a scientist had even proposed in 1999 that light might someday control specific cells.

• Mice in exposed spaces
Like people on exposed boats, mice avoid open areas where predators strike; optogenetic manipulation could make mice more or less willing to enter them.

• Sugar water preference
Normal rewards shift mouse choices to roughly 70–30 or 80–20, a benchmark for judging whether dopamine stimulation is

meaningfully rewarding.

- **The ACE2 analogy**
  Attia compares viral targeting of neurons to how SARS-CoV-2 enters cells via the ACE2 receptor: knowing a surface receptor lets you aim a vector.

OTHER RELEVANT

- **Take anhedonia seriously.**
  Loss of pleasure is a core sign of depression even without obvious sadness; it deserves professional evaluation.
- **Recognize early-life trauma's long reach.**
  Trauma can shape mental health for life; early intervention matters. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Look for causal evidence.**
  Correlations in brain imaging are suggestive; optogenetics shows how causality can be tested in animals. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch for mania after stress.**
  Major stressors can trigger first manic episodes even in people without a history. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

190 - How to heal from trauma and break the cycle of shame

Guest: Paul Conti
Date: 2022-01-10 · Duration: 2:27:21
URL: https://www.youtube.com/watch?v=HoGBkn_1Z14

KEYPOINTS

• A personal tragedy shaped Conti's view of trauma.
Paul Conti, a psychiatrist who trained at Stanford and Harvard and runs a clinic of about 15 clinicians, lost his brother to suicide when Paul was 24. His family was blindsided, and each member coped alone in their own way, typical of the generation. In retrospect he sees in himself what he now sees in patients: shame and guilt walling off grief.

• Psychiatry training and practice are misaligned with healing.
Much of what he learned as a second-year resident, Conti says, should be taught in elementary school. The DSM, now in its fifth edition and updated every 15–20 years, is descriptive, so it catalogs symptoms rather than causes. Handoffs reduce people to billing codes ('a 296.xx with a 309.81'), and 15-minute appointments make it impossible to understand anyone.

• The system pays to treat symptoms, not roots.
Insurers fund brief visits and medication, while PTSD acts as an arbitrary gating diagnosis for trauma care. Conti avoids sending patients in crisis to hospitals because they may wait 36–40-plus hours in an emergency department. Few psychiatric problems trace to a biomarker like B12 deficiency; most are rooted in experience.

• Trauma is broad and its effects are heterogeneous.
Acute trauma, such as a suicide in the family, is the obvious kind, but what pushes coping past its limits differs by genetics, early life experience and emotional sensitivity. Conti uses a 'seed and soil' image: expose 100 people to the same event and, without knowing their soil, you can't predict how each will respond. Viewed broadly, he says, trauma's contribution to mental illness approaches 100%.

• Finding the 'why' is essential.
Tools like the Adverse Childhood Experiences (ACE) questionnaire help, but Conti says data only makes sense once someone sits in front of him. The last story in his book describes a woman who insisted she had no trauma, yet a decade later it proved to be driving everything; with intelligent, likable people, that blindness 'is the norm, not the exception.'

• Untreated trauma is like an abscess.
Walled off under shame, trauma can 'spin off symptoms for years' and generate new trauma: lost jobs, broken families and more shame. Medicine hunts abscesses with advanced CT scanners, Conti notes, yet we rarely look for psychological abscesses, and patients often don't know they have one; they just feel unwell. Grief can feel as immediate 50 years later as when it happened.

• Shame is the biggest barrier to healing.
Shame tells us we are bad, not that we did something bad, and drives people to avoid talking about the past. Conti compares it to a coat tree in his childhood bedroom that looked like a monster in the dark: the antidote is understanding, turning the light on. Lancing the abscess means bringing the shame into the open.

• What we repeat to ourselves becomes who we are.
If someone tells themselves they're worthless 500 times a day, it shapes self-concept; Conti uses repetition to show how internal dialogue entrenches beliefs. Healing starts by understanding where the feeling came from ('because of this event, I feel inadequate, so I do this other thing') and then changing it, which takes far more than two to four weeks.

• Emotional health is part of healthspan.
Attia reflects that to be a 'kick-ass 100-year-old' he must be a 'doubly kick-ass 50-year-old', including emotionally, and admits this is the hardest bucket to help patients with. Conti urges primary care doctors to see that well over half of complaints have emotional drivers.

• Overdose deaths reflect trauma and shame.
The US passed 100,000 overdose deaths in a 12-month period for the first time; Conti fears it could reach 140,000 within a few years if nothing changes, and sees it as an epidemic rooted largely in trauma and shame. In addiction settings, the commonality among patients, he estimates, is about 80% trauma.

• Psychedelics are a bright hope as adjuncts.
Conti calls psilocybin and MDMA (moving toward approval for PTSD) among the brightest hopes for the future, citing both decades-old and recent data, as tools that can help people access and process trauma within therapy.

EXAMPLES

• The physicians' room
Speaking to about 300 physicians from mixed disciplines, Conti stressed that there's no shame in trauma, and many came forward afterward.

• Stress reawakens old wounds
People can do well for 10–20 years, but under enough stress and triggering, buried trauma resurfaces.

• 'That stuff dies hard'
A patient who had told himself something negative perhaps 100,000 times wasn't afraid of the work, because he understood how deeply the belief had been rehearsed.

• The unseen case
A woman described in Conti's book attested to having no trauma; years of symptoms traced back to it once it surfaced.

• Twenty years of handoffs
Conti recalls that over two decades he has repeatedly taken over patients described only by diagnostic numbers, and that the real driver of their suffering emerged only when someone took the time to ask about their history.

OTHER RELEVANT

- **Talk about the past.**
  Overcoming fear of discussing trauma is the first step; avoidance keeps the abscess sealed.
- **Replace shame with understanding.**
  Ask why you feel what you feel; context makes self-blame lose power. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Be patient with treatment.**
  Expect healing to take months or longer, not weeks. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Look beyond diagnosis codes.**
  Seek clinicians who explore root causes rather than only managing symptoms. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Get help.**
  For anyone in crisis, reach out to local emergency or crisis resources; shame is not a reason to wait.

COVID-19: Current state of affairs, Omicron, and a search for the end game | Peter Attia, M.D.

Guest: Marty Makary, Zubin Damania
Date: 2022-01-05 · Duration: 2:45:29
URL: https://www.youtube.com/watch?v=GklHGYY8vN8

KEYPOINTS

• A snapshot recorded on December 27, 2021.
Attia brings back Johns Hopkins surgeon and public-health researcher Marty Makary and internist Zubin Damania (ZDoggMD) because he'd grown frustrated with shoddy science and messaging. He stresses that the conversation is dated: three months later much more would be known. Treat the specifics as a record of what they argued at the time, not current guidance.

• Omicron looked more contagious but less severe.
Laboratory data showed Omicron replicated about 90% less efficiently in lung tissue than Delta while spreading readily in the airways, and South African epidemiology pointed to milder disease. They speculated COVID could become another endemic coronavirus 'cold', noting the hypothesis that the 1889–1891 'Russian flu' was a coronavirus.

• Protection against infection fades; protection against severe disease holds.
They cited data that primary-series vaccines were about 70% effective against symptomatic infection, with booster protection against symptomatic Omicron waning to roughly 35–45% by about 10 weeks. They argued circulating antibodies wane while B and T cells sustain protection against severe illness, so infection-blocking shouldn't be the policy goal.

• Define an end game.
Attia asks what line in the sand returns the world to something like 2019. Respiratory pathogens infect 10–25% of people every year in perpetuity, so zero COVID isn't realistic. Makary argues the remaining risk sits with the 10–20 million US adults with no immunity; about 7,000 Americans a day were being hospitalized, mostly in that group.

• Natural immunity was treated as taboo.
Makary notes only three human coronaviruses have caused severe epidemics (SARS, MERS, COVID-19); natural immunity to SARS remained solid 17 years later and to MERS at three years. A large Israeli population study suggested natural immunity was strong and durable, yet US policy largely ignored it, unlike historic practice such as assuming immunity to measles for people born before about 1960.

• Myocarditis risk is concentrated in young males, especially after dose two.
For 12–17-year-olds, blended mRNA data showed about 8–10 myocarditis cases per million doses in females but 56–69 per million in males. About 90% of complications clustered after the second dose; most were mild, though a high share were hospitalized. Several countries restricted Moderna for people under 30. For healthy young males, the panel argued, benefits such as averted ICU admissions and deaths per million doses were small relative to that risk.

• Healthy children faced very low risk.
German data covering 5–17-year-olds over about 15 months showed no deaths among healthy children before vaccines; all deaths were in kids with comorbidities. Israeli data showed zero deaths in vaccinated people under 30 after the primary series. The CDC reported 668 pediatric deaths over two years, many with underlying conditions.

• The panel criticized booster messaging for teens.
They argued the CDC strongly recommended boosting all 16–17-year-olds the day after an announcement made without releasing underlying data, while noting that 93% of people in poor countries had no vaccine. Makary also cited data on how much risk healthy young people actually faced.

• Science and advocacy got blurred.
They criticized groupthink, lack of humility from top officials, and 'data fishing' (Makary describes CDC analyses across 50 states over 15 months that cherry-picked findings). Only about 0.05% of the NIH budget went to COVID research months into the pandemic, with grants taking about five months to fund.

• Antivirals and testing changed the calculus.
Attia highlights new oral antivirals such as Paxlovid, whose trials showed no COVID deaths in the treatment arm, as tools 'we couldn't fathom 12 months ago'. They questioned mass testing of healthy people versus targeted testing and protection (N95/KN95 masks, avoiding risky events) for those at high risk.

• Lockdowns carried downstream costs.
They cited a Brown University study showing lower cognitive scores in children born during 2020, alongside delayed care and mental health harms. Makary argued that a victory like 800,000 deaths instead of 2 million came with such an erosion of trust that it may cost lives in the next public-health crisis.

EXAMPLES

• Pulling kids out of school
Attia recounts removing his kids from school about two weeks early in March 2020, showing how his own thinking evolved as data improved.

• Masked kids in summer 2021
A story of three children in a grocery store wearing masks, face shields and PPE, long after their risk was known to be low, illustrates fear outpacing data.

• Parachutes at 10,000 vs. 15 feet
Damania's analogy: mandating parachutes makes sense when jumping from 10,000 feet, not when jumping 15 feet into water; policy should scale to risk.

• Vitamin D as surrogate

They discussed whether people taking 4,000–5,000 IU of vitamin D did better because of the vitamin or because it's a marker of overall health; Attia suspects the latter.

• Flu testing, by comparison

Attia notes he had H1N1 around 2009–10 and, like most people, never thought to measure influenza infection rates in healthy people, a contrast the panel drew with the push for mass COVID testing of people without symptoms or risk factors.

OTHER RELEVANT

• Match precautions to personal risk.

High-risk and unvaccinated adults benefit most from vaccination, antivirals and masks; low-risk people face different trade-offs. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Weigh sex- and age-specific data.

For young males, consider myocarditis risk when discussing dose spacing, product choice and boosters with a clinician. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Ask for the data behind recommendations.

Policies without released evidence erode trust; look for primary sources. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Revisit conclusions as evidence changes.

This conversation reflects late-2021 knowledge and opinion; check current guidance and discuss decisions with your own clinician.

#187 - The Warburg Effect: Otto Warburg’s Cancer Metabolism Theory with Sam Apple

Guest: Sam Apple
Date: 2021-12-13 · Duration: 1:59:06
URL: https://www.youtube.com/watch?v=n6MjnI4vM7M

KEYPOINTS

• A journalist found his story in a single sentence

Sam Apple, a writer who teaches science writing at Johns Hopkins, was researching the clustering of metabolic diseases since the 19th century when he read that in 1923 a German scientist had made an important discovery about cancer metabolism. Googling Otto Warburg was a 'light-bulb moment'. He says he only writes about science when he has a central character, and Warburg became the subject of his New York Times Magazine piece in 2016 and then his book Ravenous.

• Warburg grew up among the titans of German science

Born in 1883 to Emil Warburg, a prominent physicist from a famous Jewish family who rose to the top of German physics at the University of Berlin, Otto grew up with Einstein, Max Planck and Emil Fischer visiting the house. Einstein called Emil his favourite physicist. Otto served in World War I in his early 30s, although Einstein had urged him not to go and wrote to him again in 1918. A friend described his devotion to science as a prophet's fervour, and Warburg said a scientist must be prepared to die for the truth.

• The Warburg effect: cancer cells ferment glucose even with oxygen available

Warburg had found that fertilized sea urchin eggs use more oxygen as they grow. In 1923 he expected cancer cells to do the same. Instead, they took up huge amounts of glucose and fermented it to lactate even when oxygen was present. Peter notes that fermentation yields about 2 ATP per glucose versus about 32–34 from full respiration, a roughly 17-fold difference, which is why the behaviour seemed so strange.

• Warburg insisted damaged respiration was the prime cause of cancer

He argued that fermentation compensated for defective mitochondria and occurred in 100% of cancers. Apple says today's estimate is perhaps 70% or more. Warburg distinguished a 'prime cause' (damaged respiration) from many 'secondary causes', such as carcinogens. He never had a good way to test the idea, and his own first experiments in the early 1920s showed respiration continuing.

• He won the 1931 Nobel Prize for respiration, not cancer

Warburg was nominated in 1926 for his cancer work, in what was apparently a tie that went to someone else. In 1931 he won for identifying the respiratory enzyme now called cytochrome oxidase, the last step of respiration. Apple and Peter discuss whether his later work on hydrogen transfer and coenzymes was his best science, research that ended up having a vast, mostly unseen influence on American life.

• A Jewish-descended scientist survived inside Nazi Germany

Of about 2,500 Jewish scientists at German institutions, Warburg was the only one who stayed to the end. He was useful for propaganda around the 1936 Berlin Olympics, but by 1941 that value was gone. On June 21, 1941, he was summoned to meet Viktor Brack, architect of the Nazi euthanasia killing programme, and was told he could live on one condition: that he work on cancer. Apple argues that Hitler, who lost his beloved mother to breast cancer when he was a teenager, was likely involved in that decision.

• Oncogenes eclipsed Warburg, until a 2009 rethink

After the war, Warburg feuded with critics such as Sidney Weinhouse in Science in 1956 and died in 1970. The discovery of oncogenes in the 1970s, recognized with the 1989 Nobel to Harold Varmus and Michael Bishop, pushed metabolism aside. Weinberg and Hanahan's 2000 'Hallmarks of Cancer' paper left Warburg out. The renaissance came with a 2009 Science paper by Matthew Vander Heiden, Lewis Cantley and Craig Thompson. They accepted the Warburg effect but argued the mitochondria are largely intact, and that the cells take up glucose to get building blocks for nucleotides and lipids rather than to make up for an energy shortfall.

• Apple's thesis: hyperinsulinemia may link obesity and cancer

In the late 1990s, just as labs such as Craig Thompson's and Chi Van Dang's returned to Warburg metabolism, epidemiology showed that elevated insulin and obesity both correlate with cancer. Apple thinks prevention should focus on hyperinsulinemia. Peter notes that insulin could only be measured in blood from the late 1960s. Even tumours with PI3K pathway mutations may remain responsive to insulin, he notes. Obesity's link is harder to untangle than tobacco's because its hazard ratios are far smaller.

EXAMPLES

• Fructose surprised the author

Apple assumed sugar mattered only by driving liver fat and insulin resistance. Lewis Cantley's work in colon cancer, along with Rick Johnson's ideas, suggests fructose metabolism itself depletes ATP in the cell and may directly feed tumour growth. Apple says sugar is still central, but this upended his idea of the mechanism.

• Prime versus secondary causes, using cholera

Peter applies Warburg's framework: in 19th-century London's cholera epidemics, the bacterium was the prime cause. With smoking, they agree tobacco is likely a prime cause through DNA damage, though Apple notes it comes down partly to semantics.

• How writing is taught

Apple did a two-year MFA in creative non-fiction at Columbia. Writing workshops of about 15 students critique each other's drafts several times a semester, a gruelling process of trial and error. When selecting science-writing students, he reads cover letters most closely.

• A 120,000-word gamble

Without biochemistry training or fluent German, Apple spent years on the book. He says finishing it taught him to trust himself as a writer.

OTHER RELEVANT

- **Separate the history from the conclusion**
  Warburg was right that cancer metabolism is distinctive and wrong to call damaged respiration the sole cause. Hold both thoughts.
- **Treat metabolic health as part of cancer prevention**
  Apple and Peter both see high insulin and obesity as plausible levers in cancer prevention. They frame this as a hypothesis with strong correlations, not settled causation.
- **Limit excess fructose**
  Excess fructose drives insulin resistance and may also have direct effects on tumour cells.
- **Be wary of single-cause stories**
  Warburg's certainty that he had found the one cause of cancer alienated colleagues. Apple's reporting suggests that both the mutation and metabolism camps hold part of the truth, with examples and counter-examples on each side.

186 - The Opioid Crisis with Patrick Radden Keefe

Guest: Patrick Radden Keefe
Date: 2021-12-06 · Duration: 2:21:59
URL: https://www.youtube.com/watch?v=8uXe9QvRRqM

KEYPOINTS

• The opioid crisis is a 25-year public health disaster with many players

Patrick Radden Keefe, a New Yorker staff writer and author of Empire of Pain, says at least half a million Americans have died of opioid overdoses since the mid-to-late 1990s, and by some estimates more than 2 million have an opioid use disorder. The crisis moved from prescription pills to heroin, which Mexican cartels pushed after about 2010, and then to fentanyl. He focused on the Sacklers partly for the family drama, and partly because OxyContin was, in one insider's words, 'the tip of the spear'.

• Arthur Sackler pioneered modern pharmaceutical marketing

The three Sackler brothers bought Purdue Frederick, a small 19th-century patent-medicine company once based on Christopher Street in Greenwich Village, in 1952. Arthur, the eldest, designed the advertising for Roche's Librium and then Valium, each the best-selling drug in history at the time, and was paid bonuses that rose with sales. Arthur died in 1987, before OxyContin existed, but Keefe devotes the first third of the book to him because Purdue later used the same methods.

• Purdue built OxyContin on its MS Contin playbook

Purdue's controlled-release morphine for cancer pain, MS Contin, earned perhaps $300–400 million a year. As its patent neared expiry, the company applied the same coating to oxycodone and aimed it at the much larger market of non-cancer pain. Executives reasoned that they couldn't increase the number of people dying of cancer. Since the 1970s and 1980s, a school of physicians had argued that pain was undertreated and addiction risk overstated, and Purdue amplified that view.

• 'Believed to reduce' abuse liability had no study behind it

OxyContin's original 1996 package insert said the Contin delayed-absorption system 'is believed to reduce the abuse liability of the drug'. No study supported that claim. FDA medical officer Curtis Wright, who approved the drug largely on his own, later said Purdue officials wrote the line. In 1995 the company had sent him a webcam to communicate directly. About a year after approval, he took a job at Purdue for roughly three times his government salary.

• Purdue claimed ignorance of abuse, but its emails tell a different story

Senior executives, including Richard Sackler, testified under oath that they knew of no problem until early 2000, when the US Attorney for Maine wrote to thousands of doctors. Keefe found internal emails from the late 1990s showing they knew early, and he says chief medical officer Paul Goldenheim's testimony to Congress was a bald-faced lie. In 1999, sales rep Steve May in Virginia was alarmed by one of his 'whales', the term reps used for very high prescribers.

• The black market helped pay Purdue's bills

After the crush-resistant reformulation in 2010, sales of the 80 mg pill, the strength most popular on the black market, fell 25% nationwide. Keefe infers that until then about a quarter of 80 mg sales were going to people misusing the drug. From 1996, users had chewed, crushed or dissolved pills to snort or inject them, bypassing the time release that Purdue claimed made the drug safer. The label's warning not to crush the pills worked, Keefe says, as an inadvertent how-to.

• Two guilty pleas, and almost no individual accountability

In 2007, Purdue pleaded guilty to federal charges and three executives pleaded to misdemeanours, but senior staff stayed and little changed. From about 2010 the company was 'back to committing crimes', and it pleaded guilty again in 2020 with no individuals even named. Over roughly a decade, the family took more than $10 billion out of the company. In 2019, facing thousands of lawsuits, Purdue filed for bankruptcy in White Plains. Judge Robert Drain approved a non-consensual release of third-party claims, and the family agreed to pay $4.5 billion over nine years from a fortune of about $11 billion, with most of the payments due at the end.

• Many institutions enabled the crisis

Keefe describes bipartisan capture. HR 4709 was a three-page 'sleeper bill' that passed almost unopposed and, in Peter's words, tied the DEA's hands behind its back. Linden Barber went from being one of the DEA's most credible voices against unchecked distribution to lobbying for the distributors. Pain was promoted as the 'fifth vital sign', on posters in every hospital corner, measured on a subjective 1–10 scale that varies by person and culture.

EXAMPLES

• Peter's own OxyContin story

In 2000, a disc fragment of about 5 cm pressed on Peter's S1 nerve root. The surgeon operated on the wrong side, leading to further procedures. Starting at 20 mg of OxyContin, within four months he was taking almost 400 mg a day. He didn't realize he could overdose. A girlfriend who was an anesthesiologist got him to a Stanford pain expert. After he quit cold turkey, that expert managed his remaining pain with medicines such as Neurontin. Peter says he wasn't saved by willpower but by luck: the drug didn't 'put a hook in' him.

• A 6,000-bed hospital

Before Purdue, the Sackler brothers worked at Creedmoor, a huge psychiatric hospital in Queens with about 6,000 patients in a facility designed for about 4,000. Keefe says lobotomies were still being performed there.

• The heirs' chat log

One revealing document Keefe obtained was a WhatsApp log from Sackler heirs. It shows a family disconnected from public condemnation, even as attorneys general, Congress and late-night comedians attacked them.

• Path to addiction

Peter describes several routes: a surgical patient given a legitimate prescription, someone who drifts from that into misuse, and people who obtain pills illicitly. The routes overlap, and the first can lead to the others.

OTHER RELEVANT

- **Prescribe and take opioids cautiously, but don't abandon pain patients**
  Keefe says the backlash has been agonizing for many chronic-pain patients. He argues the problem was never that OxyContin existed but how it was marketed. Shorter courses at lower doses are a good change, but pain still needs treating.
- **Address the pain, not just the drug**
  Peter's recovery depended on expert pain management after stopping, which many people don't have access to.
- **Treat 'believed to' claims as red flags**
  Ask what study a safety claim rests on. If there isn't one, assume the claim is marketing.

Cardiovascular disease & why we should change the way we assess risk | The Peter Attia Drive Podcast

Guest: Allan Sniderman
Date: 2021-11-29 · Duration: 2:25:35
URL: https://www.youtube.com/watch?v=W1geXgNEG_0

KEYPOINTS

• The 10-year risk window hides most premature heart disease

Nearly every major guideline decides who gets a statin for prevention based on 10-year risk. Sniderman calls that a big step forward in 1980–1990 that has since become a trap. Age dominates the calculators, so almost everyone under about 55–60 scores 'low', even while atherosclerosis is building through their 30s, 40s and 50s. By the time the 10-year number looks alarming, decades of disease are already in place.

• A risk percentage is a statement about a group, not a person

A 4.1% 10-year risk means about 4 of every 100 similar people will have an event. It doesn't say whether you will. Different algorithms can give the same person 10%, 15% or 20%. Treating at a 7.5% threshold also means 92.5% of those treated would have had no event in that decade, which Sniderman says is a weak motivator.

• Particles drive atherosclerosis more than the cholesterol they carry

Each atherogenic lipoprotein (LDL, VLDL, remnants, Lp(a)) carries one apoB molecule, so apoB counts the particles that can enter the artery wall. Total and LDL cholesterol measure cargo. Sniderman has argued since his first clinical paper around 1980 that particle number beats cholesterol concentration, and says the evidence for that is now very strong.

• Standard lipid panels estimate rather than measure

The LDL number on a routine panel is almost always calculated, not measured directly. Sniderman notes that the apoB assay was standardized in 1994, while HDL cholesterol measurement is not standardized. He sees no technical reason apoB can't be routine.

• Triglycerides flag risk, but the cholesterol in VLDL particles is what does harm

Sniderman says very high triglycerides raise the risk of pancreatitis, but he hasn't seen solid evidence that triglyceride itself causes atherosclerosis. What causes it is the cholesterol inside VLDL particles and how many of them get into the artery wall.

• Remnant type III dyslipoproteinemia is missed without apoB

This highly atherogenic disorder shows high triglycerides and high cholesterol but a low or normal apoB, because the particles that pile up are cholesterol-rich VLDL remnants. Without an apoB measurement, and with old diagnostic methods abandoned, most cases in the US go unrecognized. Statins and/or fibrates usually work very well.

• Mendelian randomization has been a 'slam dunk' for apoB

Long observational studies are confounded because people change over 20–30 years. Mendelian randomization uses genetic variants assigned at conception as a natural randomized trial, often in hundreds of thousands of people. Sniderman says these studies point to apoB as the causal driver.

• Lipid status at 35 is surprisingly stable

Sniderman says groups can be classified fairly accurately at 35. Someone high at that age has about a 95% chance of staying high, and the ~5% who move don't become low. That's why he favors acting early in people who are clearly high, while noting that menopause and other changes still need follow-up.

• Early treatment should be targeted, not universal

A 2019 Circulation paper by his group modeled delaying treatment from 35 to 45 to 55. With a low non-HDL cholesterol, starting at 35 gains little. The big gains go to people with high non-HDL or apoB, roughly 20% of the population by his estimate. So pills for everyone at 35 is not the conclusion.

• Consensus culture is science's crucial weakness

Sniderman compares guideline committees to groupthink behind bad decisions such as Afghanistan and the 2008 financial crisis: 'when everybody in the room has the same opinion going in,' problems get solved badly. He says medicine has become less critical, and that 'dumbing down' recommendations for doctors who see 40 patients a day is a compromise on truth. He is pessimistic that apoB will replace LDL in US training within 10 years, despite Europe's pro-apoB 2019 guidelines.

• Think in 30-year and lifetime risk, like retirement savings

A retirement calculator that only looked 10 years ahead would be useless to a 30-year-old. Peter and Sniderman argue the same applies to arteries. A 50-year-old should care about being 80, not 60. A cut from 4% to 2% over a decade looks trivial, but it compounds by 70.

EXAMPLES

• Ancel Keys and the 200 mg/dL split

In the late 1950s, early total-cholesterol assays showed a clear difference in cardiovascular risk between people above and below roughly 200 mg/dL. That launched the cholesterol-centered model. Fredrickson, Levy and Lees later worked on lipoprotein classification in the 1970s.

• The FOURIER debate

Peter recounts an email argument about FOURIER (the PCSK9 inhibitor Repatha). People already on high-dose statins with an average LDL-C around 70 mg/dL had fewer revascularizations over roughly five years, but no change in mortality. Sniderman's view is that it's almost a miracle the trial showed anything, since patients started so low and were followed so briefly.

• A familial hypercholesterolemia result he thinks is wrong

A study reported that people with a genetic FH mutation had three to five times the risk of people with the same lipid levels but no mutation. Sniderman read it repeatedly and concluded the authors had made a methodological error, while admitting he may be wrong. His point is that FH is defined by the phenotype.

• Risk factors explain little of individual risk

Citing Michael Pencina's work (the name is uncertain in the recording), Sniderman says standard variables explain only about 20% of the variance in risk. He argues that grouping people by causal, precisely measured markers like apoB or non-HDL selects patients more accurately than noisy multi-factor calculators.

• The $10 test argument

His group's cost analysis put an apoB test at about $10, a negligible share of care costs. US health spending was about $7,000 per person per year a decade earlier and is now near $10,000. Cost, he says, is not a real barrier.

OTHER RELEVANT

• Ask for apoB and Lp(a), not just a standard panel

Sniderman measures a lipid panel, apoB and Lp(a) in every patient (Lp(a) once). High Lp(a) with normal apoB may add little, but both high is a 'double whammy' that changes how he frames risk.

• Use apoB to show patients progress

Seeing apoB fall from 120 to 60 tells both doctor and patient that the medication is being taken and working. That makes it a motivational tool, not just a diagnostic one.

• Interpret calcium scores by age

A CAC of zero doesn't rule out risk in someone with very high apoB. But any calcium under age 50 is significant, even if the 10-year model calls it about 4%. Peter's view is that prevention aims to stop lesions forming, which is '100% success', rather than treating them late.

• Embrace uncertainty instead of false precision

Sniderman wants doctors to say what they believe and why, admit that confidence intervals can be wide, and welcome open challenges, such as being confronted with a specific line of your own paper. Science that says the same thing as 30 years ago may not have learned anything.

183 - Building & Changing Habits with James Clear of "Atomic Habits"

Guest: James Clear
Date: 2021-11-08 · Duration: 2:34:23
URL: https://www.youtube.com/watch?v=Tn1w7Kw8x5E

KEYPOINTS

• Much of what we do is automatic.
James Clear, author of Atomic Habits, cites research suggesting 40–50% of daily behaviors are habitual, though he notes studies typically count specific behaviors. Habits evolved to save mental effort, but modern environments, built over the last 100–500 years, are mismatched with the brain, which favors immediate rewards.

• Immediate feedback drives repetition.
Bad habits feel good now and cost later; good habits cost now and pay later. 'Ten p.m. James ruins things for tomorrow James' by staying up late. The challenge is engineering immediate satisfaction into behaviors whose payoff is delayed.

• Genes shape where effort pays off most.
Attia contrasts learning to ride a bike at 20 (easy, because balance is intuitive) with learning to swim at 20 (hard to master); he says even with parents who threw him in the water at two, he wasn't going to swim like someone gifted. Clear agrees predispositions matter, so choose arenas that fit your nature, where hard work compounds.

• Systems beat goals.
Winners and losers share the same goals; if 100 candidates apply for a job, all want it, so goals don't separate performance. Goals are useful for direction, but the system, the daily process, determines results. Losing weight is a destination; keeping it off requires a system, which is why maintenance is so hard.

• Identity change is the deepest level.
Clear describes three layers: outcomes, processes and identity. The most durable change comes from becoming the type of person who does the behavior, and each repetition is a 'vote' for that identity. Attia says exercise comes naturally to him because it's hardwired into his identity.

• Big life changes make habits easier to change.
Moving, a new job or a new family member disrupt cues and open a window. Clear's sleep habit finally stuck when he got a dog that wakes at 7 a.m. regardless; an outlet timer that kills the internet at 10 p.m. also helped.

• Social environment is powerful.
Habits that last 10–30 years often carry a strong social component, like mowing the lawn because neighbors do. We adopt the norms of groups we want to belong to, so joining a group where your desired behavior is normal is one of the most effective strategies.

• The Four Laws of Behavior Change.
Clear distills about 150 years of models into cue, craving, response and reward, and four laws: make it obvious, make it attractive, make it easy, make it satisfying. To break a habit, invert them: make it invisible, unattractive, difficult and unsatisfying.

• Variable rewards are the most addictive.
Slot machines hit a sweet spot around a 50% reward rate delivered unpredictably; animals on variable schedules pressed a button thousands of times (Clear recalls around 6,000), versus about 800 an hour otherwise.

• Make it easy with the two-minute rule.
Scale any habit down to two minutes: 'read 30 books a year' becomes 'read one page'; 'do yoga four days a week' becomes 'take out my yoga mat'. The point is to master showing up before optimizing.

• Never miss twice.
Missing once is an accident; missing twice starts a new habit. After a pizza binge on day 10 of a diet, make the next meal healthy. Self-forgiveness and quick recovery matter more than perfection.

• Coaching others requires a light touch.
Asked how to help others change, Clear says you can't install habits in someone else; you can shape their environment, model the behavior and make the group norm attractive. Attia contrasts the coach of a highly motivated athlete with a 35-year-old dad of two who just wants to get in better shape; the relationship and the level of pressure should differ. Clear recalls being a very average athlete on a team alongside future Olympian Holly Mangold, and how much the team culture shaped everyone's behavior.

EXAMPLES

• Vietnam veterans and heroin
Large numbers of soldiers became addicted in Vietnam, yet about 90% or more recovered on returning home, largely because they left the environment where the cues lived.

• Mitch's five-minute gym rule
A man who lost around 100 lb, featured in Atomic Habits, wasn't allowed to stay at the gym longer than five minutes for the first six weeks; he was building the habit of showing up.

• A friend who lost 110 lb
She kept it off for over a decade by repeatedly asking, 'What would a healthy person do?', an identity-based question.

• Twelve cigarette cues
A smoker who lights up on the commute and at a 10:30 break with a co-worker must address each cue separately; coffee might replace the commute cigarette but not the social break.

• Frozen cookies
Attia says he eats either zero cookies or 30; freezing them adds 15 minutes of friction that's just enough to stop him.

- **A 720-page first draft**
  Clear's first Atomic Habits draft ran 720 pages before he cut it to about 250.

OTHER RELEVANT

- **Track behaviors you don't yet feel intuitively.**
  Measurement makes a habit obvious and satisfying at first, but Clear thinks most people eventually internalize it; once you've walked 10,000 steps a day long enough, you can sense whether you've done it without a device.
- **Design your default environment.**
  Remove cues for bad habits and make good options the default, as with automatic 401(k) enrollment.
- **Pick one habit at a time.**
  Of 15 possible changes, choose one, start small and focus. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Use commitment devices and social plans.**
  Schedule a 6:15 a.m. run with a friend or put money on the line to beat the warm-bed problem.
- **Recognize compliance is hard.**
  Even taking medication runs about 60–70% adherence; design for that reality. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

182 - Psychedelics & Recreational Drugs

Guest: David Nutt
Date: 2021-11-01 · Duration: 1:40:34
URL: https://www.youtube.com/watch?v=qhGDV4BvQ2M

KEYPOINTS

• Drug harms can be scored on 16 dimensions.
Nutt, professor of neuropsychopharmacology at Imperial College London, began working on principles for assessing drug harms in the 1990s and advised the UK government from 1994. His framework rates nine harms to the user and seven to society. Across Europe, Britain and Australia, the most harmful drug overall is consistently alcohol — chiefly because of harms to others and because about 80% of American and British adults drink.

• Alcohol is uniquely dangerous because it combines acute and chronic toxicity.
Tobacco kills more people, but usually in their 50s and 60s and with purely chronic toxicity; alcohol kills people in their 20s through accidents and acute poisoning too. Nutt says there's no healthy dose of alcohol, though some doses may not rise to meaningful toxicity; Attia notes how easily the line is crossed.

• US politics shaped global drug law.
Nutt says every British drug law until 2016 was made at the behest of the Americans, starting with 1934-era policy, and the UN largely follows US direction. He traces cannabis hostility to Harry Anslinger's efforts to keep his bureau relevant after alcohol prohibition ended — nearly 90 years of disinformation.

• The cannabis research gap leaves basic questions unanswered.
Attia is frustrated he can't tell parents whether a 16-year-old smoking pot will harm brain development. Nutt argues that with tens of millions of users, utility and harms could have been mapped within a few years if research had been permitted.

• Fentanyl is an economic inevitability of supply crackdowns.
When heroin supply was squeezed, Mexican cartels turned to fentanyl, roughly 50 times more potent than heroin and about half the cost to make. Nutt favours studying treatments like ibogaine for opioid addiction, though its cardiac risks make research difficult; Attia notes untreated opioid addiction itself might carry something like 300-per-1,000 mortality.

• Psychedelics may work by disrupting the default mode network.
Nutt's team's thinking is that the psychedelic state profoundly disrupts the brain's default mode network, potentially breaking over-learned habit circuits in addiction and depression and letting people escape rigid patterns.

• LSD research was extensive and largely positive before it was banned.
Synthesized in the late 1930s, LSD was the subject of over 130 NIH-funded grants, about 40,000 patients and 1,000 papers; it appeared safe, didn't cause psychosis, and if anything reduced suicide. Therapeutic 'big trip' doses were around 100–125 micrograms; 25 micrograms was used to lower resistance in psychotherapy, and anything over about 10 micrograms is perceptible.

• The ban may have cost far more lives than it saved.
A modern meta-analysis by two Norwegian researchers of six old US trials of one or two LSD doses for alcoholism found an effect size of about one — twice that of any later treatment. Nutt estimates over 100 million people died prematurely from alcohol in the 50 years since; even 10% helped would be 10 million lives, versus perhaps 2,500 saved by the ban. This is his rough calculation.

• Psychedelics show rapid tolerance.
Take LSD daily and the second dose is far weaker; at some point people stop responding — unlike drugs such as acetaminophen, whose effect stays roughly constant.

• Psilocybin vs. escitalopram for depression.
In Nutt's New England Journal of Medicine trial, all patients received the same psychotherapy; one arm got 25 mg psilocybin (two doses about three weeks apart), the other escitalopram (Lexapro) with a 1 mg psilocybin placebo. It was reported as a negative study on its primary measure; Nutt says it was never powered for non-inferiority, which would need about 150 patients per arm. 25 mg of psilocybin roughly equals 4–5 g of dried mushrooms.

• Ketamine was the first new antidepressant breakthrough in decades.
Couldn't be patented, so esketamine was developed. Depression doses are modest, but recreational users escalate to grams a day.

EXAMPLES

• Bill Wilson and psychedelics
The founder of Alcoholics Anonymous escaped his alcoholism through a psychedelic experience, later tried LSD when legal, and believed it could help many alcoholics.

• Magic mushrooms in Britain
Mushrooms were legal in the UK until 2005, with about a million young people a year using them; that safety record helped persuade regulators to allow Nutt's psilocybin research. About 200 species of mushroom contain psilocybin.

• Len Bias
The University of Maryland star, drafted by the Boston Celtics, died after cocaine use; his death accelerated the US war on drugs. Nutt notes it's unclear how much he used or whether it was laced.

• Wartime methamphetamine
German and Japanese troops used methamphetamine to stay awake and became sleep-deprived, paranoid and hallucinating. Crystal meth is longer-acting and probably more neurotoxic than amphetamine sulfate, pushing the dopamine system to depletion.

• Drunken drownings

Nutt notes that in Britain 20–30 people a year die jumping, usually drunk, from piers and breakwaters — illustrating alcohol's acute harms.

OTHER RELEVANT

- **Judge drugs by evidence, not legal status.**
  Legal alcohol scores as more harmful overall than many scheduled drugs. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Avoid cocaine, especially with heart risk.**
  Nutt doesn't think it's worth the risk; cardiac events can be sudden. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't self-treat with psychedelics.**
  Trial results come with careful screening, preparation and psychotherapy; dose and setting matter.
- **Ask about newer depression options.**
  If SSRIs fail or side effects are intolerable, discuss evidence-based alternatives with a psychiatrist.
- **Push for better research, not just looser laws.**
  Nutt and Attia both argue that the biggest loss from prohibition is knowledge: without trials, clinicians cannot answer basic questions about cannabis, MDMA or psychedelics. Supporting well-designed studies — including dose-finding trials and micro-dosing work — is how claims of benefit and harm get settled.

181 - Viewing cancer through an evolutionary lens: a radically different approach to treatment

Guest: Bob Gatenby
Date: 2021-10-25 · Duration: 2:18:34
URL: https://www.youtube.com/watch?v=uR9i2aPD29s

KEYPOINTS

• Cancer is an evolutionary problem, and treatment selects for resistance.
Gatenby, a radiologist who trained in physics at Princeton, argues that oncology lacks the first principles that let physics make sense of messy data—as Newton did for planetary motion. His organizing principle is Darwinian: a tumor is a population of competing cells, and every therapy is a selective force that will eventually favor resistant variants unless it is managed strategically.

• Models don't need to predict ten years out to be useful.
Attia compared cancer modeling to economic models that can't forecast GDP a decade ahead, and Gatenby agreed that cancer sits toward the chaotic end of the spectrum (Attia rated it an eight or nine out of ten). The goal is not long-range prediction but answering 'what should I do next?' with models that are recalibrated to each patient's data as treatment proceeds.

• The pesticide lesson: maximum dose clears the field for resistant cells.
The diamondback moth has been hit with every pesticide developed and by the 1980s some populations resisted all of them. In Gatenby's illustration, a heavy spray kills the sensitive 80% and leaves the resistant 20% a whole field without competitors. Resistance mechanisms carry a fitness cost, so in a lower-pressure environment sensitive moths can out-compete resistant ones—potentially shrinking the resistant share over time.

• Adaptive therapy uses sensitive cells to suppress resistant ones.
In metastatic prostate cancer, his team gave abiraterone until PSA fell to 50% of its baseline, then stopped, letting drug-sensitive cells regrow and compete with resistant ones before restarting. The idea is to keep a controllable tumor burden rather than eradicate sensitive cells and release resistant ones from competition.

• The pilot trial roughly doubled time to progression.
Compared with patients on the standard maximum tolerated dose until progression, median time to progression went from about 14 months (consistent with the literature) to about 30 months with adaptive therapy, a 16-month difference—with less total drug. Some patients were still cycling about five years later. It was a small, non-randomized pilot, and models had predicted control would be lost somewhere between 2 and 20 cycles depending on the unknown starting fraction of resistant cells.

• The key surprise was a sevenfold fitness advantage.
The trial data implied that sensitive cells were about seven times fitter than resistant cells off-drug, versus the two- to threefold the team had assumed. Instead of plateauing, resistant populations declined, and modeling suggested three successive well-timed cycles could drive resistant cells toward extinction. They think competition for space and substrate, scarce in poorly perfused tumors, drives the differential.

• Small populations are vulnerable—hit them with a sequence, not a single strike.
Small populations can go extinct from minor shifts in birth and death rates (stochasticity), and tumors may show an Allee effect, where cells benefit from numbers, for example to build blood vessels. Gatenby favors an 'extinction' strategy borrowed from ecology: after a first strike shrinks the tumor, follow-up therapies attack the remnant before resistance emerges, as in pediatric leukemia regimens.

• Probability math explains why one drug rarely cures large tumors.
A 100-gram tumor holds on the order of 100 billion cells, so some pre-existing resistant cells are near-certain. Knocking a population down to millions and then adding a second and third drug changes the odds dramatically. Attia's analogy: the US could survive a 90% population loss in theory, but a nation of 33 million under ongoing attack would be a very different, vulnerable entity.

• Immunotherapy may work best on minimal disease.
Response to anti-PD-1 drugs is best in people with relevant mutations; first-generation interleukin-2 had perhaps 10–20% response in melanoma, but always in full-blown metastatic disease. Gatenby suggests immune approaches might perform very differently in patients with no visible disease, when the cancer population is small.

• Most cells that spread die; metastasis is about the soil.
When cancer cells are injected into mice, nearly all die at distant sites. Around 30–40% of women undergoing mastectomy for apparently localized breast cancer may have cancer cells in their bone marrow, yet not all relapse. He and Attia discussed few cancers that kill without spreading, such as glioblastoma.

EXAMPLES

• Physics under Feynman's shadow
Gatenby studied physics at Princeton in the late 1960s and early 1970s before medicine, and found medical school's rote memorization—like Catholic catechism—at odds with his search for first principles.

• Hospital antibiotics
He compared standard dosing to a fixed 10-day antibiotic course continued after the patient recovers; overuse breeds superbugs, much as maximum-dose chemotherapy breeds resistant tumors.

• The p53 vaccine
A p53 vaccine in heavily treated lung cancer patients failed on its own, yet subsequent chemotherapy produced 60–70% response rates, versus an expected under 5%—perhaps because cells downregulated p53, an evolutionary trade-off that made them vulnerable.

• Darwin's finches

With billions of genomic data points but no observation of the beak matching the seed, Gatenby doubts Darwin could have derived evolution; measuring tumors' environments matters as much as sequencing them.

- **The trial's oncologist**

He credited oncologist Jingsong Zhang for running the trial against the grain; a European philanthropic fund wants to support a phase 3 trial in prostate cancer.

OTHER RELEVANT

- **Ask about treatment strategy, not just drugs.**

For metastatic cancer, discussing intermittent or adaptive dosing and the sequence of therapies with an oncologist may matter alongside drug choice.

- **Monitoring frequency affects outcomes.**

Gatenby's team found infrequent scans (every three months) delayed decisions; patient-specific modeling needs frequent biomarker data like PSA. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Prioritize early detection.**

If small cancer populations are the most vulnerable, finding cancer early—Attia's argument for aggressive screening—gives therapies the best odds.

- **Being told you've 'failed therapy' isn't the end.**

Gatenby dislikes the phrase; patients interested in adaptive approaches need an oncologist willing to try them, ideally in trials, since he isn't a treating oncologist himself.

179 - Blood flow restriction—benefits, uses, & the relationship between muscle size and strength

Guest: Jeremy Loenneke
Date: 2021-10-11 · Duration: 2:07:14
URL: https://www.youtube.com/watch?v=3m15T_4jVzE

KEYPOINTS

• BFR lets light loads build muscle.
Jeremy Loenneke, an exercise scientist who began studying blood flow restriction around 2007–2008, explains that partially restricting blood flow with cuffs during low-load exercise (typically 20–40% of one-rep max, and he prefers 20–30%) produces hypertrophy comparable to heavy lifting. His lab has tested many combinations of loads and pressures to find what's actually needed.

• It began with KAATSU and a kneeling legend.
Yoshiaki Sato, the Japanese inventor of the KAATSU system, reportedly noticed numbness while kneeling at a Buddhist ceremony that reminded him of heavy squats, and connected restricted blood flow to training. The first published study of functional change, by Shinohara in 1998 comparing legs trained with and without restriction, came surprisingly late; much literature followed in the early 2000s.

• Pressure should be set relative to each person.
Loenneke's lab finds the arterial occlusion pressure (the pressure where flow stops), then applies about 40–80% of it, standardizing the stimulus. Muscle adaptations look similar at 40% and 80%; 80% just brings failure sooner with much more discomfort. A 40% pressure doesn't mean a 40% drop in blood flow, and perceived tightness is unreliable: people asked to rate cuffs at 7 out of 10 land anywhere from 20% to 60% of occlusion pressure.

• The standard protocol is 30-15-15-15.
Four sets: 30 reps, then three sets of 15, with 30 seconds' rest between, cuffs on throughout. Rep counts act as a rough check on pressure: if you can't get near 30 on the first set, the cuff may be too tight. Attia describes how brutally uncomfortable a leg-press version was, and how he sometimes overtightens and must loosen after the first set.

• Safety appears comparable to traditional training.
Because restriction lasts minutes, not hours, Loenneke says the safety profile resembles high-load exercise. The key question isn't whether risk exists but whether BFR adds risk; at the group level in mostly healthy people, it doesn't appear to increase blood clots or muscle damage. Fibers look structurally intact and CK levels differ little, though soreness is real. Beginners should try one exercise first.

• Strength and size are linked, but not as tightly as assumed.
Loenneke challenges the assumption that strength gains follow from hypertrophy. Studies often assume hypertrophy explains strength instead of testing it. In BFR studies, low-load training grows muscle about as much as heavy training, yet heavy training increases one-rep-max strength more, which shows that strength is specific to practicing heavy loads. Attia guesses the correlation is real but far from 1.0, perhaps an R^2 around 0.5.

• Fiber recruitment explains how light loads work.
Lifting 40% of max for 40 reps progressively fatigues type 1 fibers, then 2A, 2AB and finally 2X, so by failure nearly all fibers have been recruited, similar to 80% for 8–10 reps, just slower. Restriction accelerates this by limiting oxygen and building metabolites. Loads from about 30% to 80% of max produce similar hypertrophy when sets go to or near failure.

• Heavy-load strength depends on movement simplicity.
For a simple movement, training at a true 1RM can beat 8–12 reps for strength gains. Two reps is about 95% of 1RM, three about 90% and five about 85%. Compound lifts like squat and bench press can be done with BFR, but Loenneke prefers isolation movements for safety.

• BFR is most useful when heavy loading isn't possible.
Applications include injured athletes, people recovering from surgery, older adults with joint problems and anyone wanting volume without heavy joint stress. With low-intensity aerobic exercise, cuffs can stay on for 30–40 minutes because metabolite buildup is low, though adaptations are modest. Passive BFR (cuffs without exercise) has small evidence for slowing atrophy in immobilized people.

• Muscle preservation is critical with age.
Attia emphasizes that muscle loss after 70–80 is a major driver of frailty, and BFR offers a way to maintain muscle when heavy lifting is risky. Loenneke's dream research question is why people get stronger, beyond size.

EXAMPLES

• The 25-yard butterfly
Around 2010, swimming a 50-yard butterfly with restriction cuffs on his arms, Attia felt by 25 yards like he was finishing an all-out 200, the hardest thing he'd ever done.

• BFR deadlifts at 135 lb
Attia did 30 reps of 135-lb deadlifts with restriction, a load that couldn't hurt him but felt extremely hard. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• One arm occluded, one not
A classic design trains both arms at 30% of 1RM with 30-15-15-15, cuffing only one; the uncuffed arm also reaches near-failure for some people, which researchers must account for.

• 80 lb vs. 40 lb curls
For a person with a 100-lb curl max, 80 lb for 8–10 reps and 40 lb for about 40 reps both reach failure; the light set just takes

longer to exhaust the fiber pool.

OTHER RELEVANT

- **Start with relative pressure.**
  If possible, measure arterial occlusion pressure and use about 40–80%; otherwise start conservatively and use rep counts as a guide. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Use light loads.**
  About 20–30% of 1RM with 30-15-15-15 and 30-second rests; supersetting two muscles back and forth also works well, and one cuffed exercise is plenty when you're new.
- **Lift heavy to get strong.**
  If maximal strength matters, include heavy, specific practice of the lift you care about; BFR builds size more than it builds one-rep-max strength, so treat it as a complement rather than a replacement.
- **Consider BFR during injury or aging.**
  It allows muscle-building stimulus with less joint load; check with a clinician if you have clotting or vascular risks. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

Lance Armstrong: The rise, fall, and growth of a cycling legend | The Peter Attia Drive, Ep. 178

Guest: Lance Armstrong
Date: 2021-10-04 · Duration: 2:35:04
URL: https://www.youtube.com/watch?v=NaGLfau1tRs

KEYPOINTS

• An endurance prodigy from Plano.
Lance Armstrong started as a swimmer and runner in Plano, Texas, where elite swim training meant around 10 miles a day, then became a pro triathlete as a teenager; he says he was effectively a pro athlete at 15, around when his mother threw out his stepfather Terry Armstrong. He went to the junior world championships in Moscow in 1989 and switched to full-time cycling around 1990–91.

• Cycling was inspired by Americans like LeMond.
Seeing US Olympic medals in 1984 and Greg LeMond's dramatic 1989 Tour win made cycling exciting for Armstrong. He joined Motorola in 1992 and became world road champion in 1993. At 175 lb he was big for a climber; he raced the Tours at 160–165 lb, versus about 125 lb for Marco Pantani.

• EPO changed the sport almost overnight.
Armstrong says between 1993 and 1994 the peloton suddenly changed; in 1994 three Gewiss riders rode away together and the press exploded. He started EPO around 1995, then joined Dr. Michele Ferrari in 1996. Bjarne Riis, who won the 1996 Tour, was nicknamed 'Mr. 60%' for a reported hematocrit around 60–66. Before the 50% hematocrit limit, there was no real ceiling.

• EPO's effect: roughly 10%.
Armstrong's go-to test, a 30-minute climb of the Col de la Madone (grade around 7–8%), averaged about 500 watts at 165 lb, roughly 7 W/kg, in 1999 and 2001. He estimates he'd have done about 450 W clean, around 10% less, which is still elite; he compares Bradley Wiggins at about 440–450 W.

• Racing hematocrit was kept below the limit, with transfusions.
Under the 50% rule, teams aimed for about 46–47 to leave a margin for dehydration or illness. Armstrong says the team used one transfused bag during the 2000 Tour, later two, and in 2003 he started the Tour with a hematocrit around 38–42.

• Testicular cancer nearly killed him.
After months of denial and torturous symptoms, he was diagnosed in 1996. His hCG was around 100,000 ('very pregnant'); above two is a problem and 500 is serious. He had an orchiectomy, then discovered brain metastases only when he got to Indiana for treatment after starting chemotherapy elsewhere.

• Livestrong was born from survivorship.
Armstrong created his foundation to help cancer survivors, later spending around $600,000 on lobbying and strategy for a cancer initiative, which he views as funding advocacy rather than self-promotion.

• Return, dominance and rivalry.
After coming back in 1998 and nearly quitting, he won the 1999 Tour. The 2000 Tour brought intense rivalry with Pantani and Jan Ullrich, whom he saw as a real enemy; 2001, famous for 'the look' at Ullrich, was physically his best. He won his seventh Tour at 34 in 2005, retired, and returned in 2009 to finish on the podium.

• A near-quit in 1998 became a comeback.
After cancer, Armstrong raced Paris–Nice in 1998, quit, came home and nearly retired, then got back into shape for only about nine months before going all in for 1999. The 1998 team was so disorganized he calls it a mess, and that year's Festina doping scandal shook the sport. After his strong ride in the Vuelta, where he expected maybe a top-10 Tour finish, his director was '100% sure' he could win the Tour, a belief that changed Armstrong's ambitions.

• Coming clean.
After Tyler Hamilton's book (around 2011–12) and mounting investigations, Armstrong decided to tell the truth in January 2013. He acknowledges the people he hurt, emphasizes learning from his downfall and helping others after their own falls from grace, and says that at 50, with perhaps 40–50 years left, there's still 'a lot left to be told'.

• Advice to his younger self.
He suggests the 15-, 25-, 35- and even 45-year-old versions of himself would not have handled the downfall; growth required that experience. He is grateful that people can reinvent themselves today.

• Staying fit at 50.
Armstrong weighs about 180 lb, about 15 lb over his Tour weight, which is modest for a retired cyclist. He can still swim 100-yard repeats on about 1:10 in Austin, compared with the 1:05 touch-and-go he once managed, and says he's fitter than most 50-year-olds.

EXAMPLES

• The yes-or-no warm-up
Attia opens with rapid yes-or-no questions (Dura-Ace vs. Campagnolo Super Record, aerodynamic water bottles) before turning to doping.

• Riis' hematocrit
Riis reportedly raced the 1996 Tour with a hematocrit around 60–66, illustrating how extreme EPO use was before limits.

• Hematocrit at rest vs. racing
Attia asks whether the advantage came from walking around at 42–44 and racing at 46–47; Armstrong agrees the key was preventing the drop during three weeks of racing.

• A tractor path at 40 mph
Armstrong recalls riding off course through a farmer's tractor path at high speed in a Tour, a few feet from disaster on either

side.

- **Lunch-time hCG**
  When doctors saw his tumor markers, Armstrong had to go back to his urologist's office around 6–7 p.m.; the reading of about 100,000 signaled widespread disease.

OTHER RELEVANT

- **Doping distorts sport but doesn't create talent.**
  Armstrong's numbers suggest EPO adds roughly 10%; top riders were already elite, but the margin decides races. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't ignore warning signs.**
  Armstrong's denial delayed his cancer diagnosis; testicular changes and unusual symptoms warrant prompt evaluation. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Own your mistakes.**
  Telling the truth and helping others through their own falls is part of rebuilding. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Keep training through life.**
  Armstrong's fitness at 50 shows the long-term payoff of staying consistently active. He still swims, rides and runs regularly.

177 - The development of cancer immunotherapy and its promise for treating advanced cancers

Guest: Steven Rosenberg
Date: 2021-09-27 · Duration: 2:11:34
URL: https://www.youtube.com/watch?v=pVMl0LgdnOU

KEYPOINTS

• Metastatic solid cancers are the real problem

Rosenberg says about 600,000 Americans died of cancer in the past year, and roughly 550,000 of those deaths came from solid epithelial cancers (colon, breast, lung, pancreas, prostate and similar). Blood cancers are about 10%. Surgery and radiation cure many localized tumors. Once epithelial cancer has spread, cures are rare, which is why he has spent his career on the immune system.

• A spontaneous regression set the course of his career

As a young resident, Rosenberg found a patient whose gastric cancer had spread to his liver and lymph nodes 12 years earlier and been left in place after a palliative operation. The cancer had disappeared without any treatment. Rosenberg concluded that the body had some way to reject cancer, and that the immune system was the likeliest candidate.

• Chemotherapy has hit diminishing returns for common metastatic cancers

Chemotherapy came out of mustard-agent research during wartime around 1942. It cures some leukemias, lymphomas and testicular cancer. For most metastatic epithelial cancers, Rosenberg says progress has been incremental. Median survival in metastatic colorectal cancer rose from about 8–10 months to about 2.5 years. Some newer drugs add weeks of life at high cost and toxicity.

• IL-2 produced the first immune-driven cures

T-cell growth factor (interleukin-2), discovered in 1976 by Morgan, Ruscetti and Gallo, let researchers keep lymphocytes alive outside the body. Before that, they died within a day or two. Rosenberg's team treated dozens of patients with IL-2 or IL-2-grown cells and saw no responses. After they changed the schedule and raised the doses, a patient with widespread melanoma treated in 1984 had a complete, lasting regression.

• Only certain cancers responded, and mutations explain why

High-dose IL-2 caused regressions in about 15–20% of patients with metastatic melanoma and kidney cancer, and some of those were durable cures. Melanoma carries an unusually high mutational burden. Rosenberg's view is that mutated proteins (neoantigens) are what T cells actually recognize.

• Mutations are the antigens, and they're almost all unique

In a series of 195 patients with common epithelial cancers, his lab found T cells recognizing mutations in about 80% of them. There were 393 distinct antigens, and almost none were shared between patients. The exception was a KRAS mutation on a rare HLA type. Only about 1.3–2% of a tumor's mutations are immunogenic. He calls this good news: after decades, 'we finally understand what a cancer antigen is.'

• Tumor-infiltrating lymphocytes improved results, then lymphodepletion jumped them

Growing TIL cells from tumors in IL-2 and infusing them raised melanoma response rates from about 15% with IL-2 alone to 30–35%, though responses were often short. Wiping out the patient's inhibitory regulatory T cells before infusion pushed response rates to about 55%, with roughly 25% durable complete remissions.

• CAR T cells were engineered from a gene-insertion idea

His team inserted receptor genes so T cells could recognize CD19 on B cells. A 2009 patient with chemotherapy-refractory lymphoma, who had a kilogram-sized chest tumor after four failed regimens, was disease-free 12 years later. Losing normal B cells turned out to be survivable.

• Checkpoint inhibitors release the brakes, but most solid cancers need more

Anti-CTLA-4 and anti-PD-1 drugs (James Allison later won a Nobel Prize for his checkpoint work) unleash existing immune responses. Rosenberg says most patients with the epithelial cancers that cause 90% of deaths respond poorly, because taking off the brakes does nothing if there aren't enough reactive T cells.

• The frontier is personalized T cells against each tumor's mutations

His lab published the first mutation-targeted T-cell treatment in 2014, in a woman with metastatic bile-duct cancer. All of his work now goes into turning these unique reactivities into treatments. He also isolates libraries of T-cell receptors against recurring mutations such as p53 and KRAS, which he calls 'almost an engineering problem.'

EXAMPLES

• Kite and the path to approval

Urologist Arie Belldegrun, a former fellow, visited in 2011 and founded Kite. A 2012 cooperative research agreement (CRADA) funded the work. After more than 50 patients, over half had durable regressions. A multi-institutional study reproduced about a 70% response rate with roughly 50% durable complete regressions, and Kite was sold to Gilead in 2017 for roughly $11.9 billion.

• Operating on President Reagan

In 1985 Rosenberg was called to Bethesda Naval Hospital, partly because he already had a security clearance from an emergency medical team role. At the press conference he said plainly that the president had colorectal cancer, which displeased Nancy Reagan. The episode later cost him consideration for the NCI directorship.

• Persistence through dozens of failures

Peter compares the 1984 IL-2 breakthrough to Thomas Starzl's early liver transplants, where many patients died before success came. By Peter's recollection the 1984 responder was about the 67th patient treated, after a long run of patients who didn't respond. He reworks Pasteur: 'Chance favors the prepared mind only if the mind is at work.'

• Why he stayed at the NCI

He took over as NCI chief of surgery on July 1, 1974, the day after finishing residency, and has held the post for 47 years. He turned down offers including Johns Hopkins, where it came down to John Cameron and him, because the NIH let him research rather than 'practice today's medicine.'

OTHER RELEVANT

• Ask about immunotherapy and trials for metastatic disease

For melanoma, kidney cancer and B-cell lymphomas, immune-based treatments can cure some patients. For most epithelial cancers, checkpoint drugs help a minority, so clinical trials of cell therapies are worth exploring. Rosenberg's results come from highly selected NCI patients.

• Expect cell therapies to become practical

Critics said CAR T could never be delivered at scale. Rosenberg's view is that if something cures people, 'the genius of modern industry will figure out ways to make it available.'

• Stay present with patients who aren't saved

Peter recalls that eight or nine of every ten 'Hail Mary' patients at the NCI died. Rosenberg taught him not to retreat from them out of a sense of failure. Rosenberg still remembers individual patients, such as a 25-year-old newlywed, after more than 20 years.

175 - The biology of aging, rapamycin, and other interventions that target the aging process

Guest: Matt Kaeberlein
Date: 2021-09-13 · Duration: 2:49:45
URL: https://www.youtube.com/watch?v=_vsNw-OCciU

KEYPOINTS

• Targeting aging itself could add far more healthy years than curing diseases one by one.
Kaeberlein, an aging biologist at the University of Washington, notes that roughly a dozen or 15 interventions now extend mouse lifespan by 15–30%. Extrapolated to humans, that is about 20 years of life expectancy, and because all functional declines slow together, those years are spent in relatively good health. He calls the disease-by-disease approach '20th-century medicine' and contrasts it with targeting the biology of aging.

• Aging is the dominant risk factor, and it can't be offset by perfect health.
A 70-year-old with every risk marker in their favor still has a worse 10-year mortality outlook than a 20-year-old 'train wreck'. Kaeberlein and Attia agree that any 50-year-old is functionally impaired compared with themselves at 25, which is why they argue regulators shouldn't treat typical 65–70-year-olds as 'healthy' when weighing trial risk.

• Centenarians get the same diseases—just decades later.
Citing the centenarian studies of Nir Barzilai and Tom Perls, Attia notes that centenarians don't live longer with chronic disease; they get a 20–30-year phase shift in onset. They are more likely to carry protective variants such as APOE2 rather than APOE4. Attia's clinical takeaway: the earlier prevention starts, the more you can mimic that delay.

• Rapamycin is the best-supported longevity drug, but human dosing is guesswork.
It extends lifespan in mice even when started late in life. Kaeberlein wouldn't start it before about age 25, and admits 'we're flying blind' on dose and frequency. In their mouse study, three months of treatment between 20 and 23 months of age produced lifespan effects roughly similar to continuous treatment in the National Institute on Aging's Interventions Testing Program (ITP).

• The Novartis vaccine studies are the key human evidence.
Joan Mannick and Lloyd Klickstein's 2014 study at Novartis gave older adults (65+) the rapalog everolimus—placebo, 0.5 mg daily, 5 mg weekly or 20 mg weekly. Low-dose arms improved response to a flu vaccine, which Attia used to infer that a moderate weekly dose is the sweet spot. Old mice show a similar problem: only about a third respond adequately to vaccines.

• The follow-up trials were promising, then the phase 3 failed.
A phase 2 trial combining everolimus with RTB101 (a catalytic mTOR inhibitor specific to complex 1 at the doses used) reported improved vaccine response and fewer upper respiratory infections, though the everolimus-only arm missed significance. The company, resTORbio, then tested RTB101 alone in a phase 3 against respiratory illness; it missed endpoints, was stopped early, and the company merged with a CAR-T firm. Kaeberlein calls the endpoint noisy rather than proof the approach fails.

• Side-effect fears are overstated at these doses.
Kaeberlein argues that claims of significant side effects are 'blatantly false' at the doses tested—there's no evidence of major harm from rapamycin, everolimus or RTB101 monotherapy in healthy people—though he concedes we lack long-term controlled trials, so the true risk-benefit balance remains unknown.

• Periodontal disease would be a smarter trial endpoint.
His lab found that eight weeks of rapamycin reverses the defining features of periodontal disease in aged mice. About two-thirds of older adults have or will get periodontal disease, which is linked to dementia, cardiovascular disease and diabetes, so a short trial with a dental exam could give a cleaner signal.

• Epigenetic clocks and telomeres are not yet useful aging measures.
Attia finds clocks easily moved by short-term interventions of doubtful biological relevance, comparing them to glucose of 110 after a bad night's sleep versus 95 after a good one. Kaeberlein explains clocks are DNA chemical marks that track chronological age; both consider telomere length unhelpful for organism-level aging.

• mTORC1 versus mTORC2 explains some side effects.
Rapamycin binds FKBP12 and mainly inhibits mTOR complex 1; most lifespan evidence points to complex 1. Higher or chronic doses may affect complex 2, linked to glucose-intolerance effects in mice. Yet data shared by a physician prescribing rapamycin showed triglycerides falling from about 200 to 70 mg/dL and improved glucose in prediabetic patients—uncontrolled, so caution applies.

• NAD precursors remain unproven.
NR and NMN raise NAD and sometimes show benefits in animals, but many results—including from the ITP—don't replicate, and NR and NMN camps dispute each other's bioavailability. Because supplements can be sold without trials, Kaeberlein expects no definitive human study and would be more bullish only if NR slowed aging in dogs.

EXAMPLES

• Kaeberlein's frozen shoulder
Unable to play catch with his son, he was diagnosed with frozen shoulder and told little could be done. He tried eight-to-ten-week rapamycin courses (about 8 mg weekly) and recovered roughly half his range of motion within eight weeks and later most of it—an anecdote, not evidence.

• The Dog Aging Project
The TRIAD trial aims to randomize 350 middle-aged dogs of 40–100 pounds, 175 per arm, to rapamycin or placebo over three years, powered to detect a 15% change in lifespan—possibly the first clinical trial with lifespan as its endpoint. An earlier 24-dog safety study (16 rapamycin, 8 placebo) showed improved heart function on echocardiograms.

• Sex differences in mice
In the ITP, low-dose rapamycin extended lifespan about 14% in females and 9% in males; at higher doses males caught up,

and some very high doses began to reverse benefit in females.

- **Leigh syndrome mice**
  In a mouse model of this childhood mitochondrial disease, which normally lives about 55–60 days, rapamycin roughly doubled or tripled survival and prevented brain lesions.

OTHER RELEVANT

- **Treat rapamycin as experimental.**
  Dosing, frequency and long-term risks in healthy humans are unknown; anyone considering it needs a physician's supervision and should weigh benefits against uncertainty.
- **Start prevention early.**
  Centenarian data suggest delaying disease onset is the realistic goal, and the earlier risk reduction begins the larger the delay.
- **Be skeptical of biological-age tests.**
  Single clock readings can swing with short-term factors; don't make decisions from them yet.
- **Don't assume supplements work because they're sold.**
  NAD boosters lack replicated evidence of slowing aging.

174-The 20th anniversary of the 9/11 attacks: reflections on how they happened & lessons learned

Guest: Lawrence Wright
Date: 2021-09-06 · Duration: 3:25:25
URL: https://www.youtube.com/watch?v=ajB-qvbgyG4

KEYPOINTS

• 9/11 turned the US into a security state that young people take for granted

Wright says Americans in their 20s and even 30s don't remember a country where you could walk into an office building without ID or board a plane without a search. The country 'traded a lot of freedom for security' and became the one holding the handcuffs. He argues that people who talk a lot about freedom rarely appreciate this.

• Radical Islamism grew out of Egyptian politics

Nasser took power in the 1952 officers' revolt. He was the first native Egyptian to rule Egypt in roughly 2,500 years and enormously popular across the Arab world. He tried to co-opt the Muslim Brotherhood, then crushed it, and in 1966 executed the ideologue Sayyid Qutb. Wright says that made Qutb a martyr, perhaps the worst thing Nasser could have done. Qutb had earlier spent time at a small college in Colorado, which shaped his disgust with American culture.

• Sadat's peace with Israel and his assassination radicalized a generation

Sadat restored Egyptian pride by crossing the Suez Canal in the 1973 war, then made peace with Israel while regional rhetoric still called for its destruction. After his assassination in 1981, mass arrests and prison torture hardened militants like Ayman al-Zawahiri, a doctor. Egypt's desert and the military's grip on the Nile made guerrilla war impossible there, so Zawahiri left for Afghanistan.

• Bin Laden's celebrity came from his father's fame and the Afghan war

Muhammad bin Laden built the road that unified the Saudi kingdom and became its most famous non-royal, with dozens of children (Osama had more than 50 siblings). Osama went to fight the Soviets in Afghanistan in the 1980s. Wright says he achieved little militarily and at great personal risk, but at home he was celebrated as a hero when the Soviets withdrew in 1989.

• Kuwait 1990 was a hidden turning point

When Saddam Hussein invaded Kuwait, bin Laden offered to defend Saudi Arabia with mujahideen and earth-moving equipment against a million-man Iraqi army. The kingdom invited American troops instead. Wright sees this, and bin Laden's reading of the Prophet's saying that only one religion should exist in Arabia, as one of the biggest factors leading to 9/11.

• Bin Laden attacked America because he felt the Islamic world was encircled

Wright says bin Laden saw the US surrounding and threatening Muslim lands. Al-Qaeda was founded in May 1988 (its founding notes survive in the handwriting of the man who took them). In Sudan from 1992 to 1996 it was largely an agricultural operation, and bin Laden may have been the country's largest landowner. The embassy bombings and the attack on the USS Cole were steps toward drawing the US into a war, not the end goal.

• Warnings were ignored: the embassies and the Cole

The August 1998 East Africa embassy bombings killed 224 people and blinded more than 100. The October 2000 bombing of the USS Cole in Aden came two weeks before an election. Neither became a campaign issue. The response was one failed 1998 strike at bin Laden.

• The CIA withheld what the FBI needed

Two future hijackers, Khalid al-Mihdhar and Nawaf al-Hazmi, attended a Kuala Lumpur meeting with the Cole plotters and entered the US on January 15, 2000. The CIA knew but didn't tell the FBI, and obstructed Ali Soufan's Cole investigation. The NSA picked up calls between San Diego and an al-Qaeda house in Yemen 14 times, according to Wright. He says he doesn't blame the CIA for 9/11, but believes 9/11 would not have happened if it had worked openly with the FBI.

• Personal feuds helped open the door

The rivalry between Michael Scheuer at the CIA's Alec Station and John O'Neill at the FBI's I-49 squad was bitter. Wright says both men were right about the threat, but their contempt for each other let it slip through. The August 6, 2001 Presidential Daily Brief warned that al-Qaeda was set to attack inside the US, five weeks ahead of time, yet Wright notes almost no one was held accountable.

• Terrorism has spread, and the pandemic was also an intelligence failure

Al-Qaeda numbered perhaps 300–400 people on 9/11. Wright cites estimates of 30,000–40,000 members and affiliates today, from Morocco to southern China. He also points to domestic terror such as the 2019 El Paso massacre, in which 23 people were killed. He calls COVID, with more than 600,000 American deaths, a catastrophic intelligence failure, and thinks the US 'squandered 9/11 terribly.'

EXAMPLES

• The man who slept through his subway stop

Wright's first way into the story was a reporter who had a 9:00 appointment at Windows on the World on the 101st floor. For the first time in his life he slept through his stop, then rushed into the towers. His story shows how chance decided who lived.

• John O'Neill's obituary

About six days after the attacks, Wright read a Washington Post obituary for O'Neill. The former FBI counterterrorism chief had held the warrant on bin Laden, was forced out after taking classified material out of the office, and died in the World Trade Center weeks into his new job as head of security there. Peter says an editor wouldn't have allowed that ending in fiction.

• Ali Soufan, the irreplaceable agent

Soufan was a Lebanese-born agent in his 20s and one of only six Arabic speakers in the FBI. He was abroad on 9/11 and lost his mentor O'Neill. Wright says the CIA had hidden from him exactly the information about the hijackers that his investigation needed.

- **The Siege and the 28 pages**

  Wright co-wrote the 1998 film The Siege, about terror in New York, which became the most-rented movie in America after 9/11. He also discusses the 28 suppressed pages from the official inquiry on possible Saudi government links, which victims' families sued to see. He notes that a Saudi contact in San Diego who helped the two hijackers had received thousands of dollars from the wife of the Saudi ambassador.

OTHER RELEVANT

- **Treat institutional rivalry as a security risk**

  The key lesson Wright draws is that agencies 'got so caught up in their institutional and personal antagonisms' that they failed at their mission. Information-sharing failures, not lack of data, were decisive.

- **Read The Looming Tower for the full narrative**

  Wright's 2006 book traces the path from Qutb through Zawahiri and bin Laden to the attacks. It's the long version of what this episode compresses.

- **Use crises as chances to rebuild, not just to defend**

  Wright hopes the lessons of 9/11 and the pandemic can help the US become the country it once was and wants to be again, rather than repeating the overreach that followed 2001.

172 - Esther Perel: Trauma, how narratives shape our worldview, and accepting uncomfortable emotions

Guest: Esther Perel
Date: 2021-08-16 · Duration: 2:22:35
URL: https://www.youtube.com/watch?v=7be3O9ckZ1c

KEYPOINTS

• Perel grew up among Holocaust survivors, asking what makes people want to live.
Her parents each came from families in which every sibling had seven to 10 children; each lost about 200 relatives. Her mother went through nine camps in five years and her father 14, including a stint in Siberia. In a community where most adults had numbers on their arms, Perel's first question at two was why she had no grandparents. In 'Mating in Captivity' she distinguished survivors who 'did not die' from those who 'came back to life' — who could trust and reconnect again.

• Survivors credited luck, will and dignity.
Asked how they survived, her parents gave three answers: sheer luck (not being selected when a thousand were chosen each morning); wanting to live, in case someone was waiting; and living with dignity — her mother mended her socks and folded her clothes. Her father managed to feed about 60 young people with scraps and potato peels, which kept them able to work and therefore alive.

• Collective trauma demands collective resilience.
Her parents' community held gatherings for survivors of specific towns and camps, planted trees, celebrated and told stories. They understood instinctively what's now called collective or psychosocial trauma: they didn't try to heal alone. In the early years they spoke little, because others couldn't bear to hear more than two sentences.

• Resilience is not just an internal trait.
Responding to Susan David's line that 'the key to resilience is the radical acceptance of all emotion', Perel says there's truth in it, but it reflects an individualistic view. Another definition is the ability to face adversity, rebound and re-engage with life — drawing on community, the people who help you, luck and earlier experience. 'It's not what's inside of you; it's what's around you.'

• Adaptive parenting in trauma can become maladaptive later.
Survivors sometimes couldn't get close to their children — if I don't get too close, losing you won't hurt as much. Behaviour that was adaptive in the camps became maladaptive in peacetime. Understanding that a parent's behaviour reflects what happened to them, not who you are, can transform the relationship.

• Individualism changed what people bring to therapy.
Over about 50 years, feeling good about oneself became an organizing principle, rather than feeling good about how one acts toward others. Clinicians now hear 'I'm not happy' as a chief complaint. Children's books before the 1960s, she notes, weren't written around the child's needs; Dr Spock marked the transition.

• Generational expectations of fathers have shifted.
A son who felt he could never please his father would, 100 years ago, likely have heard 'I did the best I could; my job wasn't to pump you up.' Attia's father worked 14 hours a day six days a week, and was incredulous at being asked to do more.

• The stories we tell drive how we act.
If I believe 'he doesn't really care', I act on that story. Perel's work is reframing — not as an intellectual exercise but because a different narrative changes behaviour on both sides.

• Will and readiness are shaped by context.
When someone says they're finally ready to change, Perel asks why now — an ultimatum, a spouse about to leave, a son who hasn't spoken to them in two years? Each motive affects how the other person can receive the change.

• Relationships determine the quality of a longer life.
Attia says that five years earlier he'd never have considered it, but now believes emphatically that the quality of your relationships determines the quality of your life — what's the advantage of living longer otherwise? Numbing emotions, Perel notes, often comes from judging that you shouldn't feel them.

EXAMPLES

• Her mother's labour camp choice
At 18, hiding in the woods, her mother walked herself into a men's labour camp because waking up in the same place each morning was less dreadful than the uncertainty.

• The Mother's Day post
Tired of Hallmark sentimentality, Perel wrote with humour about her critical, superstitious mother; thousands replied, 'This is my mother.' Her mother died at 80 when Perel was 42.

• The nine-year-old who called the police
A man carried guilt for calling the police from a neighbour's house during domestic violence. Perel reframed it: he couldn't do more than a nine-year-old could, and it was one of the most loving things he could have done for his mother.

• 'You can't believe everything you feel'
Attia shares a psychologist friend's line: you can't believe everything you think, and you can't believe everything you feel. Mindfulness taught him the first half; the second was new.

• Nine languages
Perel speaks nine languages and was schooled for 12 years in Antwerp; she came to the US to study, never intending to stay.

OTHER RELEVANT

• Lean on community after trauma.

Healing often happens with others — rituals, shared stories and support networks. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Question your story about others.**
  Ask whether your interpretation of a partner's or parent's behaviour is the only one.
- **Understand inherited patterns.**
  Genograms and family history can show how a parent's survival strategies shaped you.
- **Let yourself feel.**
  Numbing usually stems from judging emotions; acknowledging them is part of resilience.
- **Invest in relationships as a longevity strategy.**
  Treat them as seriously as exercise or nutrition. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Ask "why now?" before announcing change.**
  When you tell someone you have finally done your own work, consider how your timing and motive will land; Perel suggests naming what you learned about yourself rather than presenting change as a bargaining chip.

171- Longevity science: caloric restriction studies, aging biomarkers & possible longevity molecules

Guest: Steven Austad
Date: 2021-08-09 · Duration: 2:34:59
URL: https://www.youtube.com/watch?v=WNKRSiSGvGE

KEYPOINTS

• Lower extrinsic danger leads to slower aging

Austad's first aging study compared opossums on Sapelo Island, off Georgia, which has few predators, with mainland opossums. Mainland opossums, about the size of a small cat, got cataracts by around 18 months and declined fast. The island animals aged more slowly, which fits evolutionary theory: species that face less outside death evolve to age more slowly.

• The lab mouse is a strange, narrow model

Lab mice descend from 'fancy mice' bred for odd coat colors and sizes, then inbred until every animal is genetically identical at every locus. Austad compares this to testing drugs on the same set of twins over and over, out of about 4,500 mammal species. That's why he values the Interventions Testing Program (ITP), which uses genetically heterogeneous mice at three sites.

• Calorie restriction works in lab rodents, but the effect is weaker in wild mice

The finding dates to rat work in the 1930s, whose author never seemed to grasp its importance and later moved into high-protein bread for the military. Austad brought wild-caught mice into the lab and restricted them to 70% of normal intake. For most of their lives there was no benefit. Only the last ~20% of survivors lived longer, so he expects the effect to be much smaller than in obese, sedentary lab strains.

• The two monkey studies disagreed partly because of sugar

The Wisconsin study used a purified diet that was about 28–29% sucrose. The NIA (Bethesda) study used natural ingredients with about 3% sucrose. Wisconsin restriction extended life compared with controls, but the NIA study's controls were healthier to start with, and restriction added little. Austad likens Wisconsin to 'three Big Macs, two monster fries and two jumbo Cokes a day' versus 70% of that: eating less toxic food will look good. He suspects the restricted Wisconsin monkeys had more diabetes than the NIA controls.

• Captive animals, including us, are obese compared with wild relatives

Both captive monkeys and modern humans differ from their wild counterparts. Austad's conclusion is that nutrition and aging questions ultimately have to be studied in humans.

• Human calorie restriction is very hard to sustain

The CALERIE trial aimed for about 25% restriction, but people managing their own food reached only about 11–12% over two years. Austad says only about 30% of Calorie Restriction Society members truly sustain it, with BMIs around 17–20. Those trials were also in people in their late 30s, and what's good for them may not suit people in their 60s.

• Time-restricted eating and fasting may matter more than total calories

Mouse work suggests that going many hours a day without food may account for as much of the benefit as eating less. A short fast of two or three days before surgery sped recovery in mice in the late Jim Mitchell's work, including after an ischemia-reperfusion injury. Peter and Austad also discuss 16-hour eating windows and the five-day fasting-mimicking diet of about 750 calories a day.

• Women outlive men at every age, except when it comes to Alzheimer's

Women survive better as infants and in their 20s, 30s and 40s, and die at lower age-adjusted rates of every major cause except Alzheimer's disease. Austad offers a 'private hypothesis' that Alzheimer's will turn out to have an autoimmune component, since women are more prone to autoimmune disease.

• Sex differences in ITP drug results may reflect dosing

Rapamycin favors females at low doses, a gap that shrinks as the dose rises. 17-alpha-estradiol, acarbose and canagliflozin mostly help males. Austad suspects higher blood levels in females may mean they're effectively overdosed. Peter notes that the canagliflozin and acarbose results point to glucose dynamics rather than eating less.

• Validated aging biomarkers are the biggest missing tool

The NIA put about $100 million into aging biomarkers in the 1990s without success. Austad wants markers that answer in weeks or months, across ages, so that healthy people can learn how to stay healthy without decades-long trials.

EXAMPLES

• From cab driver to lion tamer

Austad drove a New York cab in the gritty mid-1970s, then drove to LA, where a film producer hired him on the spot to care for 25 lions. One lion clamped onto his leg over food. He later went to graduate school planning to study lions, and ended up studying opossums.

• Biosphere 2

In this early, involuntary human calorie-restriction experiment, Roy Walford entered at about 66 and left at 68. He was an outlier, since most participants were young, so not much can be concluded.

• The 150-year bet

About 21 years earlier, Austad bet Jay Olshansky that the first person to live to 150 was already born by 2000. The record, Jeanne Calment, is about 122.5 years, and nobody has reached 120 since. Austad stresses that he wasn't predicting average life expectancy of 150. He sees 100 as conceivable.

• Intermittent mTOR inhibition in humans

Austad cites the everolimus study in which 5 mg and 20 mg once a week improved vaccine response in older people, with the lower dose working just as well. This supports intermittent dosing that targets mTORC1 while sparing mTORC2, whose inhibition may cause side effects.

OTHER RELEVANT

- **Rapamycin and metformin each have only half the case**

  Austad's view: 'If we go by the mouse data it would have to be rapamycin; if we go by the human data, metformin', and he calls both weak statements. He finds rapamycin plus metformin interesting. Most clinical trials fail because they're built on mouse data.

- **Be intrigued, not excited, by single mouse studies**

  He wants more human data before getting excited about SGLT2 inhibitors or NAD precursors. SGLT2 human data on kidney failure, heart failure and mortality are impressive, but they come from people with disease, not from longevity trials.

- **It's never too late to improve**

  Austad stresses that a 50-year-old who has never exercised and has eaten badly can still benefit from changing course.

169 - COVID-19 Lab Leak: Examining all sides of the debate & the barriers to a full investigation

Guest: Katherine Eban
Date: 2021-07-19 · Duration: 1:45:46
URL: https://www.youtube.com/watch?v=RmBJFDBChxA

KEYPOINTS

• 'Lab leak' covers a range of scenarios, not one theory

Eban, an investigative journalist who wrote about COVID's origins for Vanity Fair, stresses that 'lab leak' spans everything from a natural bat sample brought back by field researchers and accidentally escaping, to an infected lab worker, to a genetically modified strain getting out. 'Leak' usually means airborne exposure, not liquid spilling from a pipe. The episode was recorded on July 6, 2021.

• Lab escapes have happened many times before

Eban cites a Soviet anthrax leak and at least four SARS-1 lab escapes after the 2002 epidemic. The 1977 'Russian flu' was an H1N1 strain from the 1940s and 1950s that reappeared and mostly hit people under 25, who had no natural immunity. They note that much dangerous-pathogen work happens outside top-containment BSL-4 labs, including at Wuhan in BSL-2 settings. Attia adds that BSL-4 is miserable enough to tempt researchers into shortcuts.

• No intermediate animal host has been found

SARS-1 was traced to civets within about six months, and MERS to dromedary camels. For SARS-CoV-2, Eban reports that Chinese authorities tested up to 80,000 animal samples without finding a host. That leaves either an undiscovered intermediate animal or direct jump from bats, for which the 2012 mine case below offers some precedent.

• Gain-of-function research divides virology

This research deliberately gives pathogens abilities they lack in nature, such as greater infectiousness to humans, to gauge risk and possibly help forecast variants or design vaccines. One critic called it 'looking for a gas leak with a lighted match'. Another called bringing cave viruses to crowded cities and making them more infectious 'the definition of insanity'. Asked for proven successes, Eban mostly reports defenders' claims about vaccines and variant forecasting.

• US policy swung from a moratorium to a loophole-filled framework

After Ron Fouchier's 2011 work making a flu virus far more transmissible, which he described as among the most dangerous ever, the Cambridge Working Group pushed back. The US paused funding of gain-of-function research on flu, SARS and MERS. In January 2017 the pause was lifted and replaced by a review framework that Eban says had enough loopholes 'to drive a truck through'.

• US money reached Wuhan indirectly

The NIH funded EcoHealth Alliance, a nonprofit led by zoologist Peter Daszak with a stated mission of mapping wildlife viruses. EcoHealth passed subgrants to the Wuhan Institute of Virology, and the Department of Defense also funded EcoHealth. The NIH had not released EcoHealth's progress reports, and investigations, including by the HHS inspector general, were ongoing. Sources described a 'gain-of-function bureaucracy' in government with a stake in the answer.

• The furin cleavage site is suggestive but not a smoking gun

The site makes the virus better at infecting human cells, and one virologist called it a signature of Wuhan's genetic editing. Nicholas Wade quoted David Baltimore calling it 'the smoking gun', which Baltimore later walked back. Others note such sites occur in nature. Eban says public information on the sequence can't settle the question.

• Politics distorted the debate

In April 2020 President Trump said he was certain it was a lab leak. Eban says this was months before the government's most significant information came in, in late summer and fall 2020. Hours earlier, his own intelligence agencies had said the virus was not genetically modified. Raising the lab hypothesis became tied to xenophobia, and outlets such as Vox later removed 'conspiracy theory' labels.

• A full investigation looks unlikely

Full transparency would require China to restore its database and share sample records, lab notebooks and the medical records of lab staff. There was no public blood-test data on three lab workers reported sick in late summer and early fall 2019. The fallback is for countries to search their own files, as President Biden ordered in a review of less than 90 days, though Eban doubts there is the political will.

EXAMPLES

• The Mojiang mine: six sick miners and a 96.2% match

In 2012, miners clearing bat guano in an abandoned Yunnan mineshaft developed COVID-like pneumonia; three of six died. China never told the WHO. Wuhan Institute of Virology researchers sampled the mine heavily. One sample, later called RaTG13, is 96.2% identical to SARS-CoV-2. It became known only after an unemployed science teacher in eastern India, 'The Seeker' on Twitter, found a Chinese master's thesis about the case.

• A database went offline before the outbreak

The institute, about seven miles from the Huanan seafood market, held hundreds of samples. Its database was taken offline in September 2019, months before the known start of the outbreak, and had not returned.

• The Lancet statement and undisclosed conflicts

In February 2020, 27 scientists published a statement, not a peer-reviewed paper, calling non-natural origin theories conspiracy theories. One source said it was 'nailed to the church door'. Daszak organised it, and several signers worked for him or received his grants, yet they declared no conflicts of interest. Daszak was later the only American on the WHO-led team in China. A US government analysis Eban obtained called that team's 'highly unlikely' verdict baseless.

• Redfield's offer was refused

Former CDC director Robert Redfield told Eban he suspected the Wuhan institute from the start. He offered to send experts

to antibody-test its researchers, which he said could have ruled the lab out in a couple of weeks. China declined.

- **Competing readings of the virus's stability**

  Alina Chan of the Broad Institute argues the virus seemed already adapted to humans, without SARS-1's early burst of mutations; Attia links that to research using humanised ACE2 mice. Critics counter that it isn't optimised for human infection. Attia calls that a red herring, likening it to saying the Hiroshima bomb could have been more lethal.

OTHER RELEVANT

- **Think in separate probabilities**

  Attia breaks the question into three: was the virus brought into a lab, was it manipulated there, and could it escape? He treats the last as close to certain given history and the temptation to cut corners.

- **Real conspiracies need cover-ups**

  Attia's test, from his own conclusion that Oswald acted alone in the Kennedy assassination, is how hard a cover-up would be to sustain. Eban went from dismissive to 'even odds'. She would change her mind if a host animal turned up, but too many questions remain. She treats the barriers to investigation as the most troubling part of the story.

- **Weigh anonymous sources carefully**

  Eban interviewed members of DRASTIC, an independent research group, but excluded anonymous members she couldn't speak with, because their agendas can't be assessed.

168 - Hugh Jackman: Reflections on acting, identity, personal transformation, and being Wolverine

Guest: Hugh Jackman
Date: 2021-07-12 · Duration: 2:15:51
URL: https://www.youtube.com/watch?v=Go4PYU3hJrc

KEYPOINTS

• Hugh Jackman's career began with a gut decision, not a plan

He did a journalism degree and only acted in amateur and community plays. Then, in his last semester, he noticed he was spending far more time on a play than on his thesis. He applied to drama school in Sydney because he couldn't afford England. He says roughly 5% of graduates from his three-year program, which took 18 students a year, end up making a living from acting.

• Being 'too thin-skinned' shaped how he handles reviews

His father rarely gave advice before a decision. When Hugh said he would act, his father told him he had the talent but was too thin-skinned. Hugh took that seriously and doesn't read reviews. He asks someone for 'the temperature' instead. He argues that praise can be more dangerous than criticism on stage: a negative review can fire you up, while a compliment gets into your head and can wreck a performance.

• No public figure can please everyone

Attia points out that a politician with a 60% approval rating is considered exceptional, which still means 40% of people can't stand them. He cites a Q-rating (a measure of popularity and likability) of 99 for Jackman in Australia, with the next person at 67. Both men treat a desire to please everyone as a trap.

• Attia: arguing with bad-faith critics online doesn't work

Attia says he responds to an attack maybe once every six months and is 'oh for 20' at changing anyone's mind. Joe Rogan's advice was 'post and ghost': put it up and never read the comments. What bothers Attia is not being insulted but knowing that people with warped views about science may be harmed by them. He also admits scientists have often explained science poorly.

• Driven people often run on old fear, and the line between productive and destructive is hard to see

Hugh's mother left the family when he was eight. He says he understood more than adults assumed, was never really angry with her, and felt she loved him. Still, he had lots of fears, which he would now call anxiety. Attia describes surgical residency at 110–120 hours a week, with exercise and practising anastomoses at night as his only other priorities. Both men ask how to raise children with drive but without the damage.

• Growth is natural, but they both went past what was healthy

Hugh cites James Allen's 'As a Man Thinketh' (1904): growth is part of nature and uncomfortable, but they both went beyond that natural state, accepting unusual pain and sacrifice to achieve. Attia says his recovery contract includes journaling every day about the trade-off of putting 'eulogy over résumé'. That can mean accepting worse short-term performance and saying goodbye to some opportunities.

• Hugh's father taught him work ethic by example

After Hugh's mother went back to England to care for her own mother, his father raised the children alone from the time Hugh was eight. Hugh says he can't remember his father having a moment to himself for a decade. He learned much of his ethic of hard work from watching him.

• Performing well every night comes from respect for each audience

Hugh did 'The Greatest Showman' tour 92 times. Attia notes that most people in each audience see the show only once, so each night has to be the best version, as Muhammad Ali said about fights. Hugh says he remembers sitting in the audience himself, reading the programme and hearing the hubbub. He describes a near-spiritual connection with 2,000 or 20,000 strangers.

• 'The Fountain' made him confront mortality

Darren Aronofsky gave him the script 17 years before this conversation, after seeing him in 'The Boy from Oz'. Hugh read it that night and felt it was about the meaning of life. Attia, whose interest in longevity began about 10 years earlier, says his fear of not being here jumped when he became a father. He adds that living long without living well mentally is a kind of torture.

• Logan was a 17-year relationship with a character

He played Wolverine in nine films and pushed for a final film that got to the core of the character. Fox's key people backed it, but there was concern about leaving perhaps $100 million on the table with an R rating. There was also resistance to calling it 'Logan' after building the Wolverine 'brand'. When it ended, Patrick Stewart was in tears as they realised it had been 17 years.

• He accepts ageing on screen

Hugh says he mostly embraces ageing, while noting the industry is harsher on women. Attia raises the tension between getting better at your craft while being judged on looks.

EXAMPLES

• Knowing what he wanted at 22

Hugh asked his father whether to take a job or keep training. His father said, 'That's a decision you have to make; you're 22.' By the next morning Hugh was clear: he wanted training that would make him feel he deserved an audition at the Royal Shakespeare Company or the National Theatre.

• Working with Trevor Nunn

At 26, out of drama school, he auditioned for Trevor Nunn and later worked at the Royal National Theatre at 28. He felt like 'a thoroughbred in the paddock', a match with someone who had directed Judi Dench and Ian McKellen.

• A deal with the paparazzi at Bondi

On a year-long film shoot in Australia, his son was upset by photographers. Hugh asked them what they needed, agreed to an 8:15 a.m. shirtless swim at Bondi, then asked to be left alone. They kept their word for 12 months.

- **Praying for a path**
  Raised in a very religious home (his father was converted by Billy Graham), he prayed nightly until about 15 or 16 to be shown God's will. He sees the pull towards acting as part of that story.
- **A fan of 'The Boy from Oz'**
  One woman saw 'The Boy from Oz' 200 times out of 400 shows. That kind of devotion made him ask which version of himself was the real one.

OTHER RELEVANT

- **Ask for the temperature, not the reviews**
  If criticism or praise gets into your head, get someone to summarise the gist rather than reading it all.
- **Post and ghost**
  Share your work and don't argue in the comments. Debating bad-faith critics rarely changes minds.
- **Write your 'eulogy over résumé' trade-offs down**
  Name what you're giving up for family or health, so the cost is a decision you made rather than a source of guilt.
- **Notice when drive turns into fear**
  Ask whether the push still serves growth or is old anxiety. That question matters most when you're raising driven children.

167 - Gary Taubes: Bad science and challenging the conventional wisdom of obesity

Guest: Gary Taubes
Date: 2021-06-28 · Duration: 3:13:03
URL: https://www.youtube.com/watch?v=8js28V95flc

KEYPOINTS

• Taubes learned skepticism by covering physics that went wrong.
His first book, Nobel Dreams, followed Carlo Rubbia's team at CERN, about 150 physicists, in the period after the discovery of the W and Z bosons that won Rubbia the 1984 Nobel Prize. Watching the team chase a claimed new discovery in 1984–85, he saw how a leader who has gone out on a limb publicly stops hearing junior physicists who warn that the detectors aren't understood well enough to support the claims.

• 'Pathological science' starts with premature public commitment.
Physicists use the term for the science of things that aren't so. Its defining trait, Taubes says, is committing publicly to a result based on premature evidence without appreciating the chance of being wrong. Feynman's 1974 Caltech commencement talk captures the antidote: good science requires investigators to report everything that might undermine their result, unlike advertising.

• Cold fusion showed why controls matter.
After Pons and Fleischmann's March 1989 announcement made front-page news, Taubes wrote Bad Science (published 1991). Partly they rushed because they feared a physicist at Brigham Young, about 30–40 miles away, was working on a related idea. The story of a Georgia Tech group's neutron detectors (see examples) is his model of a missing control.

• Nutritional epidemiology can't reliably establish cause.
Cohorts like the Nurses' Health Study (about 110,000 nurses filling out food-frequency questionnaires) generate associations confounded by who chooses what. Taubes points to its 1987 observation that hormone replacement therapy appeared to prevent heart disease, an example critics flagged as confounding. He notes rigorous scientific method is less than 400 years old, dating to Bacon's Novum Organum, while pattern-seeking instincts are far older.

• Low-salt and low-fat advice outran the evidence.
Reporting for Science around 1998, Taubes found Americans had been eating low-salt diets for 15–20 years though randomized evidence never really supported it. An NIH administrator told him that when the low-fat recommendation came in 1984, they assumed rather than had the evidence. His two hypotheses for the obesity epidemic, which starts between roughly 1978 and 1991, both coincide with that era.

• Sugar and high-fructose corn syrup coincide with the epidemic.
Foods once considered fattening, starches and sugars, were rebranded as heart-healthy in the low-fat era. HFCS-55 arrived around 1977–78, could replace sugar in Coke and Pepsi, and by 1984 saturated the beverage industry, the same window when obesity rates began climbing.

• Obesity research ignored the science of fat storage.
Until about 1930 almost no one studied fat tissue. Starting in 1933, Rudolf Schoenheimer at Columbia showed fat is constantly deposited and mobilized, and by the mid-1960s intermediary metabolism was well established, yet Taubes says obesity textbooks from 1965 onward omitted it as psychiatrists and psychologists came to dominate the field.

• The 'eat too much' paradigm rests on thin foundations.
In 1930 physician Louis Newburgh published work based on a small number of patients arguing obese people simply overeat; German-speaking researchers like Julius Bauer called the argument naive, favoring hormonal dysregulation of fat tissue. In 1938 Albert Hetherington, at the lab of neuroanatomist Stephen Ranson, produced obesity in rats by lesioning the ventromedial hypothalamus, and with John Brobeck framed it as overeating. After Yalow and Berson's insulin assay (post-1960), those animals turned out to be hyperinsulinemic.

• The carbohydrate-insulin model is an alternative hypothesis, not settled fact.
Taubes argues that for people who gain weight easily, carbohydrates drive fat storage through insulin, so carbs must be restricted and replaced by fat and protein. He and Attia discuss a just-published paper by John Speakman and Kevin Hall presented as a possible refutation; Attia sees it as a mechanistic inquiry rather than a public-health solution, and they examine energy-expenditure methods such as indirect calorimetry.

• Ketogenic diets moved from 'deadly' to widely studied.
Conventional wisdom before about 2010 held that Atkins-style diets caused heart disease. Taubes notes roughly 200 trials now study ketogenic diets for conditions ranging from cancer and Alzheimer's to traumatic brain injury.

EXAMPLES

• The humidity-sensitive neutron detectors
Georgia Tech Research Institute chemists saw borrowed neutron detectors go off over cold-fusion cells and held a press conference. A local physicist told them the detectors were humidity sensitive; when they ran a water-only control, it set them off too.

• Taubes's own weight
At college he could eat 1,000–1,500-calorie late-night sandwiches; his boxing weight was 212 pounds, but after 30 he drifted upward toward 240. He tried Atkins as an experiment and is 'still waiting' for the predicted heart attack.

• The MIT economist and white rice
While reporting on markets at MIT, an economist told him his father had lost 200 pounds on Atkins and that he himself lost 40 pounds mostly by giving up white rice.

• Boxing and risk perception

Both Taubes and Attia boxed; Attia says he never felt it was dangerous because he believed he didn't get hit, which Taubes uses to illustrate how poorly we perceive behavioral risk.

- **Joslin's textbook**

Elliott Joslin opened the first dedicated US diabetes clinic around 1900; by 1916 he had seen about a thousand patients and wrote the field's defining textbook, now in its 14th edition, an example of how one authority comes to define truth.

OTHER RELEVANT

- **Demand controls and disconfirming evidence.**

Ask whether a striking claim compared against a proper control and whether its authors discuss what could prove them wrong.

- **Treat observational nutrition findings as hypotheses.**

Food-questionnaire associations can be badly confounded; randomized evidence should decide. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Experiment on yourself thoughtfully.**

If you gain weight easily, a carbohydrate-restricted trial may be informative; Taubes and Attia stress the science is contested, so monitor health markers with a physician.

- **Beware of authority overriding data.**

Dominant paradigms in obesity research formed around a few influential figures, so ask what evidence alternative explanations have.

166 - Oral health, best hygiene practices, & relationship between oral health and systemic disease

Guest: Patricia Corby
Date: 2021-06-21 · Duration: 2:14:01
URL: https://www.youtube.com/watch?v=MSMVpBrfTo0

KEYPOINTS

• The mouth is an ecosystem, not a sterile surface

Patricia (Pat) Corby trained in Brazil in periodontics and implant dentistry, and now runs clinical trials. She describes more than 700 bacterial species living in symbiosis with the host. Some are protective, some harmful, and a large share (she estimates 30–40%) can play either role depending on conditions. The aim of hygiene is to keep the community in a healthy balance by disrupting the biofilm, not to sterilise the mouth.

• Caries and gum disease are different infections

Caries are driven mostly by aerobic, sugar-metabolising bacteria on tooth surfaces. Periodontal disease and gingivitis are driven by anaerobes that thrive below the gumline. They share risk factors (poor hygiene, dry mouth, diet), but brushing reaches the surfaces while flossing reaches the protected spaces between teeth and under the gums.

• Her twin trial showed flossing matters on top of brushing

She studied identical-twin adolescents aged about 12–16, who share 100% of their genes and live in the same house. One twin brushed, while the other brushed and flossed, supervised by hygienists every day at a centre and then at home in the evening. The twins who didn't floss had more gingival bleeding and an abundance of the main periodontal pathogens, including Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans, even at that young age.

• Fluoride toothpaste is the main defence against decay

Corby disagrees with the view that flossing matters more than brushing. She calls them equally important because toothpaste is the main source of fluoride, which hardens enamel. Look for 1,000–1,500 ppm of fluoride. The American Dental Association lists toothpastes it endorses because they contain an effective amount. Not every toothpaste contains fluoride. She adds that sugar is now in almost everything we buy, a big cultural change that feeds decay-causing bacteria, and that children at high risk can also get fluoride varnish.

• Night is the riskiest time for your teeth

Saliva production drops during sleep, so bacteria flourish. That is why babies given bottles overnight get rapid, painful early-childhood caries on the front teeth. She says formula, which contains sugar, causes more decay than breast milk. Brushing and flossing before bed is the single most important hygiene habit.

• Dry mouth is a hidden risk

Saliva buffers acid and washes the mouth. Radiation, chemotherapy, anticholinergic drugs and dehydration all reduce it. She urges physicians to ask patients about dry mouth. Sipping water all day helps, since the mouth and gut are 'one system'.

• Cleaning the mouth may reduce cancer-treatment complications

Her trial enrols head-and-neck cancer patients (mostly squamous cell, many HPV-positive) receiving at least 50 Gy to the mouth. Almost all of them develop painful oral mucositis. She compares professional mechanical debridement with brushing of the oral mucosa, in blinded groups. Her earlier informal cleanings caught the attention of the radiation oncologist Nicholas Sanfilippo, and a 16-patient pilot won grant funding.

• Links to systemic disease are mostly associations

Periodontal disease is associated with diabetes, low birth weight, heart disease and markers of Alzheimer's, plausibly through bacterial insult and inflammation. Corby stresses that we don't know which comes first, and that only trials that treat gum disease and change those markers can show causation. She mentions Angela Kamer's research, including work in people with Down syndrome, who have poor oral health and early Alzheimer's. Attia notes these links could be 'true and unrelated'.

• Root canals do not cause cancer

Attia calls claims that root canals cause breast cancer and other diseases nonsensical, and says they cluster with beliefs like vaccines causing autism. Corby explains that older root-canal techniques could perforate roots and seed inflammation, but modern endodontics is far more precise. Attia's objection is partly ethical: a woman with breast cancer shouldn't be told she caused it with a root canal she had five years ago.

• Tooth colour is mostly environmental

Genetics and excess fluoride in water can affect tooth shade. But in her twin study, identical twins on the same products ended up very different, with heavy tea drinking darkening teeth. Black tea and red wine are the main stainers. People with darker skin tend to look as if they have whiter teeth because of the contrast, so perceived whiteness is partly relative.

EXAMPLES

• Attia's 'leave it alone' lesson

A dentist replaced a 20-year-old, symptom-free mercury filling because insurance would cover a white one. The tooth began to hurt and needed a root canal within weeks. Corby advises leaving intact amalgam fillings alone.

• Attia's routine and her upgrades

He brushes at about 11 a.m. after coffee, using an Oral-B with a 30-second-per-quadrant timer, and flosses. Corby added brushing the tongue with a soft children's toothbrush, and rinsing and drying the toothbrush, since bacteria love moisture. Attia joked that this adds 28 minutes a week.

• Xylitol in pregnancy

In her research, giving xylitol to mothers during gestation reduced vertical transmission of decay-causing mutans streptococci to their babies. Bacteria can't metabolise xylitol. Attia uses PUR gum and mints.

• Her own children

Corby says her two sons, now adults, have never had a cavity. She credits nightly brushing that she drilled into them early.

- **COVID and the mouth**
  ACE2 receptors, which the virus uses to enter cells, are highly expressed in the mouth. Corby argues that hospital oral care for COVID patients was neglected, but this is her hypothesis, not proven.

OTHER RELEVANT

- **Brush and floss before bed, every night**
  Use toothpaste with 1,000–1,500 ppm fluoride (check the ADA list) and clean between your teeth.
- **Clean your tongue and look after your toothbrush**
  Brush your tongue with a soft brush, then rinse your toothbrush and let it dry.
- **Don't replace sound amalgam fillings**
  Drilling an intact tooth can cause the very problem you're trying to prevent.
- **Treat dry mouth as a risk factor**
  Hydrate, and ask your doctor about medications that dry the mouth. Cancer patients should get dental care before radiation.
- **Check-ups every six months, more often if high-risk**
  People with diabetes or other risk factors may benefit from three visits a year.

164 - Diagnosing, preventing, & treating Alzheimer’s disease, & life lessons from dementia patients

Guest: Amanda Smith
Date: 2021-06-07 · Duration: 2:11:31
URL: https://www.youtube.com/watch?v=hf2ERS7MAws

KEYPOINTS

• Normal aging can be vibrant.
Amanda Smith, a geriatric psychiatrist and director of clinical research at the University of South Florida's memory center in Tampa, grew up around grandparents and their friends who led active lives into their 70s and 80s, which shaped her sense of what normal aging looks like. She came to USF in 1997 as an intern, trained under Eric Pfeiffer, who founded the center in 1980, and took over as principal investigator on many trials when he retired in 2008.

• Dementia is a syndrome; Alzheimer's is one cause.
Dementia means cognitive decline severe enough to impair daily function. In her clinic, roughly 50–60%+ of cases are Alzheimer's, about 20% vascular and about 20% Lewy body, with others such as frontotemporal dementia. Lewy body disease is often less protracted, while Alzheimer's averages 8–10 years from diagnosis and can last much longer.

• Amyloid builds for 10–20 years before symptoms.
Amyloid PET imaging showed plaques accumulate 10, 15 or 20 years before clinical decline. Before 2011, the FDA's definition of Alzheimer's required dementia, leaving no room to study prodromal patients; the 2011 redefinition introduced mild cognitive impairment (MCI) and preclinical Alzheimer's, enabling earlier intervention.

• The amyloid pathway has clear genetic clues.
People with Down syndrome have three copies of chromosome 21, where the amyloid precursor protein gene sits, make about a third more amyloid and almost inevitably develop Alzheimer's if they live long enough. Abnormal cleavage produces amyloid-beta peptides of 40 or 42 amino acids that clump; those fragments could theoretically be removed without consequence.

• APOE informs risk but isn't diagnostic.
E4 raises risk substantially, but you can carry E4 and never develop Alzheimer's, or have E2/E3 and develop it. Smith tells E2/E3 patients they have only about a 10% risk reduction relative to E3/E3 and are 'not off the hook', and tells E3/E4 or E4/E4 patients that risk is modifiable. Attia compares waiting for dementia to waiting for a heart attack: intervene on risk early.

• Behavioral symptoms affect nearly everyone with dementia.
About 90% of patients have a mood or behavioral issue at some point, such as depression, anxiety, agitation or psychosis, and caregivers need support too. Smith also spends a lot of time deprescribing: patients on 15–18 medications, like those still on three blood pressure drugs from age 50 who are now 90 and falling because their pressure is too low.

• The drug pipeline has shifted toward disease modification.
Of about 120 drugs in the pipeline at the time, roughly 29 were in phase 3, and about 80% targeted disease modification rather than symptoms, which Smith calls a watershed made possible by the 2011 redefinition. Developing one drug takes 10–15 years and about $1.3–1.4 billion. Twelve agents targeted cognitive enhancement and 12 neuropsychiatric symptoms.

• Trial design is a major challenge.
Alzheimer's trials traditionally run 18 months, because that's how long it takes for placebo patients to decline measurably; improvement rarely happens, so stability counts as success. Attia contrasts heart disease trials like FOURIER and ODYSSEY (PCSK9 inhibitors added to patients already at low LDL), arguing prevention trials in pre-symptomatic people are where the real wins will be.

• Anti-amyloid antibodies remove plaque.
Aducanumab and similar drugs clearly clear amyloid on PET; one of Smith's patients, after an anti-amyloid trial, failed screening for another trial because her scan had become amyloid negative. The aducanumab trial gave APOE4 carriers lower doses initially because of ARIA (amyloid-related imaging abnormalities) risk, later amended to allow 10 mg/kg. The FDA decision was due June 7, 2021, and families were pressing after nearly 20 years without new treatments.

• Healthy aging should be measured by function.
Smith argues outcomes should reflect what matters to patients and families, like independence and quality of life, not only test scores. She graduated from medical school in 1997, the year donepezil (Aricept) was approved, and has seen almost no new approved drugs since.

EXAMPLES

• Don't wait for the beach condo
Smith and her husband bought an old 1972 beach condo as soon as they could afford it, a lesson from patients: don't postpone the things you want to do until retirement, because cognitive decline can steal that time.

• The amyloid-negative patient
A patient whose amyloid cleared during one antibody trial was turned away from the next because she no longer had amyloid, an illustration of how effectively these drugs remove plaque, even if clinical benefit is debated.

• The over-medicated 90-year-old
Patients prescribed blood pressure drugs decades earlier keep taking them into frail old age, causing falls, a case for routinely reviewing medications.

• Attia's cardiology analogy
Waiting until someone has dementia to treat Alzheimer's is like waiting for multi-vessel coronary disease to start treating cholesterol, or waiting until 10-year risk exceeds 5%, which Attia calls equally nonsensical.

• Twenty years without new drugs
Smith notes families and patient advocates pushed hard for the aducanumab approval because, apart from symptomatic

drugs like donepezil, they had gone almost two decades without any new treatment; she sees that urgency alongside legitimate scientific debate over the drug's clinical benefit.

OTHER RELEVANT

- **Start prevention decades early.**
  Pathology begins 10–20 years before symptoms; address vascular and metabolic risk factors in midlife.
- **Use APOE as a risk tool, not a verdict.**
  Know your status if useful, but nobody is off the hook and nobody is doomed.
- **Review medications with age.**
  Ask whether every drug is still needed, especially blood pressure and sedating medications.
- **Support caregivers.**
  Behavioral symptoms are near-universal; families need help too. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Live now.**
  Don't defer meaningful experiences until later life. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#163 - Layne Norton, Ph.D.: Building muscle, losing fat, and the importance of resistance training

Guest: Layne Norton
Date: 2021-05-24 · Duration: 2:51:54
URL: https://www.youtube.com/watch?v=aRdEZIyyhJA

KEYPOINTS

• Muscle protein synthesis spikes and fades faster in trained lifters.
Norton, who earned a PhD studying leucine and protein metabolism, explains that a training session raises muscle protein synthesis by about 100–150%. The peak is similar for trained and untrained people, but in untrained people it lasts roughly 48–72 hours, while in trained lifters it returns toward baseline within about 10–12 hours and is no different by 24 hours. That argues for training muscles more frequently as you get more advanced.

• The net amount of muscle built per day is tiny.
Because muscle is about 70% water and 30% protein, Norton estimates only around 10 grams of amino acids are actually deposited in muscle per day even in favorable conditions. Turnover is large relative to net gain, which is why building muscle is slow and why consistency over years matters more than any single meal.

• Leucine was the key nutrient signal in his research.
In animal work during the mid-2000s, Norton's lab found the protein-synthesis response to a meal peaked about 90 minutes after eating and returned to baseline by about three hours, later validated in humans. Attia ties this to how leucine acts through sestrin 2 to trigger mTORC1, and asks whether leucine timing around training matters. Pure carbohydrate, even 100 grams of glucose with a large insulin response, doesn't meaningfully raise muscle protein synthesis.

• Muscle growth is mostly regulated locally, not by hormone spikes.
In the late 1990s and early 2000s, the field focused on systemic hormones—testosterone, IGF-1, growth hormone—whose levels rise for 30–60 minutes after lifting. Elegant studies, many by Stuart Phillips, suggested growth is mostly intrinsically regulated inside the trained muscle. In one Phillips study, the hormone most associated with hypertrophy was cortisol.

• Cortisol is misunderstood.
Norton argues the cortisol association likely reflects that the most stressful, hardest sessions produce the most adaptation, not that cortisol causes growth. Correlated signals can run in parallel without causing each other, a recurring theme in how he reads studies.

• Acute exercise inflammation is not chronic inflammation.
He criticized an argument from a public debate that eating meat after training 'compounds' exercise-induced inflammation, saying it confuses acute, localized inflammation, part of adaptation, with chronic systemic inflammation. Reductionist thinking about a single nutrient or pathway, like warning against leucine because it activates mTOR, misses context.

• Lose fat slowly with diet breaks to protect muscle and strength.
To cut 30 pounds while moving weight classes, Norton dieted aggressively for two to three weeks (aiming for about 1.5–2 pounds a week), then spent periods at maintenance (about 3,200–3,400 calories for him). He would spend more time at maintenance than dieting even for a small cut, and says that kept his strength.

• Lean mass is a powerful predictor of survival.
Norton cited a study finding that after age 65, lean body mass was the strongest predictor of who lived longest; Attia added grip-strength data. Norton's message: people who scroll social media for two hours but 'don't have time' to train are missing the most powerful tool for health and body composition.

• Ketogenic diets take a long time to adapt to and are not optimal for anaerobic performance.
Attia described starting a ketogenic diet in May 2011 without cutting his heavy training volume: five weeks in he was miserable, at 12 weeks his aerobic base had only just recovered, and it took 18 months to regain previous anaerobic fitness. Norton thinks aerobic work under about 60% of VO2 max is likely unaffected, and points to lifters who pull 500–700 pounds on low carbs as anecdotes, not trial evidence.

• Back pain is common and often unrelated to imaging.
Norton notes that if you MRI 100 people over 35, about half will have herniated discs without symptoms. His approach to his own back injury combined rehab with analyzing how his form broke down at heavy loads.

EXAMPLES

• From 'can't get off the floor' to world record
Norton went from being unable to move off his floor with back pain to squatting 668 pounds at about 201.5 pounds bodyweight, winning gold and setting a squat world record at the 2015 IPF World Championships. After a December 2017 flare, he took about nine months off spinal loading and in 2019 squatted 666 and deadlifted 727 pounds.

• Fasting while lifting
Attia did five-to-seven-day water-only fasts each quarter. Doing only heavy resistance training (like deadlifts every other day) during them, with longer rests, he lifted the same weight and appeared to preserve muscle, losing mainly water.

• Attia's decade of 'stable weight'
Attia weighed exactly the same in January 2021 as in May 2011, but his body fat had risen from about 7% to 16%.

• The Canadian meat and cancer cohort
In about 100,000 Canadians, high meat intake was associated with cancer, but those with the highest meat and fruit-and-vegetable intake had the same risk as low meat eaters with high produce intake, suggesting confounding by overall diet and lifestyle.

• ADHD and study habits
Norton took Ritalin and Adderall growing up, learned to study in 30–45-minute blocks, and weaned himself off medication by

graduate school.

OTHER RELEVANT

- **Train each muscle frequently if you're experienced.**
  Shorter synthesis responses in trained lifters favor hitting muscles more than once a week.
- **Use diet breaks during a cut.**
  Alternate a few weeks of moderate deficit with maintenance periods to preserve strength and adherence.
- **Prioritize protein and resistance training over hormone hacks.**
  Local muscle signaling and total protein drive growth; acute hormone spikes matter little.
- **Read studies for context.**
  Ask about confounders, populations and whether an association is causal before changing behavior.
- **Build resilience through small wins.**
  Norton's comeback came from gradual confidence-building and consistent habits rather than motivation. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#162 - Sarah Hallberg, D.O., M.S.: Treating metabolic disease, & a personal journey through cancer

Guest: Sarah Hallberg
Date: 2021-05-17 · Duration: 2:29:54
URL: https://www.youtube.com/watch?v=0e6u9JR-o6o

KEYPOINTS

• Carbohydrate restriction changed how Hallberg treated diabetes

For the first half of more than 25 years in obesity care, Hallberg, trained in exercise physiology, prescribed low-calorie, low-fat diets, the dogma of the 1980s. Patients with type 2 diabetes kept progressing on insulin and insulin-raising drugs. Cutting carbohydrates let many lower or stop medication. That eventually led her to Virta Health, which treats type 2 diabetes remotely with continuous support toward nutritional ketosis.

• Most American adults are already on the path to metabolic disease

About 10% of the US population has type 2 diabetes, and the rate is well into the teens in Hispanic, African-American and Pacific Islander populations. Recent studies suggest over 50% of adults have prediabetes or metabolic syndrome. Prediabetes means an HbA1c of 5.7–6.4%.

• Even 'normal' cut-offs are too loose

Hallberg's practice targets blood pressure under 120/80 (the CDC cut-off is under 130/80) and triglycerides under 100 mg/dL rather than under 150. Fasting glucose under 100, HDL above 40 (men) or 50 (women), and a waist under 40 inches (men) or 36 (women) round out the usual definition of metabolic health.

• Triglycerides on a lab report mostly reflect VLDL

Peter explains that most of a reported triglyceride level is carried in VLDL particles. In his example panel, triglycerides of 150 mg/dL go with a VLDL cholesterol of about 25, and he says most of those triglycerides sit inside VLDL, with some in intermediate-density lipoprotein. High triglycerides mean the liver is exporting a lot of fat.

• Dietary fat and blood fat are not the same thing

In a feeding study, participants started under 50 g of carbohydrate a day and had carbs raised every three weeks across six phases, up to 346 g. Saturated fat intake fell from about 84 g to 32 g. Yet blood levels of certain fatty acids, especially palmitoleic acid, rose as carbohydrates went up. You are not simply 'what you eat'.

• Palmitoleic acid (16:1) is an early warning sign

The liver turns excess carbohydrate into palmitic acid (16:0), and the enzyme SCD1 converts that to palmitoleic acid. Fructose via GLUT5, glucose via GLUT2 and insulin all push this pathway. Peter suggests it may be the liver protecting itself in the short term. Rising palmitoleic acid signals that carbohydrate intake is exceeding the person's tolerance.

• HbA1c flags trouble 10–20 years late

Nobody 'rings the bell' until HbA1c passes 6.5%, often a decade or two after molecular warning signs appear. Hallberg cites studies linking palmitoleic acid in childhood (the PANIC study) to later health, and a Dutch study linking levels at 50 to C-reactive protein at 70. Data in non-white populations are lacking, since most studies enrolled middle-class white participants.

• Treatment should be individualized and early

Hallberg says the only data that matter in the room are the patient's own. She also stresses that insulin is not benign: someone controlling glucose on 100 units a day is in a very different state from someone needing 20. Catching people earlier may mean they don't have to stay very low-carb forever.

• Lung cancer in never-smokers is common and often driven by specific mutations

On June 30, 2017, at 46, a fit and health-focused never-smoker, Hallberg was diagnosed with stage IV lung cancer. About 12–14% of lung cancers occur in non-smokers, often EGFR- or ALK-driven. She has an EGFR exon 19 mutation. Median survival for stage IV lung cancer is often 12 months or less, though it depends heavily on the type.

EXAMPLES

• Low-carb versus low-fat at about 1,500 calories

In a 12-week trial, the very-low-carb group's triglycerides fell from about 211 to 104 mg/dL, roughly 50%. The low-fat group went from 187 to about 150, roughly 20%, despite eating about a third as much saturated fat (12 g vs 36 g).

• 'Just 11 years'

Hallberg's children were 7, 12 and 14. First she asked to reach 50; she's now 49. Then she set a non-negotiable goal of 11 years, until her youngest graduates, even though typical survival with her treatment was 24–30 months. She and her husband used to joke about dying at 95 in a car crash on the way home from a ski trip.

• An unconventional treatment path

When Tagrisso (osimertinib) stopped shrinking the primary tumor in March 2018, it was radiated. Chemotherapy followed, then anti-estrogen therapy targeting a second mutation, then very-low-dose single agents starting with cisplatin. By fall 2019 a PET scan showed no detectable tumor.

• A near-fatal complication

Gemcitabine (Gemzar), usually considered well tolerated, triggered atypical hemolytic uremic syndrome within about four weeks. Her hemoglobin fell to the low 6s (normal is about 13–14), she needed plasmapheresis, and doctors weren't sure her kidneys would recover. She says over 70% of people with this condition die or end up on dialysis.

• A four-month delay, even for an expert

After a recurrence was diagnosed in mid-September, Hallberg, an experienced patient advocate, didn't start a clinical trial until December 30. She asks how many people without her advantages die during such gaps. That fuels her work on health equity.

OTHER RELEVANT

- **Ask for more than HbA1c**

  Track triglycerides, HDL, blood pressure, and waist against the stricter targets. Where it's available, a fatty-acid profile showing high palmitoleic acid may reveal carbohydrate intolerance years earlier. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Advocate hard, and get second opinions**

  Hallberg's outcomes depended on finding doctors willing to try unusual plans and on pushing for referrals when a recommendation seemed wrong. She warns against implying that people who die of cancer 'gave up.'

- **Spend time deliberately**

  She calls time the most important currency. She stayed in her Aspen Institute fellowship despite misgivings, makes room for an occasional 'pity party', and sees her advocacy as part of the legacy her children will remember.

#160 - Paul Offit, MD: Latest on COVID-19 vaccines and their safety, herd immunity, & viral variants

Guest: Paul Offit
Date: 2021-05-03 · Duration: 1:26:49
URL: https://www.youtube.com/watch?v=da2AuPN1ehI

KEYPOINTS

• Two vaccine platforms were in wide use by spring 2021

The mRNA vaccines (Pfizer and Moderna) deliver instructions for the spike protein. The J&J vaccine uses a replication-defective adenovirus 26 vector, which had already been given to about 200,000 people in West Africa against Ebola. More than six million US doses of J&J had been given, and more than 20 million AstraZeneca doses in the UK and Europe. Russia's vaccine used Ad26 followed by Ad5. Offit traces the lineage back to cowpox in the late 1700s and Pasteur's killed rabies vaccine about 100 years later.

• Rare vaccine side effects show up within about six weeks

Offit says serious vaccine side effects historically appear within weeks of a dose. Examples include narcolepsy from one adjuvanted 2009 pandemic flu vaccine (about 1 in 55,000) and Guillain-Barré after flu vaccine (about 1 per million). Others are vaccine-derived polio from Sabin's oral vaccine (about 1 per 2.4 million) and yellow-fever-like illness from the yellow fever vaccine (about 1 per million). That's why he discounts fears about '10 years of data' for mRNA, which cells translate into protein and can't reverse into DNA.

• Why HIV beat vaccine makers, and SARS-CoV-2 hasn't

HIV mutates its surface glycoprotein again and again within a single infection, and it grows in T helper cells, the orchestrators of the immune system. Several billion dollars, including an adenovirus-vector vaccine that may have made things worse, failed to produce an HIV vaccine. SARS-CoV-2 mutates far more slowly, more like measles, whose 1960s vaccines still work 50 years later.

• Variants so far are close enough for current vaccines

The original D614G strain killed about 570,000 Americans and is the target of every vaccine. B.1.1.7 (UK) is close enough to be covered. Offit watches whether a variant arises that natural or vaccine immunity can't touch, which would put us 'back to square one'. He thinks SARS-CoV-2 won't be a 'one and done' vaccine but needn't be yearly like flu.

• Sterilizing immunity is unlikely, but disease protection should last

Viruses with short incubation periods, like this one, let infection get started before memory B and T cells can respond. Diseases like measles, with 10–14-day incubation, can be eliminated, as measles was in the US by 2000 and rubella by 2005. Offit expects antibody levels to fall over 6–18 months, while memory cells keep protecting against severe disease for a few years, not decades.

• Get the second mRNA dose

One dose gives about 80% protection and two give 90–95%. Offit says the second dose also gives more complete immunity and more breadth against variants that have drifted from the original strain.

• Relative and absolute risk reduction were poorly communicated

When J&J was authorized, headlines compared it with Pfizer's '96%' and Moderna's '95%' efficacy. In Pfizer's roughly 40,000-person trial there were about 165 cases among 20,000 placebo recipients versus 8 among vaccinated people, an absolute risk reduction of about 0.9%. J&J's absolute reduction was about 1.7% and Moderna's about 1.2%. By absolute measures, the 'weaker' J&J vaccine looked at least as good, and all three are great vaccines.

• The J&J pause was an overreaction that chilled confidence

With about one case of cerebral venous sinus thrombosis per million doses, Offit estimates roughly 1,850 deaths prevented per million vaccinated. He understood the goal of warning doctors not to treat these clots with heparin, but believes the pause sent 'a chill' that would spill over to every COVID vaccine.

• Herd immunity needs about 80%, and hesitancy is the obstacle

Offit estimates 22–30% of Americans had been infected and that about another 120 million people needed full vaccination. Surveys then showed about 30% of Christian evangelicals refusing, and about 14% of Black Americans saying they definitely wouldn't get vaccinated. He expected vaccines approved down to age 12 soon and to age 6 by early the next year.

EXAMPLES

• Michigan's surge without a death surge

Cases rose but deaths didn't, because about 55–57% of over-65s were fully vaccinated and about 75% had at least one dose. People over 55 account for about 92% of deaths. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Why a healthy 50-year-old should get vaccinated

Offit points to long-term neuropsychiatric complications, reported in up to a quarter of patients 6–12 months out. He also notes about 500,000 Americans can't be vaccinated because of chemotherapy or biologic drugs, and depend on everyone around them.

• Polio as an analogy

Only about 1 in 200 polio infections caused paralysis, so silent spread was rampant, as with COVID. The US hasn't seen natural polio since the 1970s because children are still vaccinated.

• Testing failure

The viral sequence was known by January 2020. By the time US testing problems were sorted out, South Korea had run about 500,000 tests versus fewer than 5,000 in the US. The US has about 4% of the world's population and about 20% of its COVID deaths.

OTHER RELEVANT

- **Judge vaccine safety by timing and scale**
  Most rare harms appear within six weeks, and well over 100 million US doses by then had revealed no rare serious mRNA signal at that point. Use that framework rather than 'it's too new'.
- **Interpret efficacy numbers carefully**
  Compare vaccines on outcomes that matter (hospitalization, death) in similar settings. Use absolute risk reduction and number needed to vaccinate (100 ÷ 1.7 is about 60 for J&J against any illness in its trial) alongside relative efficacy.
- **Prepare for the next pandemic**
  SARS (2002), MERS (2012) and SARS-CoV-2 came within about 20 years. Offit urges stockpiles of protective equipment and ventilators, and global vaccine capacity, since 'we're only as strong as our weakest nation.' Peter and Offit also weigh the natural-spillover and lab-leak theories of the virus's origin.

#159-Peter Hotez MD, PhD.: The anti-vaccine movement, causes of autism, & COVID-19 vaccine update

Guest: Peter Hotez
Date: 2021-04-26 · Duration: 2:08:58
URL: https://www.youtube.com/watch?v=eAD0XIYd-Bs

KEYPOINTS

• The anti-vaccine movement survives by moving the goalposts.
Hotez, a vaccine scientist and pediatrician at Baylor, dates the modern movement to Andrew Wakefield's 1998 Lancet paper linking the MMR vaccine to autism. As each claim was refuted it shifted: to thimerosal, then to vaccine spacing, then aluminum, then vague 'chronic illness' and HPV-vaccine infertility claims. He calls these versions 1.0, 2.0 and 3.0; the autism thread never fully disappeared.

• The Wakefield claims collapsed, but slowly.
By around 2007–2008 nearly every Wakefield claim had been debunked, and the Lancet retracted the paper in about 2010 after an earlier expression of concern. Attia stresses that open discussion won't dissuade the roughly 20% firmly convinced vaccines are evil; Hotez's goal is helping undecided parents.

• Thimerosal was removed before the autism hypothesis gained steam.
Thimerosal, a preservative in multi-dose vials that contains ethylmercury (not the more toxic methylmercury), was proposed in 2001 as an autism cause. Hotez notes its removal from childhood vaccines was already underway around 1999, and that the 2001 hypothesis was reasonable to raise at the time—it just didn't hold up.

• Spacing out vaccines has no supporting evidence.
Hotez says he isn't aware of data showing a benefit from delaying or spreading vaccines, and there are no trials supporting alternative schedules, while delays leave children unprotected during their most vulnerable months.

• The Hib vaccine shows how dramatic a vaccine's impact can be.
As a pediatric resident at Massachusetts General in 1987–88, Hotez admitted a child with Haemophilus influenzae type b meningitis every couple of weeks. A conjugate vaccine attaching the bacterial capsule to a protein produced infant immune responses and was licensed in 1989; Hib meningitis became rare.

• HPV vaccination is cancer prevention.
Several high-risk HPV strains, including 16 and 18, cause cervical and other cancers. Australia expects to eliminate cervical cancer by 2030 through vaccination. Attia, father of a 12-year-old girl, walks through a parent's instinct to wait until 18 and why vaccinating before any exposure gives the best protection.

• Autism begins in fetal brain development, not after vaccines.
Hotez's daughter Rachel was diagnosed at 19 months; full clinical expression often appears around 18–24 months, which is why vaccines given then are falsely blamed. Brain changes are detectable in infancy (a UNC Chapel Hill group) and prenatally (Eric Courchesne's group at UCSD), and the Broad Institute has identified about 100 autism-linked genes involved in early fetal brain development, many in neuronal communication.

• Genetic testing explains only a portion of cases.
Whole-exome sequencing finds a relevant mutation perhaps 30–40% of the time, reflecting non-coding and other factors. Hotez thinks rising prevalence (figures around 1 in 54–62 were discussed) mostly reflects broader diagnosis and longer survival; he's seen no convincing evidence of a true rise in incidence, though it is hard to prove.

• Vaccine hesitancy has become politicized.
Starting around 2014–2015, the movement allied with 'health freedom' politics on the far right, after California tightened exemptions following a measles outbreak tied to Disneyland. A PBS/NPR/Marist poll found about 41% of white Republicans saying they wouldn't get a COVID vaccine, matching his Texas A&M collaborators' findings.

• Early-2021 COVID vaccines all performed well, with variant caveats.
Pfizer's adolescent (12–15) trial had about 1,200 per arm, with 18 COVID cases in the placebo group and none vaccinated, high but small numbers. The B.1.1.7 variant (N501Y substitution) was covered well; the South African variant reduced protection, with AstraZeneca showing about 10% efficacy against mild-to-moderate disease. Hotez expected J&J might become two doses and boosters to be needed.

• Global vaccine supply is the next crisis.
With 1.1 billion people in sub-Saharan Africa and 650 million in Latin America, Hotez feared the world had little for them. His team adapted their SARS/MERS work into a low-cost recombinant-protein COVID vaccine produced in yeast, like hepatitis B, scalable to around 100 million doses a month.

EXAMPLES

• Measles in the Somali community
In 2017, after anti-vaccine town halls Wakefield attended in Minnesota, MMR coverage in the Somali immigrant community fell from over 90% to about 40%, and an outbreak sent around 21 children to the hospital.

• Orthodox Jewish communities in 2018–2019
Similar targeting in Brooklyn and elsewhere led to an outbreak with about 50 hospitalizations and 18 ICU admissions; Hotez notes measles' reproductive number of 12–18 makes it the 'canary in the coal mine'.

• 'COVID is a hoax' last words
Hotez cited an ICU nurse describing a dying patient whose last words were that COVID-19 was a hoax, illustrating how fringe health-freedom messaging went mainstream.

• Rachel's gene
Whole-exome sequencing of Rachel and her parents at Baylor Genetics identified a mutation in a neuronal spectrin gene, a

cytoskeleton gene consistent with early brain development.

- **Hepatitis B vaccine as a low-risk benchmark**
  Discussing infant hepatitis B shots, Hotez described it as about as low-risk as vaccines get: a recombinant protein produced in yeast, used for almost four decades in hundreds of millions of children with an excellent safety record. Attia framed the question for parents as what, exactly, they lose by vaccinating.

OTHER RELEVANT

- **Don't delay or space vaccines without evidence.**
  Alternative schedules lack supporting data and prolong vulnerability. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Consider HPV vaccination before exposure.**
  Vaccinating around ages 11–12 maximizes protection against cancer-causing strains. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Address hesitancy with empathy.**
  Hotez and Attia focus on undecided parents who need clear explanations, not on the committed minority.
- **Understand autism's timing.**
  Signs appearing around 18–24 months reflect prenatal brain development, not recent shots.
- **Watch for the same claims recycled onto new vaccines.**
  Hotez noted that anti-vaccine groups largely copy-pasted older assertions onto COVID-19 vaccines; recognizing recycled arguments helps separate genuine new safety signals, which the scientific community does investigate, from repackaged ones.

Q&A on Zone 2 Exercise with Peter Attia, M.D.

Date: 2021-04-21 · Duration: 0:55:48
URL: https://www.youtube.com/watch?v=txLrNhv8GW0

KEYPOINTS

• Attia defines Zone 2 by lactate, not by heart-rate percentages

Wearables define zones as percentages of maximum heart rate, so a Garmin's 'Zone 2' (60–70%) doesn't match his. Attia uses blood lactate as a proxy for when your effort exceeds what your mitochondria can handle. Zone 2 is the highest output you can sustain while keeping lactate at or below about 2 mmol/L. He stresses that this is the definition he uses personally and with patients, following Iñigo San Millán.

• Why it matters: mitochondrial function declines with age

Attia believes Zone 2 is the most important intensity for training mitochondria. Since mitochondrial deterioration is a hallmark of ageing, anything that delays it should help. The more Zone 2 you do, the better you are at both insulin-dependent and insulin-independent glucose uptake, which makes for very efficient glucose disposal.

• Dose depends on your starting fitness

A deconditioned person might manage only 30 minutes three times a week, at an exertion so low it feels like nothing. Elite cyclists can spend 20–24 hours a week in Zone 2. Attia recommends at least three sessions a week (he does four). Iñigo San Millán thinks 45 minutes is about the minimum per session, so three 45-minute blocks beat daily 20-minute ones. Start at 30 minutes if you're new to the activity.

• Do Zone 2 before strength work, and stay in the zone

If both are in one session, do Zone 2 first so cardio doesn't eat into your strength goals. Drifting into Zones 3–5 changes the stimulus, which is why Attia rides indoors where he can control his output. He admits riding indoors is boring, but says the control is worth it.

• Watts per kilogram is the number to track

Attia thinks everyone should know their Zone 2 power in watts per kilogram, and care about it as much as VO2 max or deadlift strength. People with type 2 diabetes can have a Zone 2 threshold as low as 1 W/kg, while the fittest reach about 4 W/kg and are extremely carbohydrate-sensitive. Holding 3 W/kg for 45 minutes on any machine is very good.

• His training spans two extremes

He trains almost only in Zone 2 and Zone 5, occasionally Zone 6, with almost no time in Zones 3 or 4, because he doesn't race. He is optimising for metabolic health. High-intensity interval training (HIIT), he argues, is overrepresented in research because it's easy to study: a four-minute Tabata twice a week is a simple 'pill' to give. That doesn't make it a substitute for Zone 2.

• Heart-rate formulas are starting points

MAF (180 minus your age) and 80% of your true maximum heart rate are reasonable starting estimates, but they aren't the same thing. For Attia, 180 minus his age comes out about 8 bpm lower than his measured Zone 2. To use a percentage you need your actual maximum, for example from a carefully done Bruce protocol, the 21-minute cardiac stress test.

• Zone 2 sits well below FTP

In power-based training every zone is a percentage of functional threshold power (FTP), which sits in upper Zone 4. So app-based zones built on FTP won't line up with a lactate-defined Zone 2, and you should calibrate with a lactate meter or your perceived effort.

• Metformin appears to lower Zone 2

In Attia's experience with himself and patients, metformin consistently lowers Zone 2 thresholds. On and off the drug he sees a 15–20 W difference. Whether that matters is unknown. A study of non-diabetic people led by San Millán at the University of Colorado, delayed by COVID, is meant to look at it.

• Anecdotes: better deep sleep and post-workout carb tolerance

He has seen no data on heart rate variability (HRV), but many patients with Oura rings report deep sleep rising from 45–60 minutes to about 90 minutes a night. After Zone 2, Attia can eat a couple of hundred grams of glucose with barely a rise in blood sugar. Both observations are anecdotal.

EXAMPLES

• Attia's own fitness

When he restarted a few years earlier, his Zone 2 was only about 170–175 W. By this Q&A it was 215–220 W, and he was aiming for about 240 W (3 W/kg) the following year.

• The cost of lactate testing

The meter cost about $250 and the strips about $4 each ($100 for 25), roughly $16 a week. One reading of 2.1 mmol/L showed he was slightly over. Another at 1.4 told him to trust how he felt.

• Zone 2 on a treadmill

Use an incline and a brisk walk instead of running on the flat. Start around 6% incline and 3 mph, hold steady for at least 15 minutes before checking, and leave about 15 minutes between changes. Attia once used roughly a 15% incline at under 4 mph.

• His swimming years

He once swam 27,000–28,000 yards without stopping. He held exactly the same split for every 500 yards so he only had to count five-hundreds.

• Finding the steady state

At 175 W, checking every 10–15 minutes, lactate may read 1.5 at 15 minutes and creep towards 2 by the end. True steady state usually arrives 30–45 minutes in. Test while still riding, because lactate clears within about a minute of stopping.

OTHER RELEVANT

- **Retest as you get fitter**
  Zone 2 power rises with training, so reassess every few months.
- **Without a meter, start with an estimate and adjust**
  Begin at MAF or 80% of your measured maximum heart rate, then adjust based on how sustainable the effort feels.
- **Watch what you eat before Zone 2**
  Anecdotally, Attia says a high-carb meal slightly impairs his Zone 2 and he tires earlier, perhaps because it suppresses the release of fatty acids. Experiment with fed versus fasted sessions.
- **Choose a machine where you can control your output**
  A bike, rower or stair climber lets you hold a precise intensity.
- **Prioritise specific training when time is short**
  Attia now does almost no Zone 1. With 12–14 hours a week to train, he wants every session to be specific.

#158-Brian Deer: A tale of scientific fraud—Andrew Wakefield & the belief that vaccines cause autism

Guest: Brian Deer
Date: 2021-04-19 · Duration: 2:04:25
URL: https://www.youtube.com/watch?v=icJtTHgR_Ds

KEYPOINTS

• The MMR–autism scare grew from one researcher's fixation on measles.
Deer, the investigative journalist who exposed Andrew Wakefield, traces the story to the late 1980s. Wakefield, trained as a surgeon, observed early whole-bowel transplant attempts at Toronto General Hospital, then moved into research. Influenced by the AIDS era's search for infectious agents, he theorized that Crohn's disease was a disease of the gut's blood supply caused by an infection, and settled on measles virus.

• Wakefield clung to his hypothesis when others couldn't replicate it.
In 1993 he published in the Journal of Medical Virology claiming measles in Crohn's tissue using immunohistochemistry. About two years later a Japanese group using PCR, the more specific emerging gold standard, couldn't find it. Wakefield argued PCR missed it, yet later switched to PCR himself when it suited the MMR claims, which Deer sees as evidence the conclusion came first.

• The research was set up to serve a lawsuit.
Lawyer Richard Barr, building a case against MMR manufacturers, hired Wakefield in early 1996. In June 1996 they applied to the Legal Aid Board, a government fund that paid for people suing drug companies, and the grant application promised PCR findings before any child in the eventual paper was investigated. Deer says none of this was known until his Sunday Times investigation.

• The 1998 Lancet paper was a 12-child case series—and the format wasn't the problem.
Published in February 1998 in one of medicine's top journals, it reported that parents of eight of 12 children (two were brothers) said symptoms began within 14 days of MMR. Attia and Deer note case series are legitimate: Crohn's disease was characterized from 14 patients, autism from 11 children at Johns Hopkins, and AIDS from five men in Los Angeles in 1981. The issue was what was misrepresented.

• The children were pre-selected through the litigation network.
None of the 12 lived in London; the nearest was about 60 miles away and some were 280 miles. Many came via a campaign group whose founder, Jackie Fletcher, had a child who became Wakefield's 'sentinel case'. Autism had only recently become a formal diagnostic category in the early 1990s.

• Not one child's case was accurately reported.
When Deer obtained the medical records, some children's developmental issues predated vaccination, others began months after, not within 14 days, and some reported diagnoses didn't match. The sentinel case's mother admitted in court papers that her child showed no issues for nine months after vaccination.

• PCR is powerful, but past about 35 cycles a 'positive' is unreliable.
Each PCR cycle doubles the target, so 35 cycles means up to about 2^35 copies. Because the method is so sensitive, contamination produces signals at high cycle counts; a negative is almost certainly negative, while a late positive is uncertain. Attia notes reporting cycle thresholds matters: positive at 20 versus 30 cycles reflects a very different starting amount.

• At the epicenter of the fraud were manipulated machine outputs.
Biopsies went to a lab in Dublin run by John O'Leary, using an ABI Prism 7700, certified as a research tool and not for clinical diagnosis. Its 96-well trays held samples, positive measles controls, distilled water and empty wells. After drug companies' lawyers obtained the data through the London and Irish High Courts, an expert, Stephen Bustin, found wells the machine had read as positive reported as empty and empty wells reported positive—manual changes that made results fit Wakefield's thesis.

• Wakefield's own scientist found nothing.
A second set of samples went to Wakefield's researcher Nick Chadwick, who froze them in liquid nitrogen; testing found no measles virus. Chadwick later left science, Deer believes partly from disillusionment.

• The consequences came late but were decisive.
A General Medical Council hearing ran for 217 days, longer than O.J. Simpson's trial, costing about £10 million. Wakefield lost his license and the Lancet retracted the paper in 2010. The litigation consumed roughly $100 million in today's money and never reached trial.

• Autism's diagnostic history made it easy to misattribute.
Deer stresses that autism is a construct—a checklist diagnosis clustering signs and symptoms—rather than a disease with a single lesion like Crohn's. Formal categories from the American Medical Association and World Health Organization arrived only in the early 1990s, so diagnoses were rising just as Wakefield's network went looking for vaccine-injured children.

EXAMPLES

• The children's ordeal
Deer describes children taken from home for bowel preparation, colonoscopy into the small intestine, lumbar punctures and multiple blood draws without proper ethical review; one child later in the series suffered catastrophic damage from the procedure, leading to a large settlement.

• Corporate fraud comparisons
Attia compared the manipulated results to Enron's books and Volkswagen's rigged emissions tests, arguing the behavior was as nefarious, even if its perpetrators claim they believed MMR caused autism.

• Lawsuits as a weapon
Wakefield sued Deer in the UK and then sought to freeze the case; he later sued in Texas over Deer's BMJ series, which let

Deer use further documents.

- **Fact-checking the book**
  Johns Hopkins University Press checked Deer's manuscript against about 2,000 footnoted references.
- **The Wellcome Trust connection**
  After Toronto, Wakefield took a post at the Royal Free medical school in Hampstead, north London—which Deer calls third-rate at the time—while still funded by the Wellcome Trust, giving his unusual theories a respectable institutional base.

OTHER RELEVANT

- **Judge research by its underlying data.**
  Deer's lesson: a paper's text can't be fully trusted; records, raw outputs and controls reveal the truth.
- **Look for financial and legal conflicts.**
  Wakefield's undisclosed litigation funding shaped the study design long before publication.
- **Understand what a test result means.**
  High-cycle PCR positives and research-only instruments need cautious interpretation.
- **Remember the real victims.**
  Attia stresses parents still wonder whether they harmed their children; the evidence says MMR did not cause autism.

#156-Jake Muise: Humanely harvesting axis deer while alleviating its impact on Hawaii’s ecosystems

Guest: Jake Muise
Date: 2021-04-05 · Duration: 2:33:49
URL: https://www.youtube.com/watch?v=Fy1dMjULbXo

KEYPOINTS

• Axis deer are an invasive species reshaping Hawaii.
Muise, founder of Maui Nui Venison, explains that in 1868 King Kamehameha V had the deer brought from India, with the first animals arriving on Oahu and then Molokai. By 1898 newspapers estimated 7,000 deer already decimating upland forests. Lanai received deer in the 1920s and Maui in the 1960s, and private individuals secretly introduced them to the Big Island around 2010–2011.

• Their reproduction produces 'hockey stick' growth.
Gestation is about 238 days, similar to humans, and the population can grow roughly 33% a year. Of the roughly 15,000 animals Maui Nui has harvested and measured, about 89% of females were lactating or pregnant at harvest. Maui's population, about 60,000, is still emerging and could peak around 210,000; Molokai holds roughly 60,000–70,000 deer alongside about 7,000 people.

• Hawaii's deer densities dwarf the mainland's.
Muise says the densest US deer states have about six deer per 100 acres; established Hawaiian areas have about 25, at least three times higher. Lanai is roughly in balance at about 20,000 animals; Molokai is past capacity, with deer crowding roadsides.

• The deepest damage is to watersheds.
Native Hawaiians equated water with wealth, and the islands' layered forests capture fog and rain into aquifers. Native plants evolved without hoofed grazers, so deer strip the understory, worsening erosion and sediment runoff when big rains come. Downhill, they compete with cattle at roughly seven deer per cow, a herd of about a thousand can wipe out 10 acres of lettuce overnight, and they hop six-foot fences.

• Axis deer are among the hardest animals to approach.
Their senses are so acute that getting within 100 yards requires doing everything right, and even inside 50 yards they can dodge an arrow. Muise ties this to evolving alongside tigers in India.

• Field harvest at night under USDA inspection is the core innovation.
Maui Nui built its process around the 1930s-era Federal Meat Inspection Act, with an inspector present at night using thermal optics so precise the bullet appears as a tracer. Animals are assessed before harvest at up to about 200 yards; if they stand calmly, unstressed, the process proceeds. A brick-and-mortar plant is asked to operate at about 95% efficiency; Muise says they run at about 99.99%.

• Humane standards mean deliberately missing.
Shooters target a small zone in the brain and train to miss 30% of the time—a perfect night is 70% efficiency—and the miss is always high so no animal is wounded. New shooters are expected to shoot at about 50% to widen the safety margin, using a .308 at about 100–200 yards.

• No stress at harvest changes the meat.
Attia notes stressed animals produce cortisol and lactate that affect wild-game taste. With unstressed animals, rigor mortis proceeds gradually over 16–24 hours as glycogen converts and pH shifts, avoiding the color and texture changes of stressed meat.

• Venison tested as an exceptional protein source.
A typical axis deer is about 60 pounds whole carcass and yields about 50 pounds for human use, with hides, hooves and organs used too, including in pet food—Maui Nui's starting business. In testing Muise described, their venison came out about 33% higher in protein per ounce than the best regenerative beef.

• Total eradication isn't possible; managed balance is.
Aerial surveys let them manage density precisely, for example bringing one ranch from 6,000 to 2,000 deer. Muise says no deer left by 2030 is technically impossible, and recreational or subsistence hunting can't match commercial-scale harvest.

• Tracking collars revealed what the deer actually eat.
Maui Nui fitted satellite telemetry video collars that recorded in 10-second increments for 48 hours, showing the deer's diet directly. The footage confirmed what harvest data already suggested: the animals eat almost anything, including native plants that evolved no defenses against grazing, which is why their effect on forest regeneration is so severe.

EXAMPLES

• The Big Island hunt
Muise and partner Mike tracked deer secretly dropped in a 70-square-mile area, walking 12 hours a day, deploying camera traps and flying aerial thermal surveys covering about 10,000 acres an hour. The helicopter pilot who dropped the deer was sentenced to 300 hours flying with them. After three years they were confident they had the last one in that area.

• Airlifting cattle from lava
A fast lava flow about 500 yards wide trapped ranch animals. Over a week or two of missions they slung 40–50 cattle, including 2,000-pound bulls, on a 100-foot line beneath a helicopter.

• Volleyball to Molokai
A Canadian raised 14 hours north of Edmonton on moose meat, Muise came to Hawaii on a volleyball scholarship, hit a vertical leap above 40 inches, played professionally in Europe and missed the Olympic team by one spot.

• Feeding Hawaii during COVID

With food banks empty and tourism collapsed, Maui Nui donated about 50,000 pounds of venison, over 100,000 meals.

- **Returning to meat**
  People who hadn't eaten meat for 20 years have written to say they chose Maui Nui venison because of its humane harvest.
- **Skipping long shots to harvest more**
  Carrying a 200-pound buck over rough terrain from 200 yards leaves shooters exhausted, so the team learned they could harvest more animals per night by passing on deer beyond 200 yards—a lesson Muise says took thousands of animals to learn. Attia admits he couldn't carry his own buck for the first stretch.

OTHER RELEVANT

- **Ethical meat can serve conservation.**
  Harvesting invasive deer protects watersheds, native species and farms while producing food.
- **Stress at slaughter affects quality.**
  Calm, instant harvest improves meat texture and taste. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Consider nose-to-tail use.**
  Using organs, hides and trim reduces waste and adds nutrition.
- **Look for data-driven management.**
  Muise credits nightly tracking of proficiency rates and aerial counts for precise, humane population control.

#155 - Chris Sonnenday, M.D.: The history, challenges, and gift of organ transplantation

Guest: Chris Sonnenday
Date: 2021-03-29 · Duration: 2:30:17
URL: https://www.youtube.com/watch?v=fiDggmQgtJE

KEYPOINTS

• Transplantation is a young field

The first kidney transplants were done in the 1950s, and the first liver, heart and lung attempts in the 1960s. Chris Sonnenday, a transplant surgeon at the University of Michigan who trained with Attia at Johns Hopkins, notes that when they were residents in the 1990s, much of today's practice had been operational for only about a decade. Much of his current work was invented in the 1990s and early 2000s.

• The first successful kidney transplant avoided the immune system

Joseph Murray performed it in 1954 at what is now Brigham and Women's Hospital, between identical twins, and later won the Nobel Prize. Michigan's first kidney transplant, in 1963, was also between twin sisters; the programme recently celebrated its 5,000th. In the 1960s and 1970s, some published series reported patient mortality of 50–70% after kidney transplantation, not just graft loss.

• Cyclosporine was the turning point

Matching by blood type and the HLA system helped, but one-year graft survival was still only about 60–70% with the best regimens of the time. Cyclosporine, a fungal compound that Sir Roy Calne showed prevented rejection in preclinical models, interferes more selectively with T-cell activation after an antigen is presented. Both men agree its spread through the 1980s and early 1990s is what made transplantation work.

• A transplant beats dialysis within months

For similar patients, the survival curves for dialysis and transplantation cross within about 90–250 days, even counting surgical risk and the start of immunosuppression. After that, dialysis 'loses'. Dialysis only became widely funded through a rider to the Medicare legislation.

• Living-donor kidneys outperform deceased-donor kidneys

Deceased-donor organs go through brain death or circulatory death, cold storage, transport and 6–72 hours of ischaemia. Living donation is an elective operation in side-by-side operating rooms. The laparoscopic donor nephrectomy, pioneered at Hopkins by Louis Kavoussi and Lloyd Ratner, made donating easier, and US volume grew to about 18,000–20,000 kidney transplants a year.

• Paired exchanges widen access

A willing but incompatible donor can swap with another pair. Swaps began in the 1990s and took off in the 2000s. Sonnenday describes a recent day when he and a colleague each removed a donor kidney, both kidneys were shipped to other institutions, and two kidneys came back that afternoon for their own recipients. Donor and recipient operations are now completely decoupled. Attia raises the catch: trading a healthy young kidney for a 75-year-old's isn't an equal exchange.

• Paying for organs remains unresolved

Organ donation has been treated as a gift, grounded in donor autonomy. The worry about an open market is that it could coerce economically disadvantaged people into selling organs. Sonnenday calls it a frequently debated, never-resolved question.

• Attia wants kidney decline caught early

Rising prediabetes and metabolic syndrome are driving chronic kidney disease. A GFR in the low 40s may be acceptable in someone in their early 70s, but Attia argues that blood pressure of 130/85 is 'not really acceptable'. It could take someone from a GFR of 95 to 85 in a decade, which he considers too steep a decline.

• Organ allocation and the line around death

Organs are coordinated by 58 organ procurement organisations (OPOs). Geographic variation has fallen, so the sickest patients get transplanted quickly wherever they live. That system, which Attia found unjust 20 years ago, is fairer now. But 'medium-sick' patients wait behind sicker ones, which shows the need for more donors. Death must be declared by a separate team, using brain-death criteria or tests showing blood flow to the brain has stopped. Otherwise organ procurement could be seen as hastening death.

• Liver transplant indications are shifting

Hepatitis C, often acquired in the 1970s and silent for decades, dominated liver transplants for about 20 years. Old drugs worked in only 15–30% of patients, and the virus always recurred after transplant, but it is now curable. Fatty liver disease (NAFLD/NASH) is predicted to become the leading indication by around 2030. Alcohol-related liver failure has also exploded, often in people in their 20s and 30s.

EXAMPLES

• The 2007 Lake Michigan crash

In June 2007 a Michigan team flew to Milwaukee to procure lungs. Their plane crashed into Lake Michigan after take-off, and all six on board died: two pilots, two perfusion staff, a cardiac surgeon and a fellow. Sonnenday uses it to show how many people each transplant depends on.

• The Webster family's gift

Jeff and Tina Webster donated every organ of their 21-year-old son Aaron after a Jeep rollover. They later got to know the recipients. More than 100,000 people are on US waiting lists, and only about 40,000 or fewer transplants are done each year.

• Tylenol and acute liver failure

Attia recalls a 21-year-old who overdosed on Tylenol after a break-up. He notes its lethal dose may be only about 10–20 times a normal dose.

- **The baboon experiment**
  Mel Williams' story from Hopkins: to treat acute liver failure, a baboon's liver was connected to a patient's circulation to filter toxins, and the baboon was put in a body cast because it couldn't easily be sedated. Every attempt at external liver support has failed so far.
- **Taking responsibility in morbidity and mortality conference**
  Attia recalls a case missed on a day when '35 things' were happening. At the review conference, Sonnenday shouldered it as a team failure instead of blaming individuals. He still holds that blame has no value and only system improvement does.

OTHER RELEVANT

- **Register as an organ donor and tell your family**
  Families decide in the worst moment. Knowing your wishes makes it easier.
- **Treat early kidney decline as actionable**
  Control blood pressure and metabolic health long before you reach dialysis territory.
- **Respect acetaminophen doses**
  The gap between a normal dose and a dangerous one is narrow. Keep within label limits, watch for it in combination products, and keep large supplies out of reach of anyone at risk.
- **For a kidney transplant, explore living donation**
  Living donation and paired exchanges give better outcomes than waiting for a deceased donor.

#154 - Steve Levitt, Ph.D.: Climate change, mental health, the ethics of experiments, and more

Guest: Steve Levitt
Date: 2021-03-22 · Duration: 2:13:35
URL: https://www.youtube.com/watch?v=kGZi3OxitKk

KEYPOINTS

• Microeconomics with real data is where the action is.
Levitt, the University of Chicago economist and Freakonomics co-author, came to economics through a Harvard intro course and took only one math class there. He considers macroeconomics too hard a problem for its models, and says the Clark Medal has gone mostly to people combining theory with messy data through econometrics in the last 20–30 years.

• Agree on the facts before arguing about the models.
Levitt's rule: first establish the three, five, nine or twelve facts that any reasonable person looking at the data would accept, then build models on them. Data alone rarely establish causation, except in randomized experiments, which are rare in economics. He'd like debates to start with each side listing ten facts they believe, to see whether disagreement is about facts or implications.

• Climate change is unlikely to be solved by behavior change alone.
Revisiting SuperFreakonomics, about ten years on, Levitt says its point was that asking billions to change behavior is a weak strategy. He and Attia point to smoking: even after the Surgeon General's report around the 1960s, with risk ratios around 14 times, it took roughly 40 years for smoking to fall substantially.

• Geoengineering deserves serious study.
The book described an untested plan in which about 10,000 GPS-guided, solar-powered dinghies spray seawater to seed reflective clouds over dark oceans. Levitt says nearly everyone now expects geoengineering to be part of the solution, though such ideas are short-term relative to a real fix.

• Run a 'Manhattan Project' for climate.
If president, Levitt would gather the 1,000 smartest scientists somewhere like Los Alamos for five years to look for a cheap solution such as carbon sequestration. He argues it's insurance: a few hundred million dollars is trivial next to government spending and to the potential payoff.

• Small risks of catastrophe justify large payments.
Standard economic models surprised him: people should pay perhaps 10–15% of their wealth to avoid a 1% chance of death, and around 50% to avoid a 5% chance (numbers he called ballpark), because death is final. That changed his view on how seriously to treat climate tail risks.

• Blurring climate science with advocacy undermines trust.
Levitt says the backlash to their climate chapter came from all sides partly because of conflating objectives, strategies and tactics, which he lists among humanity's big failures, and because people react to how results are portrayed rather than what was written.

• Mental health deserves a 'common core' in schools.
Raised by a no-nonsense father who saw therapy as embarrassing and crying as forbidden, Levitt came to value mental health through parenting. He'd have the Department of Education mandate a mental-health curriculum alongside math, while letting school districts experiment to find what works.

• Most bad decisions are failures to act.
Levitt says 99 of his 100 worst decisions were about inaction; Attia says his were the opposite. Behavioral economics over the last 40–50 years shows how poorly people decide, and Levitt's best 'decision' was to stop caring what people think.

• Ethics rules block learning that would save lives.
Levitt argues the US should have run COVID challenge trials, and that basic questions like the origin of the six-foot distancing rule went unexamined. He supports a regulated, high-priced market for living kidney donors, since dialysis costs a measurable share of GDP and a price set well above market would avoid exploiting the poor; he imagines millions signing up.

• Chicago taught him to engage with his intellectual opponents.
Despite loving Cambridge, Levitt chose the University of Chicago because presentations there drew such different questions; he went 'to get to know the enemy.' Gary Becker, among the most influential economists of the past 50 years and widely demonized, turned out to be brilliant, curious and a real mentor. Levitt now worries that macroeconomics has narrowed into what Chicago looked like 40 years ago, losing diversity of thought.

EXAMPLES

• The 25-hour interview
Stephen Dubner interviewed Levitt for about 25 hours over three days. Levitt asked him nothing for the first 24.5 hours, then asked who else he'd written about, and their partnership began.

• Naming Freakonomics
After terrible title ideas, Levitt's sister produced ten better ones in half an hour and insisted on Freakonomics. The publisher, having paid a lot, fought it for months. Levitt thinks 99 times out of 100 the book wouldn't have succeeded.

• Abortion and crime
Their most expected controversy, legalized abortion leading to less crime about 18 years later, was misportrayed in the media; one paragraph on child car seats drew about as much negative feedback.

• Secretariat's heart
In 1973 Secretariat won the Belmont by about 31 lengths, a time still unmatched. A vet who later autopsied runner-up Sham estimated Secretariat's heart was at least 15% larger, perhaps twice normal size, a trait linked to the X chromosome.

- **His daughter's anorexia**
  Levitt approached his daughter's eating disorder with unusual calm, which he thinks helped her feel comfortable with him; he credits her for almost all of her recovery.
- **The golf experiment**
  Levitt took up golf seriously around 40. For a planned chapter, Attia proposed spending real money to bring a 20-handicap golfer down to a five within 12 months; the coach they found turned out, Levitt jokes, to have the worst student ever, since Levitt barely did the work.

OTHER RELEVANT

- **Separate facts from interpretation.**
  In disagreements, list the facts each side accepts first.
- **Treat tail risks seriously.**
  A small chance of catastrophe can justify substantial prevention spending.
- **Bias toward action.**
  If your regrets are mostly things you didn't do, lower the bar for trying.
- **Practice language-free observation.**
  Inspired by Sam Harris's Waking Up, Levitt tries to experience the world through his senses without words, like peeling a potato without naming it, and finds it reduces the grip of negative emotions.

#152 - Michael Rintala, D.C.: Principles of Dynamic Neuromuscular Stabilization (DNS)

Guest: Michael Rintala
Date: 2021-03-08 · Duration: 1:44:56
URL: https://www.youtube.com/watch?v=y6OALVINgqI

KEYPOINTS

• DNS grew out of the Prague School of Rehabilitation.
Rintala, a San Diego chiropractor and one of about 18 international DNS instructors, traces the method to the 1950s Prague School at Charles University's medical faculty. Behind the Iron Curtain its three founding neurologists—Vladimír Janda, Karel Lewit and Václav Vojta—relied heavily on observation and palpation for diagnosis and treatment.

• Each founder contributed a piece.
Janda, who had post-polio effects himself, described postural habits in which certain muscles tend toward tightness and others toward weakness, and linked these patterns to where imaging shows the most degenerative and disc changes—accumulated rather than traumatic. Vojta studied motor development in the first 12 months of life and used it to help children with cerebral palsy form motor patterns around brain lesions.

• Pavel Kolá ’ GW&æVB F†W6R –FV 2 –çFò G–æ Ö–2 æWW omuscular Stabilization.
Kolá ’Â v†ò uns the rehabilitation department in Prague, began applying developmental kinesiology to athletes in the late 1990s and early 2000s, including javelin thrower Jan Železný and hockey player Jaromír Jágr. Through the early 1990s the Prague School's work was mainly rehabilitation for cerebral palsy and the general population.

• The diaphragm is a postural muscle, not just a breathing muscle.
Picture the trunk as a cylinder: the diaphragm is the top (attaching to the lower ribs, the xiphoid and around L1–L2 at the thoracolumbar junction), the pelvic floor the bottom, and the abdominal wall the sides. When the diaphragm descends it creates intra-abdominal pressure; the pelvic floor and abdominal wall load eccentrically 'like wind blowing into a sail,' then hold that pressure to stabilize the spine.

• How you generate pressure matters.
Lifting 300 pounds requires abdominal pressure, but DNS favors an 'inside-out' strategy—pressure loading the abdominal wall, followed by an interplay of concentric, eccentric and isometric work—over relying on concentric bracing alone. When the deep system can't create a fixed point through the trunk and pelvis, the brain compensates with overactive superficial muscles.

• Infant development is a blueprint for ideal movement.
Around three months, maturation lets genetically ingrained motor programs coordinate the deep stabilizers. Milestones follow: rolling to the side around seven months, oblique sitting around eight, crawling around nine, kneeling at 10–11, squatting about 12, standing at 13–14 and walking about 14–16 months, with variation (Rintala's son walked at 10 months). He cites an observation that about 70% of infants mature normally while the rest sit on a spectrum toward pathology.

• Modern childhood interrupts that process.
Shoes too early, propping devices and walkers, then six or seven hours a day in school chairs, can disrupt alignment between the pelvic floor and thoracic diaphragm. Postural habits that follow undermine pressure management and force transfer through the spine.

• Most low back pain is chronic overload, not injury.
Outside trauma like a car crash or fall, Rintala sees inefficient deep stabilization paired with overactive flexors and extensors, producing hinging at the lumbosacral region—'like bending a spoon' repeatedly—until passive structures such as discs and facet joints give way. Attia notes roughly 80% of people will experience back pain.

• Train inside your functional threshold.
The functional threshold is the load at which you can keep quality stabilization; beyond it lies the 'functional gap,' where bracing strategies get the job done at the cost of efficiency. Athletes live in that gap, and poor programs or overtraining keep them there, risking long-term stability.

• Adherence is the biggest limitation.
Of 100 athletes in pain, Rintala estimates only 10–20% stay with the program until better, partly due to access to one-on-one care. DNS requires slow practice, such as relearning to breathe, which Attia frames as efficacy versus effectiveness: it may work when practiced, but must be stuck to.

• Eccentric and concentric loading both matter.
Rintala defines concentric loading as a muscle shortening under load (the lifting phase of a biceps curl) and eccentric as lengthening under load (the lowering phase). Neither is 'right'—they serve different purposes, and more eccentric emphasis tends to drive hypertrophy—but most people train the concentric and neglect the eccentric. In DNS, eccentric loading of the pelvic floor and abdominal wall is central to stabilization.

EXAMPLES

• Rintala's own spondylolysis
Premature at birth, overtraining with poor recovery, he developed a pars stress fracture in college; his L4–L5 region gave way, starting a chronic pain cycle that led him to Kolá ’ &÷VæB # c# à

• Long careers at the top
Železný, holder of the javelin world record of 98.48 meters, had a roughly 20-year career; Jágr was still playing at 48. Kolá ’w2 work with them emphasized awareness and quality over quantity.

• Roger Federer and PGA golfers
Rintala points to Federer and well-coached tour players as athletes who stay within their functional capacity while still pushing performance.

- **The 89-mph fastball**
  At the other end of his practice are uninjured athletes seeking performance—like a pitcher stuck at 89 mph who needs a better 'whip' between hand, opposite leg and hip; Major League Baseball increasingly integrates DNS.
- **An infant's hands-to-mouth task**
  Placed on their back with hips and knees at 90 degrees and ankles neutral, a healthy infant can bring hands together and to the mouth. Attia notes most adults take this for granted, but it requires a stable trunk as a fixed point; observing whether an adult can reproduce such positions reveals stabilization gaps.

OTHER RELEVANT

- **Relearn diaphragmatic breathing.**
  Practice breathing that expands the lower trunk in all directions as a foundation for stability.
- **Build quality before load.**
  Increase strength thresholds only once you can maintain stabilization; pair DNS with a coach's strength program.
- **Move from rehab to prehab.**
  Once out of pain, keep practicing developmental positions to prevent recurrence.
- **Reduce prolonged sitting for kids and adults.**
  Varied positions help preserve the pelvic floor–diaphragm alignment that supports the spine.
- **Find trained practitioners.**
  DNS certification has clinician, trainer and pediatric tracks, the last culminating in Prague; video and hands-on teaching beat verbal explanation.

#151 - Alex Hutchinson, Ph.D.: Translating the science of endurance and extreme human performance

Guest: Alex Hutchinson
Date: 2021-03-01 · Duration: 2:31:55
URL: https://www.youtube.com/watch?v=LRlpoMjaHK0

KEYPOINTS

• A mistaken split time showed Hutchinson how much the brain limits performance.
A Canadian 1500-meter runner stuck at around 4:01–4:03, Hutchinson heard a timekeeper at an indoor meet in Sherbrooke, Quebec call his first 200 meters at 27 seconds—about five seconds faster than four-minute pace. Believing he was having an amazing day, he ran 3:52. The split was wrong (he'd actually run about 30). Afterward he didn't revert: he ran 3:49, then 3:44, qualifying for the Olympic trials.

• The central governor model reframed endurance limits.
Around 2007–2008 Hutchinson found a Journal of Physiology debate on Tim Noakes's 'central governor' idea: we slow down not because muscles can't go faster but because the brain applies the brakes before we push dangerously far. Once fringe, it connected to his Quebec breakthrough and became the core of his book Endure.

• VO2 max is engine size, and it's normalized by weight.
VO2 max measures maximal oxygen use, often expressed per kilogram (sometimes scaled to weight to the power 0.68–0.7 to approximate lean mass). Hutchinson's peak was 5.2 liters, about 70 ml/kg/min. What limits it—heart, lungs, blood or muscle—is debated because each can be the bottleneck in different circumstances.

• A higher VO2 max isn't always better.
Norwegian cyclist Oskar Svendsen started at 74 ml/kg/min, then 83, 85, 92, and was reported at 97.5 in December 2012, though verified values were lower and weight gain pulled a later test from about 96 to 89. A later reanalysis found he was most efficient when untrained; as VO2 max rose, his efficiency fell, using more oxygen for the same power. He retired back at about 77.

• Attia would have trained Svendsen differently.
Attia argues he'd have put far more volume into zone 2—just under 2 mmol of lactate, perhaps around 300 watts for him—to build mitochondrial efficiency, accepting a VO2 max of 85–90 that might have made him a better cyclist.

• The sub-two-hour marathon came from optimizing everything.
Hutchinson's 2014 Runner's World article noted the record was 2:02:57 by Dennis Kimetto, versus 2:06:50 by Belayneh Dinsamo in the late 1980s. Optimized courses, pacers, weather timing and new shoes let Eliud Kipchoge run 1:59:40 in an unofficial event; the official record then stood at 2:01:39. He compares the shoe controversy, especially 2016–2019, to swimming's tech suits banned around 2009.

• Training, not equipment, explains most mile progress.
Roger Bannister broke four minutes in 1954 training about half an hour a day, for example 10 x 400 meters. By the 1960s Jim Ryun ran 3:51 as a teenager on enormous volume, such as 40 x 400; adjusting about four seconds for cinder tracks puts him near today's American record of about 3:46.8. The world record is about 3:43, and fewer people have broken four minutes than have climbed Everest.

• A small exercise dose captures much of the benefit.
A Cooper Clinic study of about 50,000 people suggested 5–10 minutes of running a day, roughly an hour a week, yields large benefits. Hutchinson doesn't fully believe it and thinks optimal routines add high-intensity work and strength, while 'nothing is good for you if you push it far enough.'

• Aerobic decline with age is punctuated, not smooth.
Tables show about 9% loss per decade, but individual losses come in drops: a week of bed rest can cost about 7% of aerobic capacity with only about 2% regained, and months off after injury are worse. Avoiding injury and inactivity may let people hold on better than once thought. Attia reverse-engineers the VO2 max and muscle he'll need at 90.

• Most 'all-out' intervals aren't truly all-out.
In a Tabata (20 seconds hard, 10 seconds rest, eight times—named after Izumi Tabata, who didn't design it), people subconsciously pace; Attia now caps all-out efforts at 10 seconds. Researchers moved to 60 seconds on, 60 off because people accept it more readily; protocols as short as four seconds exist but require total commitment.

EXAMPLES

• The 800 as the most painful race
Hutchinson's friends called the 800 meters the worst; Attia compares it to the 200 individual medley in swimming—about two minutes of all-out effort.

• Physics and running
He did a three-year PhD in semiconductor physics (1997–2000), sometimes working 12–16-hour lab days and leaving for runs, before turning to journalism after one last shot at the Olympic team in 2004.

• The Hayward Field mile
After a knee injury kept him out from 1998 to 2001, he ran a mile at Hayward Field in Oregon in about 4:06; he never broke four minutes in his only two career miles, a regret.

• Headline fatigue
Attia says nothing annoys him more than friends forwarding a health headline without a question; Hutchinson's column moved from Runner's World (2012) to Outside (2017) to provide better context.

• The hypoxia experiment Attia wants to see
Attia proposed running athletes to max while progressively lowering inspired oxygen from 21% to 20%, 19%, 18% and below: if the lungs aren't the limit, the absolute oxygen extracted should stay the same. Hutchinson explains why such debates persist—

heart, lungs, blood and muscle can each be the bottleneck under different conditions, so every camp has evidence.

- **Bjørn Dæhlie's rumored VO2 max**
  The Norwegian cross-country skier reputedly tested around 96 ml/kg/min in the late 1990s, but it was never published; Hutchinson notes extreme values spread easily and verified numbers rarely exceed the high 80s.

OTHER RELEVANT

- **Test your perceived limits.**
  Hutchinson's breakthrough suggests some ceilings are mental; well-designed challenges can reveal more capacity.
- **Build efficiency, not just VO2 max.**
  Zone 2 work improves how much power you produce per unit of oxygen.
- **Include intervals in a healthy routine.**
  Hutchinson recommends some high-intensity work for nearly everyone, alongside aerobic base and strength.
- **Protect against long layoffs.**
  Avoid injuries and prolonged inactivity, which cause steep, partly irreversible drops in fitness.
- **Know what you're training for.**
  Plan backward from the capacities you want in your 80s and 90s.

#150-Senator Bill Frist, MD: A modern Renaissance man's journey through science, politics & business

Guest: Bill Frist
Date: 2021-02-22 · Duration: 2:23:51
URL: https://www.youtube.com/watch?v=xkqDebPOfJ4

KEYPOINTS

• Bill Frist's career has had three or four acts, all of them about health

Frist trained at Princeton and Harvard Medical School, then learned transplant surgery at Stanford under Norman Shumway. He built the largest transplant programme east of the Mississippi at Vanderbilt, was elected to the US Senate in 1994 having never held office, and became the 18th Senate Majority Leader in 2002. Later he moved into private equity and education. He describes roughly ten-year cycles of learning and delivering, and sees them as 'all the same thing'.

• Heart transplantation succeeded through patience, not bravado

Shumway spent about 10 years in the lab working out the science before operating on people. Christiaan Barnard, whom Frist calls more opportunistic, did the first transplant in South Africa in 1967. Around 1968–69, competing Texas surgeons did roughly 110 heart transplants 'Texas style', and nearly all the patients died. Most programmes shut down, while Shumway kept doing 10–15 a year and working out why patients died.

• Cyclosporine changed the odds

When cyclosporine, a drug discovered by chance in a fungus, was added around 1982, mortality fell from perhaps 50% to 20%. Frist says about 80% of his heart recipients lived at least five years, and those who got past that often lived 10–30 years. Some of the people he transplanted 28 years earlier were still alive.

• Building a programme required an institution willing to cover early risk

At Vanderbilt, with no heart transplant programme in Tennessee, the institution agreed to cover his first 10 transplants if insurance wouldn't. Donor hearts were the bottleneck: he had 50–60 people coming in but could transplant only one every four or five days.

• Physicians used to fill the Senate

Frist says about 24 or 25 physicians served in the Senate in its early decades. The number roughly halved every 50 years until none had been elected since 1928. He argues physicians bring a habit of listening to 20 patients a day. Arriving in a chamber of 63 lawyers turned out to be an advantage.

• Frist opposes term limits

Attia finds term limits appealing. Frist initially did too, but now calls them 'a huge mistake' for the Senate because the job is complicated and institutional memory matters. As the most junior senator (100th in seniority), he relied on colleagues who had served 18–24 years. His physician father told him to replace the 'Honorable' nameplate with 'Dr. Bill Frist': senators rent the office, they don't own it.

• PEPFAR was one of the largest health interventions in history

George W. Bush, who had never been to Africa, announced the President's Emergency Plan for AIDS Relief in the 2003 State of the Union. Only Frist and perhaps five or six others knew in advance. US spending rose from about $200 million a year to $3 billion in the first year, and roughly $60 billion over time, in Attia's words. Frist credits Bill Clinton's later work on the issue.

• He changed his position on stem cells, guided by principles

A 1996 amendment banned federal funding of embryonic stem-cell research (the cells were discovered in 1998). Frist, who is pro-life, backed Bush's 2001 limit on existing cell lines. He then laid out 10 principles in 2000 and again in 2005 to expand funding with ethical guardrails, such as stopping women from being paid to create embryos for destruction. His 2005 bill was vetoed, but he says those principles now govern the field.

• The Terri Schiavo case shows the clash between law, ethics and technology

She collapsed in 1990 and was left in a persistent vegetative state. She had no living will, and her husband and parents disagreed. In 2003, five court-appointed doctors split 3–2 on whether she was vegetative or minimally conscious. Frist's bill guaranteed federal review, 'a process, not an outcome'. The courts declined the petition and the feeding tube was removed. Many call it his biggest mistake; he says he'd probably pass the same bill.

• The pandemic warnings went unheeded

In 2005, citing the 1918 Spanish flu, Frist said a pandemic was a question of when, not if, in about 20 speeches. He notes that bioterror agents can be made in an 8-by-12-foot room. His biggest disappointment is that the brief non-partisan unity after 9/11 hasn't been matched since, and he blames misinformation on social media and cable TV for much of the polarisation.

EXAMPLES

• The Cooley–DeBakey rivalry

Denton Cooley and Michael DeBakey were brilliant surgeons with huge egos in the same city, Houston. They were early to heart transplantation but abandoned it after the deaths.

• A rapid rise

Frist went from 100th in seniority to Majority Leader in about six years. He calls it 'crazy', a feat Lyndon Johnson also managed. As NRSC chair he oversaw the 2002 midterms, when Republicans 'won big' despite the usual midterm swing against the president's party, a result he partly attributes to the shift after 9/11.

• Education after Africa

After about 20 trips to Africa, Frist focused on K–12 education. He says Tennessee has improved dramatically over the decade since.

• Access to palliative care

Good palliative care is available near major centres, but 30–100 miles away, families with a declining relative often can't get it.

OTHER RELEVANT

- **Write an advance directive now**
  Schiavo's case turned on having nothing written down. Frist and his wife did theirs 12 years before this interview.
- **Bring disciplined iteration to hard problems**
  Shumway's lab-first patience outlasted rivals who rushed to operate. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Value institutional memory**
  Ask long-serving colleagues what things were like 20 years ago before trying to reinvent the system.
- **Prepare for pandemics in calm times**
  Political capital for preparedness shows up after a crisis, and that is when to spend it.

#148 - Richard Miller, M.D., Ph.D.: The gold standard for testing longevity drugs: the ITP

Guest: Richard Miller
Date: 2021-02-08 · Duration: 2:14:25
URL: https://www.youtube.com/watch?v=g8bXYKeeWnc

KEYPOINTS

• The Hayflick limit sent aging research down a side road
Normal human cells in culture divide about 50 times and then stop. Miller says many excellent cell biologists spent their careers on this 'Hayflick system' believing they were studying aging. He thinks it has little to do with why organisms age.

• The key question is whether aging can be slowed, and it can
Before the 1990s many believed aging 'is what it is.' Cynthia Kenyon's 1993 daf-2 work in C. elegans showed that single genes (daf-2 resembles the IGF receptor, daf-16 resembles FOXO) can greatly extend lifespan. That came the same year a Nature paper argued no single gene mutation could do so. Miller argues that aging is at least partly a single process a drug might slow, not a 'spaghetti bowl' of 30–50 separate ones. He once had a friendly fight about this with George Martin.

• The ITP is built for statistical power and generality
The Interventions Testing Program runs each drug at three sites: Jackson Labs, Miller's lab in Michigan and Randy Strong's lab at UT San Antonio. Each year each site has 50 males and 50 females per drug and 100 controls of each sex. That's enough to detect a roughly 8–10% lifespan change with 80% power. Anyone can suggest a compound, and a steering committee, advised by five outside scientists, chooses.

• Genetically heterogeneous mice are the point
About 90% of mouse research uses a single inbred genotype, usually 'Black 6', where every mouse is identical. In the ITP's four-way cross, no two of the more than 20,000 mice are the same, though any two share half their genes. Results are more likely to generalize. The NIA stopped supplying such mice for lack of demand.

• Rapamycin works even when started late, in both sexes
In the second cohort (started 2005), 90–95% of oral rapamycin was destroyed in the stomach. Reformulating it with a coating took a year, so treatment began at 19–20 months, roughly a 60-year-old human. By then 15–20% of males had already died. Rapamycin still extended lifespan strongly in both sexes and remains the only drug with a very strong effect in females. Peter cites 90th-percentile lifespan gains of about 9% in males and 14% in females.

• Acarbose and canagliflozin probably work by blunting glucose spikes
Acarbose, suggested by David Allison and Daniel Smith as a calorie-restriction mimic, blocks starch digestion and works mainly in males. Canagliflozin, an SGLT2 inhibitor, also blocks peak glucose and also extends life mostly in males. That supports the view that cutting post-meal glucose peaks, not eating less, is the mechanism.

• 17-alpha-estradiol helps only males
This weak, non-feminizing form of estrogen extended male lifespan, and Peter and Miller compare a 14.4 ppm dose with a lower one. In another lab, males started at 16 or 20 months got stronger muscles and better glucose tolerance; females didn't. Female mice already outlive males, and their estrous cycles stop around 8–11 months.

• Negative results are valuable
Resveratrol failed at doses about 3–10 times higher than in David Sinclair's original paper (Miller wasn't sure of the exact multiple). Green tea extract, curcumin and methylene blue also failed. Miller notes that drinking enough wine to match the mouse dose would take about 600 bottles a day. No ITP drug has significantly shortened lifespan.

• Starting late and measuring the tail are tougher, fairer tests
Starting a drug when 35–40% of animals have already died asks a lot of it. Miller considers age at the 90th percentile of survival more informative than percentage change in median lifespan, because it shows whether a drug delays death in already-old animals. Rapamycin, 17-alpha-estradiol and acarbose all still work when started in middle age. In rapamycin mice, tissue changes in organs such as the adrenal gland resembled those of younger controls.

• Metformin's failure in mice isn't the final word
Metformin alone didn't extend lifespan in the ITP; it worked only when paired with rapamycin, which may just be the rapamycin. Miller lists reasons: mice and people are organized differently, it was tested at one dose with continuous dosing, and a different dose or schedule might work. Observational data showing diabetics on metformin outliving non-diabetics justify the human TAME trial, he says.

EXAMPLES

• Aspirin in the first cohort
Aspirin was among the first four ITP compounds, along with NDGA and nitroflurbiprofen. It was given at a dose approximating a human baby aspirin. It initially showed a male benefit that didn't replicate. NDGA has worked three times, but only in males.

• Hydrogen sulfide donor SG1002
Suggested by a colleague, it increased median male lifespan by about 14% with a 9% maximum extension, and did nothing in females. About 80% of ITP mice die of cancer, a third of it hematologic, whereas humans mostly die with atherosclerosis.

• 'Statistics shopping'
Of a compound reported elsewhere to help male mice, Miller suspects the authors tried the standard log-rank test, failed, then picked a test that weights early deaths and got p = 0.046.

• Nicotinamide riboside
Tested at the supplier's suggested dose (the company agreed to publication either way), NR didn't extend lifespan. The team also couldn't show consistent NAD changes in brain, muscle or heart, possibly because NAD turns over in seconds to minutes.

OTHER RELEVANT

- **Use acarbose as a targeted tool, with caution**

  Peter says he has used about 100 mg of acarbose as a 'cheat meal drug' before pizza to blunt glucose spikes. Too much causes GI distress.

- **Weight evidence by sex, dose and timing**

  Many ITP effects are sex-specific and dose-dependent. A single dose and schedule that fails isn't proof a drug can't work, and a single mouse result isn't proof it will in humans.

- **Aim for realistic gains**

  Miller and Peter see nothing that suggests immortality, but a 10–15% improvement in human lifespan and healthspan would be a remarkable achievement.

#147-Hussein Yassine, M.D.: Deep dive into the “Alzheimer’s gene” (APOE), brain health, and omega-3s

Guest: Hussein Yassine
Date: 2021-02-01 · Duration: 2:06:30
URL: https://www.youtube.com/watch?v=2tH6P00RhFY

KEYPOINTS

• The brain is an energy-hungry, lipid-rich organ behind a tight barrier.
Yassine, a USC physician-scientist studying APOE and brain lipids, notes the brain is about 2% of body weight but uses roughly 20% of the body's energy. Astrocytes take up glucose and fat to fuel neurons, and microglia, immune cells, clear debris such as amyloid. About 40% of the brain's fatty acids are polyunsaturated—DHA, EPA and the omega-6 arachidonic acid.

• Brain glucose uptake runs through GLUT1, not insulin-driven GLUT4.
Muscle glucose uptake via GLUT4 responds to insulin, exercise and body weight, but the blood-brain barrier relies mainly on GLUT1, which the brain regulates to protect itself: it lowers GLUT1 in chronic high blood sugar such as type 2 diabetes and raises it in prolonged fasting. Yassine says APOE4 makes GLUT1 less effective at the barrier.

• APOE regulates the speed of lipid traffic.
Unlike apoB, a structural protein of lipoproteins, APOE and apoC3 regulate how quickly particles are processed and cleared, including remnants of dietary chylomicrons. APOE4 binds the LRP1 receptor, expressed at the blood-brain barrier, more tightly than E3 or E2. Its multiple roles in the periphery and the brain make it hard to study.

• APOE4 is the ancestral variant, shaped by diet and infection.
E4 is the oldest isoform; Attia cites E3 appearing roughly 50,000 years ago and E2 roughly 10,000 years ago. Yassine's view is that E4 was strongly protective against inflammation when humans faced parasites and sepsis, and thrived on a meat- and fish-rich diet in Africa. Migration to Europe and plant-based farming may have pressured it, favoring E3 and E2.

• The Alzheimer's link was found at Duke around 1988–89.
Allen Roses's group found Alzheimer's patients had substantially more APOE4, though the variant had been known since the 1960s. Two copies raise Alzheimer's risk about 12-fold; one copy raises it about two- to fourfold. E2 is protective, which makes E2/E4 carriers harder to classify.

• APOE4 alone may not be sufficient for disease.
APOE sits on chromosome 19 in a region with about 20–30 co-inherited genes, such as TOMM40 and apoC1, which can modify risk. In one dataset Attia examined, healthy E4 carriers had risk barely above non-carriers, while E4 with diabetes was much higher. Yassine cautions that APOE4 itself promotes insulin resistance with age, so it may help cause the diabetes rather than simply interact with it.

• Americans eat little DHA, but supplement trials are inconsistent.
US intake of DHA averages about 100 mg a day, which may not supply enough to the brain. Yet supplement studies conflict, products vary in production, concentration and quality, and most trials last only three months to a year, too short for brain outcomes.

• REDUCE-IT versus STRENGTH shows how trial design shapes answers.
REDUCE-IT gave 4 grams of pure EPA to high-risk people with high triglycerides, inspired by Japanese data, and cut cardiovascular events, but its mineral-oil placebo drew criticism that the placebo may have raised risk. STRENGTH used a mostly EPA mix with some DHA versus corn oil and found no difference. Possible explanations include placebo, dose, EPA:DHA ratio, or participants without a deficiency; almost 80% had type 2 diabetes.

• Young E4 brains crave DHA; older ones lose access.
When Yassine's team infused labeled DHA into 35-year-old E4 carriers, their brains took up omega-3s avidly. But somewhere between 55 and 70, E4 brains' ability to capture DHA from blood declines—alongside GLUT1 failure and blood-brain-barrier breakdown—suggesting a critical window for prevention.

• DHA failed in mild Alzheimer's, especially for E4 carriers.
In a large 2010 JAMA trial led by Joseph Quinn, 2 grams of DHA for 18 months in patients aged 65–80 with mild Alzheimer's had no overall effect. On reanalysis, E4 carriers showed no response while non-carriers appeared to improve on cognitive scores. DHA builds synapses; EPA acts more as an anti-inflammatory signal.

• Early-life DHA matters most while the brain is growing.
Yassine notes that large studies in the 1990s linked low DHA in infancy—via formula or diet—to poorer school outcomes, prompting the FDA around 2001–2002 to allow DHA in infant formula. Brain growth slows considerably between ages 6 and 12–13, after which lipid pools are relatively stable. What happens between 6 and 60 is elusive: no large study shows that 35-year-olds eating no omega-3s are in a disease state.

EXAMPLES

• The PreventE4 trial
Begun in 2019 and slowed by COVID, it gives high-dose DHA (about 2 grams, based on pilot data that E4 carriers need more) to cognitively healthy 55–70-year-olds; results were expected around 2024–2025. Yassine admits that age range may already be too late, but trials in 35-year-olds would take decades.

• DHA kinetics
Blood levels plateau after three to six weeks of maximal supplementation and clear within three to six weeks of stopping, while DHA stays in neuronal membranes far longer, consistent with the brain's need for stable lipid pools.

• The cPLA2 enzyme
Yassine's lab found cPLA2, which strips fatty acids from membrane phospholipids, hyperactivated in E4 brains with Alzheimer's compared with E4 carriers who died without it.

- **Exercise and amyloid**

A PET imaging study from John Morris's team at Washington University found E4 carriers who exercised had less amyloid plaque than sedentary carriers—epidemiology, not proof.

OTHER RELEVANT

- **Eat fatty fish at least once a week.**

Yassine doesn't think evidence supports supplements yet; epidemiology suggests E4 carriers eating one serving of fatty fish weekly may supply enough omega-3s to the brain.

- **Control blood pressure.**

A Swedish analysis found education and hypertension control protected E4 carriers from dementia; much of E4's risk runs through blood vessels.

- **Exercise throughout life.**

Even modest activity is a modifiable lever on E4 risk. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Know your genotype in context.**

APOE4 raises risk but isn't destiny; neighboring genes, diabetes and lifestyle shape outcomes.

#146 - Guy Winch, Ph.D.: Emotional first aid and how to treat psychological injuries

Guest: Guy Winch
Date: 2021-01-25 · Duration: 1:57:40
URL: https://www.youtube.com/watch?v=TNMyGoS5dP0

KEYPOINTS

• We treat physical injuries reflexively but ignore emotional ones

Guy Winch, a New York psychologist in practice for nearly 30 years and co-host of 'Dear Therapists' with Lori Gottlieb, wrote 'Emotional First Aid'. He was annoyed that every home has a medicine cabinet but none has a psychological one. He argues that failure, rejection, guilt, loneliness and low self-esteem are injuries that worsen when untreated, just as a wound gets infected.

• Our instincts for emotional injury are evolutionarily young

Every animal worries about physical injury, but caring for emotional injury depends on language, which may be only about 50,000 years old. Winch's conclusion is that we don't have another 5,000–50,000 years to work it out, so the skills need to be taught deliberately.

• Rumination is replaying, not thinking

Rumination feels productive ('something's troubling me and I'm thinking about it'), but it is an emotional hamster wheel. Research suggests two to three minutes of a task that needs concentration, such as a memory task or a puzzle, is enough to make the urge pass. Then reframe the worry as a problem to solve. 'I have so much work' becomes a scheduling problem, and putting it in your calendar eases both the stress and the urge to ruminate.

• Guard rails between work and home matter most

Winch calls this the most important step. Choose a time, say 7, 8 or 9 p.m., after which you're off, tell everyone, and build rituals of transition: change out of work clothes, put on music, change the lighting, and get into 'ten-year-old mode' with your kids or romantic mode with your spouse. You have an obligation to show up mentally for the people at home.

• Change the habit rather than medicating rumination

Winch says referring a ruminating patient to a psychiatrist straight away often skips the real fix. The habit sets you up to ruminate, so changing it is more effective than suppressing the symptoms.

• Most complaining is venting, and venting makes you feel powerless

Research from customer service shows that about 95% of people with a complaint about a product never raise it, because it seems too hard. Instead they tell 12–16 people about it. Retelling a story of being wronged without acting on it reinforces a sense of victimhood. Complaining used to be transactional: if the blacksmith fitted the horseshoe wrong, you went back.

• Social comparison can make success invisible

Winch says that on any metric he could name, he could find 10 people better than him in 30 seconds. He sees patients who went from nothing to $20 million but don't feel successful because a peer made $50 million. Attia admits he struggles to acknowledge any achievement, such as shaving a lap from 1:16 to 1:14 after months, before moving the goalposts.

• Positive affirmations can backfire

Positive affirmations are a multi-million-dollar industry. Research shows that generic ones ('I am going to be a great success') help one specific group but harm those with low self-esteem, the very people they target. The statement doesn't feel believable, so it reminds them how much they feel like failures. Useful affirmations are believable, hopeful and goal-setting, and too long for a fridge magnet.

• A good therapist retells your story so that you're no longer stuck

In a first session, Winch listens and then tells the story back with a different account of why you feel stuck and what to do. Attia compares it to being shown an onion and seeing it has 12 layers.

• The pandemic changed how organisations see emotional injury

Winch says it moved the dial more than anything else because few people escaped stress, grief, loneliness or relationship strain. Organisations that would never have contacted him now ask for talks; one was to 7,000 front-line health workers. Therapists are already full, so online interventions for loneliness and anxiety are being studied as a way to scale.

EXAMPLES

• Getting stuck in a lift

On a hot July night, his neighbour, an ER doctor, panicked when their lift stalled. Winch heard himself mock him, so out of character that he realised his own stress was out of control.

• A visa deadline

On a J-1 visa, he had five years to finish a PhD whose average completion time was eight years, plus 18 months of practical training. The pressure gave him panic attacks, including in libraries. He also cut back from 50–60 hours a week of clinical work.

• Fourteen years unpaid

He wrote screenplays for 14 years without publishing a word or being paid, until one was optioned for a second time in 2008. Those years taught him to take opportunities when they come. When his first book stalled in early 2011, his agent told him to sell a second one before the paperback came out, so he put everything else aside.

• Attia's 47 affirmations

During three weeks of residential therapy (about 10 hours a day), Attia was asked to write one affirmation for each year of his age. He couldn't write two for most of it, then wrote all 47 in one sitting after a breakthrough. The point was that he had to believe them.

• 'Emotional First Aid' found its audience

His first book, 'The Squeaky Wheel', did poorly in the US but sold in 12–15 countries. 'Emotional First Aid' is in 27 languages.

OTHER RELEVANT

- **Interrupt rumination, then turn it into a task**
  Do two or three minutes of something demanding, then rewrite the worry as a problem with a next step in your calendar.
- **Set an 'off' time and a transition ritual**
  Change your clothes, the music and the lighting, so your brain registers that work is over.
- **Complain to whoever can fix it**
  Skip the 12–16 retellings. Make a clear request to the person who can act on it.
- **Use believable affirmations**
  Write your own, specific, hopeful statements rather than slogans that contradict how you feel.
- **Measure progress against yourself**
  Comparing yourself with peers finds someone better every time. Acknowledge a finished goal before setting the next.

#144 - Phil Maffetone: Optimizing health and performance through maximal aerobic function

Guest: Phil Maffetone
Date: 2021-01-11 · Duration: 1:22:19
URL: https://www.youtube.com/watch?v=VrTPk4avbMs

KEYPOINTS

• Maffetone's methods came from treating injured runners.
Phil Maffetone, a clinician, coach and author since the 1980s on exercise, sports medicine, biofeedback and nutrition, began seeing patients during the 1970s running boom, when local 5K, 10K and marathon runners kept getting hurt. His question was why, and by the mid-1980s he was working with professionals in most sports and spending summers in Boulder, where many endurance athletes trained.

• Fit is not the same as healthy.
Crossing the finish line of the 1980 New York City Marathon, Maffetone realized many athletes were fit but unhealthy: fast, yet injured, sick, or burned out. Fitness and health are separate and need to be balanced, whether you're a grandmother walking four or five times a week or a professional training for the race of your life. He designed tools like the MAF test for ordinary people first.

• VO2 max doesn't predict performance well.
Despite an academic grounding in VO2 max testing (a method dating back to the 1920s) and the 220-minus-age max heart rate formula, Maffetone found that the aerobic system's development at sub-maximal intensities better explains endurance performance and health.

• The 180 Formula sets your MAF heart rate.
Start with 180 minus age, a number with no physiological meaning on its own, then adjust: subtract 10 if you're on medication or recovering from major illness, subtract 5 if you've been injured, regressing, getting frequent colds or are just starting back, and add 5 if you're a competitive athlete progressing without problems. The hardest part, he says, is being honest.

• The formula came from watching gait.
Maffetone observed athletes on treadmills at heart rates of 120, 130 and 140 and saw gait irregularities appear at a certain point. He matched those observed thresholds to athletes' ages and tweaked the numbers into the 180 formula. In the early days he had just three heart monitors in his office and rotated them between athletes.

• The MAF test tracks aerobic progress.
Run at your MAF heart rate and record pace over time. Someone starting at a 9:00 mile at 130 bpm might progress to 8:30 and then 8:00 at the same heart rate. Maffetone keeps people at their number rather than nudging it up to 132–133 bpm, because cheating usually means being back where you started two months later.

• Faster sub-max pace raises max pace.
As aerobic speed improves at MAF heart rate, race performances improve too, even though races like a 10K (around 30 minutes for elites, 32–34 for strong recreational runners) are run well above MAF. Attia asks whether the evidence supports that link; Maffetone says his clinical experience consistently shows it.

• Fat-burning capacity matters, and diet shapes it.
Attia once measured a max fat oxidation of 1.73 g/min just below VO2 max, and later learned world-class athletes on very low-carbohydrate diets hit 2.1–2.2 g/min. Maffetone calls insulin resistance 'carbohydrate intolerance' because people relate to it more easily, and notes tolerance varies between people and declines with age; Attia's own fell from his teens into his late 20s and 30s.

• The two-week test probes carbohydrate tolerance.
Patients remove junk food and sharply cut even natural carbohydrates (lentils, beans, rice, fruit, juice) for two weeks, then reintroduce them gradually while watching symptoms, weight and energy. It's a self-experiment, not a permanent diet.

• Low-carb diets and high intensity are debated.
They discuss a four-week study putting athletes on under 10% carbohydrate, and whether low-carb diets impair anaerobic performance. Maffetone thinks most endurance work is aerobic, so fat adaptation pays off, while acknowledging limits at the highest intensities.

• Being 'overfat' is widespread.
Maffetone uses 'overfat' for excess body fat that impairs health and performance, including in normal-weight people. Reducing it through diet and aerobic training improves both health and racing.

EXAMPLES

• A six-day race
Maffetone helped an athlete through a six-day race, with a strategy along the lines of walking 18–20 hours and sleeping 4–6 a day; it was exhausting for him too because he had to be awake longer than the athlete.

• The 1:59 prediction
In his 2014 book 1:59, Maffetone predicted a sub-two-hour marathon, an idea he'd floated half-jokingly in the 1990s. In October 2019, Eliud Kipchoge ran 1:59:40 in a non-record-eligible event, after an earlier attempt just over two hours.

• Peak marathoners are older than you'd think
Maffetone argues a runner might have only about 12 truly world-class marathons over 15 years, and that the ideal sub-two runner may be in his mid-to-late 30s, combining earlier 10K speed with a deep aerobic base; he has worked with remarkable 40-year-olds.

• A disastrous 5K
As a track runner, Maffetone jumped into a 5K and it went terribly, an early lesson in how different aerobic and anaerobic

demands are.

- **One-use heart monitors**

  Maffetone recalls that once athletes had felt what a 130 or 150 heart rate was like, he assumed they could reproduce it without a monitor; in practice, without the device it never happened once.

OTHER RELEVANT

- **Calculate and respect your MAF heart rate.**

  Use 180 minus age with honest adjustments and do most easy training at or below it.

- **Retest monthly.**

  Track pace at MAF heart rate; plateaus or regressions signal overtraining, illness or stress. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Balance life stress with training load.**

  Someone working 60 hours a week with three kids shouldn't train like a professional. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Try the two-week test.**

  Use it to find your personal carbohydrate tolerance, then reintroduce natural carbohydrates one at a time, noticing which ones bring back fatigue, cravings, bloating or weight gain; tolerance can change over the years, so revisit it.

#143 - John Ioannidis, M.D., D.Sc.: Why most biomedical research is flawed, and how to improve it

Guest: John Ioannidis
Date: 2021-01-04 · Duration: 1:52:11
URL: https://www.youtube.com/watch?v=gzLANQ7xkD8

KEYPOINTS

• Evidence-based medicine is young.

John Ioannidis, a Stanford physician-scientist trained in mathematics and medicine, describes a field that until recently ran on expert opinion. He met Thomas Chalmers, a pioneer of randomized trials and meta-analysis, in 1992, about five years before Chalmers died, and credits him with showing how to weigh evidence systematically.

• Most published research findings are probably false.

His 2005 paper (close to 10,000 citations, though not his most cited; the PRISMA statement for meta-analyses has more) argued that with small studies, small effects, flexible analyses, bias and many teams chasing the same question, a nominally significant finding at p just under 0.05 has a high chance of being a red herring.

• Significance thresholds should be stricter.

Ioannidis supports using $p < 0.005$ instead of 0.05 for new claims, noting most scientists are trained 'statistics light'. Large databases can produce astronomically small p-values (10^{-100}), so p-values alone say little about whether an effect matters or is real.

• Genetics fixed its reproducibility problem; nutrition hasn't.

Genetics measures exposures with high accuracy (genotyping error under 0.01), nobody has ideological attachments to a polymorphism, and the field adopted genome-wide significance of 10^{-8} plus replication. Nutritional epidemiology still relies mostly on post-hoc, unregistered analyses with $p = 0.05$ thresholds and noisy dietary measurement.

• Real large effects look like tobacco.

Smoking studies in the 1950s–60s consistently showed about a 10x, on average about 14x, higher lung-cancer risk across physicians and non-physicians alike. Most nutrition findings are odds ratios like 1.14, a 14% relative increase, not 14x. Ioannidis says that if he ever sees an odds ratio of 20 in his own calculations, he assumes he made a mistake; genetics often deals in real effects of 1.01.

• Bradford Hill's criteria still guide causal inference.

Attia and Ioannidis walk through the classic criteria using smoking: strength of association (a roughly 14x risk), consistency (every 1950s–60s series pointed the same way), specificity, temporality and dose-response. Specificity is rarely met for single risk factors, since smoking causes many diseases, but the overall pattern made the tobacco case overwhelming. Nutrition findings usually fail on strength and consistency, and the small effects they report are easily produced by residual confounding, measurement error and selective reporting.

• Nutrition needs more and larger randomized trials.

Thousands of nutrition RCTs exist, but most are small and underpowered; there are over 200 large ones, mostly on specific nutrients or supplements. Ioannidis wants more large, long-term trials, and sees Mendelian randomization as a useful quasi-randomized design with its own assumptions.

• Consortia can bake in belief.

When investigators pool data, invitations often go to the roughly 100 teams that already believe in an association rather than the 3,000 who might have looked, so the cleaned, combined result confirms the prior. Pre-existing beliefs shape which questions get asked and how data are analyzed.

• Funding should tolerate failure.

Ioannidis sees distinct roles for public, private and philanthropic funders. Public and philanthropic money is best placed to back high-risk research asking important questions that industry won't fund, but only if funders accept that most projects will fail. Incentives that reward positive, flashy results push researchers toward questionable practices, from p-hacking to selective reporting.

• Bias is nearly universal; transparency is the antidote.

Ioannidis thinks bias may approach 100% if defined broadly, often without researchers being aware. Remedies include registration, data sharing, replication and reporting null results; funders should accept that perhaps five of 1,000 grants find something important and that's what makes the difference.

• Even top trials can be flawed: PREDIMED.

The Mediterranean-diet trial PREDIMED, published around 2013, looked like strong evidence until it emerged that randomization had been subverted at some sites; the New England Journal of Medicine retracted and republished it with new analyses. It's now partly randomized and partly observational, with hundreds of spin-off publications making varied claims.

• COVID science became hyper-politicized.

Ioannidis' early 2020 seroprevalence study suggested infections were about 50 times more common than documented cases, which drew intense animosity. He emphasizes a very steep risk gradient: many people have minimal risk, while nursing home residents can face an infection fatality rate around 25%.

EXAMPLES

• Everything we eat causes cancer

His 2012 paper sampled common recipe ingredients and found most had been studied for cancer associations, with many claiming increased or decreased risk; vanilla was a rare exception only because of how they searched.

• Twelve hazelnuts a day

Attia recalls a finding that eating 12 hazelnuts a day extended life by about 12 years, a comparison that reveals how

implausible effect sizes from observational nutrition data can be.

- **Five of 1,000 grants**
  Ioannidis argues science should be able to say 'we found nothing' for most efforts, since the rare successes drive progress; we should tell young scientists that most of them will fail.
- **A methodology only centuries old**
  Attia notes systematic scientific methodology didn't exist 500 years ago, a tiny fraction of our lineage, which calls for empathy toward people without training.
- **Over- and under-powered studies**
  Ioannidis explains that tiny studies produce inflated effects when they happen to reach significance, while enormous databases make trivial or biased associations 'significant', so both extremes generate false positives without careful design.

OTHER RELEVANT

- **Discount single observational findings.**
  Small relative risks from nutritional epidemiology rarely justify changing behavior on their own.
- **Look for big, consistent, replicated effects.**
  Strength, consistency and dose-response, like tobacco's, are what make causation credible. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prefer pre-registered, large trials.**
  Check whether a study was registered, adequately powered and transparently reported.
- **Stay humble about your beliefs.**
  Everyone, including scientists, is vulnerable to motivated reasoning. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#142- Robert Abbott: The Bobby Knight story—the cost of unchecked anger, ego, & winning at all costs

Guest: Robert Abbott
Date: 2020-12-21 · Duration: 2:14:43
URL: https://www.youtube.com/watch?v=QLqzxsSsAqg

KEYPOINTS

• Bobby Knight survived decades of abusive behavior because winning made him more powerful than the university itself.

Abbott (six-time Emmy winner, E60 co-creator, director of ESPN's 30 for 30 'The Last Days of Knight') calls Knight as the most powerful man in Indiana: three national titles (1976, 1981, 1987), an undefeated 1976 season and the 1984 Olympic gold. Over his 29 years at Indiana several university presidents came and went while Knight stayed.

• The university knew about Knight's conduct at least 13 years before it acted.

During his 1999 reporting Abbott found that in 1987 Indiana's Bloomington Faculty Council was so offended by John Feinstein's book about Knight's program, 'A Season on the Brink,' that it tried to do something. Knight then won the 1987 championship and the effort went nowhere. Abbott calls that moment the 'shot across the bow' that showed everyone who was really in charge, and says it protected Knight until 2000.

• Knight didn't fundamentally change; what changed was media access and his results.

Abbott thinks Knight in 2000 was largely the man of the early 1970s; growing coverage simply exposed more. Earlier he pushed players and then 'reeled them back in' enough to win titles. In the 90s his teams won 20 games a season but kept losing early in the tournament.

• The story began with a simple question: why were Indiana's best players leaving?

In April 1999 star Luke Recker, the team's leading scorer and minutes leader, announced he was transferring, the third notable departure in about two years. Abbott's CNN boss Steve Robinson assigned him to find out why; Abbott suspected elite teenage recruits no longer accepted Knight's style.

• A 90-minute phone call with former player Neil Reed produced three allegations that became the backbone of the story.

Reed said Knight had grabbed him by the throat at practice, had thrown the university president out of a practice, and had come out of a bathroom stall and shown the team soiled toilet paper to tell them how badly they were playing. Abbott first wondered whether Reed was a disgruntled ex-player exaggerating, and spent months confirming each account before CNN aired a 16-minute piece.

• Patient, trust-based sourcing is what got people to talk.

Abbott reported 'at my tempo' for about 18 months and filled roughly a dozen notebooks, which sat in a box in his basement for 15 years until he made the film. He started on the edges, with Hoosier Basketball magazine founder Gary Donna, before approaching insiders. His rule on calls: keep a source talking for two minutes and you can keep them for five. Tracking down Recker in Chicago and getting him on camera was the breakthrough.

• The practice tape vindicated the reporting, and CNN refused to be intimidated.

After the first piece drew attacks on CNN, Abbott and Reed, a videotape of the choking incident arrived in Abbott's mailbox. Indiana's trustees and vice presidents flew to Atlanta. When they hinted at legal action, Abbott's boss Steve Robinson calmly offered to walk them to the legal department, adding that the tape would be airing on CNN, CNN International, Headline News and some 300 affiliates before the elevator doors opened. Abbott calls it the most powerful moment of his 34-year career.

• Anger can act like an anesthetic for shame, a pattern Attia sees in Knight and in himself.

Attia, drawing on his conversations with therapist Terry Real, describes anger as briefly numbing an inner hollowness and inadequacy, with grandiosity standing in for real strength, followed by shame that feeds the next outburst. A mid-1970s story from journalist Dave Kindred suggested Knight knew he had a temper and kept asking why he kept ending up in these situations. In Abbott's view that self-awareness never turned into change.

• Indiana's 'zero tolerance' compromise was a failure of nerve.

Abbott calls Indiana's decision to keep Knight under a 'zero tolerance' policy in 2000 one of the great acts of institutional cowardice. In the fall of 2000 Knight grabbed a student's arm and was fired.

• Abbott's biggest regret is missing the human story of Neil Reed.

At 35 he focused on the journalism and treated Reed mainly as a source. Rewatching his reporting 16 to 18 years later, he saw a young man whose whole identity, from a Bob Knight camp T-shirt at under age 10 onward, had been built around Knight. He says he should have done a follow-up years earlier, and he made Reed the heart of the film.

EXAMPLES

• The 1988 Connie Chung interview

In a special on stress, Knight said something to the effect of 'if rape is inevitable, lie back and enjoy it.' The university's response was a mild statement that the remark did not reflect Indiana. Abbott says it would get a coach fired within 15 minutes in 2020, 2005 or even 1995, but Knight was untouchable then.

• The Argentina hunting trip

A professor, speaking on background and since deceased, told Abbott he had watched Knight get into a fight with his own son at a hunting lodge. Abbott asked Indiana's spokesman how the school could then reassure other parents.

• Neil Reed's later life

Reed married, had children and became a much-loved teacher and coach at a California high school, mainly coaching golf. The principal said he worked there about three years before she even knew his basketball past. He wore Nike gear every day as a reminder of how he got there. The abused did not become an abuser. He died of a massive heart attack at 36.

• Reed's final tweet

About 10 days before he died, Reed tweeted bitterly that kids apparently deserve to be 'punched, spit on, choked' and abused, written around a contemporary abuse scandal. Attia reads it as a sign of lasting trauma (PTSD), even though the people who knew him described a man who had largely moved on.

• Knight's intellect and his grudge

Hoosiers screenwriter Angelo Pizzo told Abbott that he once talked Russian history with Knight for six straight hours, a reminder of how brilliant Knight could be. Even so, Knight held a grudge over his firing for 20 years before returning to Assembly Hall.

OTHER RELEVANT

• Greatness doesn't justify the means

Abbott finished Feinstein's book believing the ends justified the means; his reporting changed his mind. A warning for coaches, parents and leaders.

• Watch for institutions that protect stars

Each protective decision raised Knight's leverage and the cost to people around him.

• Anger is often a cover for shame

Attia's takeaway is that real change requires examining the inadequacy underneath anger. Simply knowing you have a temper, as Knight apparently did by the mid-70s, is not enough.

• Trauma doesn't have to be passed on

Reed's life after Indiana shows a cycle of abuse can be broken, though the scars may remain. Abbott ends the film by thanking Reed for trusting him to tell his story.

• Note the date

This episode was recorded in late 2020. It covers events from 1999–2000 and the documentary, so later developments about the people involved are not included.

#140 - Gerald Shulman, MD, PhD: Insulin resistance—molecular mechanisms and clinical implications

Guest: Gerald Shulman
Date: 2020-12-07 · Duration: 2:08:42
URL: https://www.youtube.com/watch?v=OzZUnl3b49U

KEYPOINTS

• Insulin resistance is the soil the big chronic diseases grow in

Peter tells patients that heart disease, cancer and Alzheimer's sit on a foundation of insulin resistance. Shulman credits Gerald Reaven's 1988 Banting lecture with getting the field to see insulin resistance as a driver, not a bystander. Shulman himself won the Banting Medal in 2018.

• Seeing inside living cells with carbon-13 NMR

About 99% of the body's carbon is C-12, which NMR can't see. The 1% that is C-13 can be tracked. By infusing C-13-labeled glucose, Shulman's group can watch glucose being turned into muscle glycogen in awake humans, without radioactive tracers or biopsies.

• Muscle is the first site of insulin resistance

After a meal, about 80–90% of glucose is normally stored as glycogen, mostly in muscle. In lean, healthy, non-smoking Yale students around 20 years old (BMI about 22–23) who were insulin resistant, glucose flow into muscle glycogen was already about 50% lower than in insulin-sensitive peers, before any weight gain or diabetes.

• The block is glucose transport, not what Randle predicted

Philip Randle's 1960s model predicted that fat would raise glucose-6-phosphate inside muscle. Shulman's NMR studies found both glucose-6-phosphate and free glucose fell, pointing to a problem moving glucose into the cell through the GLUT4 transporter. That shifted the field's view of where the problem lies.

• Diacylglycerol and novel PKCs are the culprits

When fatty acid delivery outpaces oxidation, intermediates such as acyl-CoAs and diacylglycerol (DAG) build up. In muscle this activates PKC-theta, and in liver PKC-epsilon, which blunts insulin-receptor and IRS signaling. Gene knockouts confirm it. Specifically, the sn-1,2 DAG form at the plasma membrane matters, which can be missed if only total DAG is measured.

• Muscle insulin resistance diverts carbs to the liver and makes fat

When muscle can't store glucose, more of a carbohydrate meal reaches the liver. There it is turned into fat through de novo lipogenesis, which was more than twofold higher in insulin-resistant young people, with liver fat up about 2.3-fold. That leads to higher triglycerides and lower HDL. Shulman says lab cut-offs (triglycerides under 150) miss this; these young people had about 100–105 versus 60.

• Exercise bypasses the block

Six weeks of StairMaster (three 15-minute bouts at about 65% VO2 max) normalized muscle glycogen synthesis, likely via AMPK moving GLUT4 independently of PI3-kinase. A single 45-minute session shifted ingested glucose into muscle and cut de novo lipogenesis and liver triglycerides. Type 1 diabetics walking briskly for hours a day can need far less insulin.

• Insulin resistance evolved to protect the brain during starvation

Rats fasted 48 hours develop fatty liver, DAG build-up, PKC-epsilon activation and hepatic insulin resistance. That switches off glycogen storage and preserves glucose for the brain. Cahill showed humans still got about 40% of brain energy from glucose after 40 days of starvation.

• Fatty liver is becoming the leading reason for liver transplants

Fatty liver disease is now the most common liver disease in the world. Peter notes that within about 10 years, NASH and cirrhosis may be the top reason for liver transplants in the US, compared with under 2% of transplants when he was in medical school.

• Metformin likely works through redox, not complex I

Most studies used millimolar concentrations of metformin. Plasma levels at the usual dose of 1 g twice a day are about 30–50 micromolar, and perhaps about 100 in the portal vein. At those levels, Shulman says metformin inhibits mitochondrial glycerol-3-phosphate dehydrogenase, changing the cell's redox state and reducing glucose production in the liver.

EXAMPLES

• 1,200 calories reverses it quickly

Putting type 2 diabetics on short-term hypocaloric feeding of 1,200 calories a day reversed hepatic insulin resistance and fasting hyperglycemia. Bariatric surgery works the same way, by limiting energy intake.

• The 5-gram difference

Fasting blood sugar of 200 versus 100 mg/dL represents only about 5 extra grams of glucose circulating. Small shifts in where glucose goes, rather than how much exists, separate health from diabetes.

• DNP, from diet pill to liver-targeted drug

Dinitrophenol, a mitochondrial uncoupler, was sold over the counter for weight loss in the 1930s until overdoses caused fatal hyperthermia. Removing it was one of the first actions of the new FDA in 1937. Shulman's team designed liver-targeted uncouplers that 'melt' liver fat in animals and widened the safety margin about 100-fold. The plan is to start in humans with orphan conditions like lipodystrophy.

• A threonine conserved from flies to humans

The insulin receptor's activation loop has three tyrosines (1158, 1162, 1163) that become phosphorylated when insulin binds, with a threonine between them conserved from fruit flies to humans. Shulman's team made mice with that threonine (position 1150 in mice) swapped for alanine. On normal chow they had normal insulin sensitivity, and the team used them to test how PKC-epsilon acts on the receptor.

- **Weight-loss drug mechanisms**
  GLP-1 agonists work mainly by cutting food intake. SGLT2 inhibitors spill about 400 calories a day into urine, but weight loss plateaus after several weeks.

OTHER RELEVANT

- **Exercise is first-line therapy for muscle insulin resistance**
  Even single bouts help. Find an activity you like enough to stick with long-term, since short-term weight loss often reverses. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Look beyond fasting glucose and standard cut-offs**
  Fasting and post-meal insulin, triglycerides around 100 rather than under 150, and fatty liver can reveal insulin resistance decades before HbA1c rises. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Metformin for healthy people is an open question**
  Shulman sees metformin as a net positive in insulin-resistant people even without diabetes. For lean, insulin-sensitive, vigorously exercising people, he suspects it may not help and Peter raises whether it could even work against the benefits. Peter says he's undecided too.

#139 - Kristin Neff, Ph.D.: The power of self-compassion

Guest: Kristin Neff
Date: 2020-11-30 · Duration: 1:16:41
URL: https://www.youtube.com/watch?v=oPkoLHbjQAU

KEYPOINTS

• A personal crisis led Neff to self-compassion

As a graduate student at UC Berkeley studying moral development, Neff left her husband for another man, who then died of cancer within a year. Her ex-husband hated her, and she describes herself as full of shame and 'a basket case'. She joined a nearby Thich Nhat Hanh meditation group. Actively speaking to herself with kindness ('Hey Kristin, I know you're hurting') worked almost immediately.

• Self-compassion has three components that work as a system

The three are self-kindness, mindfulness and common humanity, the sense that suffering connects us rather than isolating us. Neff says they 'operate as a system'. Self-kindness on its own can become a self-focused 'poor me' state. Mindfulness gives perspective, and common humanity reminds you that you aren't the only one who fails.

• Self-esteem is contingent; self-compassion is stable

Since William James, self-esteem has meant feeling worthy because you are good at something you value. That makes self-esteem rise and fall with outcomes. Self-compassion says you are worthy because you are human, so it fluctuates less. She isn't against self-esteem, and the two are fairly strongly correlated. The problem is the unhealthy routes to it: feeling better than others, and bullying, which she links to middle schoolers trying to feel good by comparison.

• Self-compassion is unrelated to narcissism

When self-esteem and self-compassion were entered together in a regression predicting narcissism, Neff says self-compassion's correlation came out at 0.0. She calls it 'totally orthogonal'. Self-esteem showed what she recalls as a moderate correlation, though she said she'd have to check the figure.

• Harsh self-criticism works, but at a cost

Neff admits that many people have got through medical or law school on harsh self-criticism, so it does 'kind of work'. The side effects include anxiety, fear of failure and avoidance: the next big task feels threatening because failing means another beating. She argues that self-compassion is a better motivator than either self-criticism or self-esteem.

• The inner critic is trying to keep you safe

We criticise ourselves because we want to be well and loved, and we fear that failing will harm us or others. Neff says we shouldn't beat ourselves up for beating ourselves up. Instead, we should have compassion, and even gratitude, for the critic's motive. When her programme skips that step, the shift to compassionate motivation 'actually doesn't work', because the critical part feels it is fighting for its life.

• Childhood trauma makes self-compassion harder, and sometimes frightening

Early sexual, emotional or physical abuse hinders adult self-compassion, mainly through the attachment system. If care was unsafe, the inner programme may say you're worthless and not worthy of care.

• Self-compassion appears to influence physical health through the nervous system

Neff cites a meta-analysis finding a small-to-medium correlation (about 0.28–0.30) between self-compassion and better physical health. She calls it 'significant, not mind-blowing'. In experiments that induce all three components, for example by writing a self-compassionate paragraph about a current problem, sympathetic markers such as inflammation and cortisol go down. Heart rate variability, a marker of parasympathetic activity, goes up. Immune function also looks better. Attia notes the field is nascent and partly speculative.

• Children can learn it from around age 7 or 8

There is no good measure of self-compassion in children. Neff suspects it becomes teachable once kids understand friendship, reciprocity and fairness, what Piaget called two-way thinking. Self-criticism kicks in later, because young children have a positivity bias unless parents tell them otherwise. Adolescence, when abstract thinking and identity formation start, is when it matters most.

• You don't need to meditate to learn it

In her randomised trial of the Mindful Self-Compassion programme, gains in self-compassion were linked to practice. It didn't matter whether that meant formal meditation or informal 'self-compassion breaks' during the day. A hand on the heart and a kind sentence in the supermarket is 'portable' and 'scalable'.

EXAMPLES

• The failed vocabulary test at Berkeley

Undergraduates all failed a test made of the hardest SAT vocabulary items. One group was told to be kind to themselves about the failure. A second got a self-esteem boost ('you got into Berkeley, you're smart'). A third got no instructions. Given free time to study before a retest, the self-compassion group studied longer and harder than the other two, and study time predicted their next score.

• Attia's five months of voice memos

Archery and his racing simulator had become barometers of Attia's self-worth, and bad sessions led to anger, tantrums and feelings of worthlessness. His friend and mentor Ric Elias, a past guest, suggested he picture a close friend making the same mistakes and console him instead. Every day for five months, after each session, Attia recorded a voice memo to himself as if to a friend: 'Hey Peter, I know you just had a really bad day shooting... but it doesn't mean you're bad.' Eventually he could forget a bad session within about three minutes.

• A one-week self-compassion letter

In one study, people wrote themselves a compassionate letter once a day for seven days, covering mindfulness, common humanity and kindness. It reduced depression for three months and increased happiness for six months. Neff cites it as proof

that you don't need meditation for the practice to help.

- **Her son's autism and The Horse Boy**

  Trained as a developmental psychologist, Neff noticed her son's delayed language early. What helped most was letting herself feel her grief and fear without suppressing them, while actively supporting herself because of them. Her husband turned it into an adventure, a horseback trip to Mongolia that became the book and documentary The Horse Boy. Their son 'basically learned to speak on horseback'. Neff speculates that constant rebalancing aids brain integration via the cerebellum.

- **Self-compassion and addiction**

  Neff knows of no randomised trial with addiction as the outcome. She cites research suggesting that part of why AA works, when it does, is that it increases self-compassion. She speculates, without firm evidence, that compassion and connectedness may be an active ingredient in psychedelic therapy.

OTHER RELEVANT

- **Talk to yourself the way you'd talk to a friend**

  When you fail, picture a close friend making the same mistake and say what you'd say to them, using your own name. Attia's daily practice shows it can take months for this to become automatic.

- **Take a self-compassion break in the moment**

  Notice that you're suffering (mindfulness), remember that others struggle too (common humanity), then offer yourself kindness, for example with a hand on your heart. Neff uses this when her mind races at 3 a.m. and says it helps her fall back asleep.

- **Thank the critic before you replace it**

  Don't attack your self-criticism. Recognise that it is trying to keep you safe, then show it that kindness is a more effective way to do the same job and keep you motivated.

- **Root your worth in being human, not in performance**

  If your self-worth depends on how well you perform, you are 'doomed to fail at some point'. Keep high standards and strive, but don't make your worth conditional on the result.

- **Further resources**

  The Mindful Self-Compassion Workbook, co-developed with Chris Germer, takes you through the 8-week programme on your own. It can feel hard at first if you have a trauma history.

#138-Lauren Rogen & Richard Isaacson MD: Alzheimer’s disease prevention—patient & doctor perspective

Guest: Lauren Miller Rogen & Richard Isaacson
Date: 2020-11-23 · Duration: 2:11:50
URL: https://www.youtube.com/watch?v=AJmf1ZLwCuA

KEYPOINTS

• Lauren's mother developed symptoms at about 52

Lauren Miller Rogen's maternal grandfather had Alzheimer's, with symptoms in his late 50s or early 60s. He was in a nursing home for most of her childhood. At Lauren's college graduation, when she was 22 and her mother was 52, her mother repeated the same story several times. Her mother had been a sharp, vibrant first-grade teacher. By Lauren's wedding, when her mother had just turned 60, she couldn't stand with the family at the ceremony. Lauren's father, who was in denial at first, became an exhausted full-time carer.

• Most Alzheimer's is late-onset, and true genetic early-onset is rare

Isaacson has seen roughly 1,500–2,000 patients. He says he can count on two hands those with deterministic early-onset mutations, such as amyloid precursor protein mutations, which cause disease in the 40s or 50s. These account for well under 1% of cases. Lauren's family didn't fit that pattern. Theirs was late-onset Alzheimer's that had been pushed earlier.

• APOE sets a baseline risk, and the genes around it matter too

E3 is neutral, E2 is protective and E4 raises risk, more so with two copies. Isaacson sees E4 as increasing vascular risk and the build-up of harmful proteins. He says E4 carriers may even have smaller brains at birth. He adds that 'not all APOE4s are created equal': nearby genes such as TOMM40 may change how an E4 behaves. He describes that point as his belief, not a certainty. Every patient in his clinic gets an APOE test.

• Alzheimer's has three stages, and the first is silent

Stage one is preclinical: the disease has started in the brain but there are no symptoms. Isaacson cites a figure of about 46 million Americans in this stage while admitting the exact number is uncertain. Stage two is mild cognitive impairment due to Alzheimer's. Stage three is dementia. He says roughly 12–16% of people with MCI progress to dementia each year, depending on the study. He sees the preclinical stage as the most important target for prevention.

• Women with E4 face a distinct, compounded risk

Alzheimer's disproportionately affects women, and Attia argues that women's longer lifespan doesn't fully explain the gap. Isaacson credits Maria Shriver with pushing him to study it. Lauren's mother was E4/E4. She also had a hysterectomy with removal of her ovaries at about 46, an abrupt surgical menopause. She didn't exercise, and the household ate dessert most nights. Isaacson calls it 'the perfect storm' of genetics, sex, loss of hormones and lifestyle.

• Her uncle was also E4/E4 but became ill about 15 years later

Lauren's uncle, her mother's older brother, also carried two copies of E4. He was a lifelong athlete and an obsessive cyclist, and his symptoms began in his late 60s or early 70s. Because both siblings had the same genotype, Isaacson attributes the gap to sex, the hormone loss and lifestyle, probably in combination.

• Body fat, especially belly fat, matters more for women

Isaacson says that as waist size grows, the brain's memory centre gets smaller. He cites a 39% higher risk of dementia in women with enlarged waist circumference. For women he tracks body-fat percentage and where the fat sits, not weight. He also flags widowhood as a major risk factor for cognitive decline.

• Prevention runs on the ABCs, rechecked every six months

A is anthropometrics: body composition, fat and muscle. B is blood biomarkers: lipids, inflammation, metabolism, nutrition and genetics. C is cognitive function. Repeating them on a schedule shows whether the plan is working.

• Hearing loss may be the largest modifiable risk factor

Isaacson cites the Lancet Commission's 2020 report, which found hearing loss to be the most impactful modifiable risk factor. Attia raises the question of whether it actually causes dementia or simply rises with age alongside it. Isaacson says he doesn't have a perfect answer, but he is considering referring high-risk patients for hearing checks. He blames short 10–15 minute appointments for the lack of screening.

EXAMPLES

• Lauren's supplement and lab protocol

Lauren is APOE3/4. Isaacson's view is that E4 carriers need more omega-3, so she takes at least about 2 g of combined EPA/DHA a day, adjusted to a red-blood-cell omega-3 index of at least 12–14. She also takes purified cocoa flavanols, a specific curcumin formulation and low-dose B vitamins to keep homocysteine down. High homocysteine is linked to brain shrinkage. Isaacson aims for vitamin D around 50 (50–70) ng/mL rather than the 'normal' 30, while noting that the exact optimum isn't known.

• Her cognitive scores went from below average to the top tier

Lauren has done Isaacson's test battery six or seven times. Her memory started 0.87 standard deviations below the mean. It is now about one standard deviation above it, and she is above the 90th percentile on many tests. Isaacson cautions that the results include practice effects and good and bad days. One visit went badly when she had let her habits slip, and she calls it 'a good kick in the behind'.

• Better smell scores turned out to be learning

Loss of smell can be an early sign of Parkinson's, and odour identification is being studied for Alzheimer's. Lauren's score improved, but she points out that she had simply learned to tell apart the coffee and gasoline cards. Isaacson uses it as an example of subjectivity creeping into an 'objective' test.

• Testing a couple's teenage children

Attia describes an E4/E4 husband and wife whose children would each have a 25% chance of being E4/E4, 50% of E3/E4

and 25% of E3/E3. He suggested testing the children in their 20s, and sooner if a boy wanted to play football, given that head trauma and E4 may interact. The family's GP called him, furious about the testing.

• Hilarity for Charity

Lauren and her husband Seth started the charity with a comedy fundraiser in January 2012. It became its own 501(c)(3) in 2017. It focuses on families: paying for care so carers like her father get a break, and support groups organised by age. At 26, she had found little in common with a 56-year-old in a support group.

OTHER RELEVANT

• Know your APOE status, with context

A commercial test can tell you your status. Isaacson's point is that a 3/4 result is not a sentence: it is a reason to act. Lauren's brother panicked over an early 23andMe 'Alzheimer's risk' report before he understood it.

• Treat cannabis as an individual experiment

Isaacson is not against THC or CBD. He thinks the CBD-to-THC ratio matters and prefers edibles to smoking, but he admits this isn't grounded in solid science. He suggests changing one thing at a time and tracking cognition and sleep over three to six months.

• Start prevention early

Isaacson would start omega-3s for E4 carriers 'as early as possible'. Lauren started in her 20s. The underlying point is that Alzheimer's pathology begins decades before symptoms.

• Support the carer, not just the patient

Many carers are with a loved one 24/7 with no relief. Respite care, peer support from people at a similar stage of life, and sharing the load protect the carer's health as well.

#137 - Paul Offit, M.D.: An expert perspective on COVID-19 vaccines

Guest: Paul Offit
Date: 2020-11-16 · Duration: 1:36:05
URL: https://www.youtube.com/watch?v=CZJYoi_VIic

KEYPOINTS

• A childhood hospital stay shaped Offit's career

In the 1950s Offit had a clubfoot operation that the surgeon himself advised against, and it failed. He then spent about six weeks in a chronic-care children's hospital ward of about 20 children, many with polio, some in iron lungs. Parents could visit one hour a week, on Sundays from 2 to 3. He says the experience pushed him toward pediatrics and preventing childhood disease.

• The modern anti-vaccine movement grew from fraud

Andrew Wakefield's Lancet paper on 12 children was not just wrong but 'knowing fraud', misrepresenting both clinical and biological data. Since then, many studies have found no link between MMR and autism. Offit cites an Autism Science Foundation survey showing about 85% of parents of autistic children no longer believe vaccines caused it. He worries that COVID disrupted routine childhood vaccination, which had been near the 95% needed for measles.

• Rotavirus shows why big trials and caution matter

Before vaccines, rotavirus hospitalized about 75,000 US children a year and killed about 500,000 children worldwide, up to 2,000 a day, mostly under age two. Offit's rotavirus vaccine took 26 years. Its final trial enrolled about 70,000 babies, half on placebo, partly because RotaShield, an earlier vaccine, was pulled within about 10 months of licensure. It caused intussusception (bowel blockage) in roughly 1 in 10,000 to 1 in 30,000 recipients, which pre-licensure trials were too small to detect.

• Normal vaccine development takes 15–20 years and at least $1 billion

Phase 1 tests doses in about 20–100 people. Phase 2 expands to hundreds or thousands. Phase 3 involves tens of thousands. Operation Warp Speed compressed this by running steps in parallel and paying to manufacture tens of millions of doses before knowing whether they worked, a financial risk no company would normally take.

• The mRNA candidates differ in dose and cold chain

Moderna's vaccine came out of NIH work and uses 100 micrograms per dose in a two-dose series. Pfizer's uses a lower dose but must ship and be stored at -70 to -80°C, compared with Moderna's -20°C, an 'ultra-cold chain' challenge.

• How the phase 3 trials judge efficacy

With about 30,000 people randomized one-to-one, the trials needed roughly 150–160 symptomatic cases to show statistically robust efficacy. Offit, who sits on the FDA's vaccine advisory committee (meeting October 22), explained why the first vaccines would come via Emergency Use Authorization rather than full licensure, simply because of time.

• Adenovirus vectors carry real but rare risks

The adenovirus vaccines deliver about 10 billion particles per dose. Offit recalls Jesse Gelsinger, who died about 20 years earlier at Penn of a massive cytokine reaction to an Ad5 gene-therapy vector. The vaccine dose is about 1/300th of what Gelsinger received, but rare events surface only in millions of people. AstraZeneca's trial holds were for neurological events, including transverse myelitis (about 1 in 200,000 in the general population), which was judged likely coincidental.

• Coronaviruses don't change type the way flu does

Measles has never really changed serotype, so the 1963 vaccine still works. The four common cold coronaviruses, identified in the 1960s, cause about 15–20% of the respiratory illness seen in hospitals. Offit hoped SARS-CoV-2 would behave more like measles, so that a vaccine that works now still works years later.

• Other platforms were coming too

Purified-protein vaccines use the approach behind the hepatitis B vaccine (since the early 1990s), the HPV vaccine (around 2006) and the flu vaccine Flublok, so their record is long. Merck was a step behind, with candidates including a replication-competent vesicular stomatitis virus vector. Russia's vaccine (Ad5 then Ad26) was announced by Putin in late August before any phase 3 results.

• Vaccines may do better than natural infection

Short incubation periods let infection outrun memory cells. Measles' 10–14 days gives memory cells time to activate. Offit sees some hope that a vaccine could induce better immunity than infection does.

EXAMPLES

• Two vaccine disasters of the 1960s

Formalin-inactivated RSV vaccine from NIH (Bob Chanock's lab) made children who later caught RSV more likely to develop pneumonia and be hospitalized, and two died. A killed measles vaccine in 1963 caused 'atypical measles' pneumonia. These cases are why researchers watch for vaccine-enhanced disease.

• Children and COVID

People under 21 are about 26% of the US population but about 0.08% of COVID deaths. About 120 children had died, similar to the roughly 140–160 who die of flu each year. Trials were only beginning to move down to ages 16 and 12.

• Fever helps immunity

Offit explains that the immune system works better at higher temperatures. Studies repeatedly show that treating post-vaccine fever with Tylenol or ibuprofen blunts the immune response, though heat can be dangerous for people who can't tolerate the metabolic strain.

• Rationing at roughly 230,000 deaths

Two-dose vaccines would need hundreds of millions of US doses, which wouldn't be available at once. Priority would go to people over 65 and those with high-risk conditions (obesity alone affects about 30% of Americans). Peter likens it to the end of the film Contagion.

OTHER RELEVANT

- **Older adults should look for trial data in their age group**

  Offit, over 65, wanted to see adequate representation. For example, about 10,000 trial participants over 65 with no serious adverse effects in three months would reassure him.

- **Rare side effects need population-scale monitoring**

  Even 50 years of study didn't predict RotaShield's intussusception. Expect post-authorization surveillance to matter, and judge vaccines on phase 3 data, not on announcements like Russia's. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Don't reach for fever reducers reflexively after a shot**

  Unless discomfort or the strain of fever is a problem, letting a mild fever run may support a stronger response. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#135 - BJ Miller, M.D.: How understanding death leads to a better life

Guest: BJ Miller
Date: 2020-11-02 · Duration: 1:54:43
URL: https://www.youtube.com/watch?v=WKrBVOVOXOc

KEYPOINTS

• BJ Miller's accident reshaped his life and work

Shortly after Thanksgiving in 1990, Miller, then a Princeton sophomore nearly 6'5", climbed on top of a parked commuter train, the 'Dinky', with friends on the way to a Wawa store. Electricity arced to his metal watch, entered his left arm and grounded through his body. He survived, but lost both legs below the knee and his left arm below the elbow, after a touch-and-go stay in the burn unit at Saint Barnabas in Livingston, New Jersey. He now thinks of it as perhaps not a change for the worse.

• Trying to be tough delayed his grief

Miller absorbed the American idea that you get straight back on the horse. When his mother, disabled by polio for most of her life, came in crying, his first response was an almost cheery 'now we have so much more in common.' Later, a burst of tears felt like a dam breaking, and he noticed he felt no physical pain while crying. He wonders about a link between crying and pain relief.

• Accepting his new body was liberating

Miller says the work wasn't asking 'why me' but cultivating a mindset that cuts down on regret and second-guessing, rather than living with 'if only I had four limbs'. Visible suffering, he says, gives him something that able-bodied clinicians may lack in connecting with patients.

• A broad education can make a better doctor

While bored in a hospital bed, he switched from East Asian studies to art history. He argues that most pre-med content is relearned in medical school, while studying perspective in art translates into seeing patients differently. His advice is to love the nuts and bolts, not to do chemistry merely as a means to an end.

• His sister's suicide nearly drove him out of medicine

On 1 December 2000, almost exactly 10 years after his injuries, his sister Lisa took her own life. She was posthumously diagnosed with manic depression, which he had studied in medical school without seeing it in her. He started making a list of reasons to quit medicine, then found palliative care at a programme where he happened to train, watching a mentor discuss code status with a patient on his first day.

• Palliative care is not the same as hospice

Palliative care is for anyone with serious illness who cares about quality of life. You don't have to be dying soon. Because people conflate it with end-of-life care, many suffer for years without support they could have had. Miller argues that the definition of palliative care, focusing on the person rather than the disease, should be the mission of all of healthcare.

• Healthcare's problem is its design, not its people

Healthcare is full of people who care and are trained 'at the hilt', yet care falls short because the system is organised around diseases, not people. Medical training reinforces this: 100% of patients die and 100% suffer, yet no rotation is built around that. Miller says medicine is a victim of its own success over the last 150 years, which has fed a death-phobic culture.

• Separate fear of being dead from fear of dying

Fear of the process of dying is the more tractable one: its physiology is understood and medications help. Fear of being gone is existential. Miller sees a two-phase effect: people notice how fear has gripped them, and then, once failure is guaranteed anyway, it stops being worth fearing. Death becomes a reason to try and a way to forgive yourself for 'failing'.

• The deepest regrets are about not living as yourself

Beyond the stock regret of working too much, dying patients say things like 'I wish I'd dared to love more,' 'I wish I hadn't been so afraid' and 'I wish I hadn't been so hard on myself.' The common thread is wishing they had come to terms with death earlier, because it would have changed their decisions. Since most people now die of chronic illness, they often have months or years to reflect.

• Physician-assisted dying is spreading state by state

Miller believes about nine jurisdictions allow some form of it, starting with Oregon in 1997 and California in 2016. He prefers language other than 'suicide'. He worries that making it too easy can cut short a meaningful final stretch, as Randy Sloan's story showed.

EXAMPLES

• Randy Sloan

Randy was a 27-year-old mechanic at Scuderia West in San Francisco who adapted a motorcycle for Miller. He later developed an aggressive cancer and needed urgent whole-brain radiation. Asked what he was proudest of, he answered immediately: 'I want everybody I ever come into contact with to know that I love them.' He let his illness play out, reached many more friends and got out onto the Bay, 'playing every cell all the way out.'

• Attia's NCI patients

As a student and fellow at the National Cancer Institute, Attia met patients with treatment-resistant metastatic cancer, 80–90% of whom would die within about six months. He wished he could write down what they told him.

• Dying wishes

Miller has helped arrange trips such as a visit to the Grand Canyon. He notes that many people instead come to let go of the things they never got to.

• Hospice is no longer mostly cancer

Fewer than 50% of US hospice deaths are now from cancer, with progressive neurological diseases and organ failure rising.

OTHER RELEVANT

• Separate palliative care from hospice

Ask for palliative care early in any serious illness, not just at the end.

- **Look at death now**
  Coming to terms with mortality while you're well changes what you dare to do and how hard you are on yourself.
- **Ask what matters most**
  Ask 'what are you most proud of?' or 'what do you want to protect?' Those questions can redirect care when treatment options run out.
- **Psychedelic-assisted therapy is promising, but the evidence is still early**
  Miller is most excited about psilocybin and MDMA research, alongside ketamine, for existential distress in serious illness. He says there's 'a little ways to go' on the data.

#134 - James O’Keefe, M.D.: Preventing cardiovascular disease and the risk of too much exercise

Guest: James O'Keefe
Date: 2020-10-26 · Duration: 2:09:16
URL: https://www.youtube.com/watch?v=8kytXpshGks

KEYPOINTS

• Atherosclerosis is less a plumbing problem than a 'zit' problem

The idea that you just clear the clog has been hard to shake for 40 years. O'Keefe describes plaques as pustules under the artery's inner lining, full of oxidized LDL and triglycerides, that draw in inflammatory cells. They thin out, rupture, attract clots and heal over decades, with each episode laying down smooth muscle, collagen and eventually calcium. Opening stenoses helps in acute coronary syndromes but doesn't prevent most heart attacks.

• A calcium scan is 'the mammogram for the heart'

O'Keefe recommends a CT calcium score, with minimal radiation, for men over 40 and women over 60. He has read about 150,000 scores, and his practice has done about 600,000. One very fit, metabolically healthy patient scored just over 100 (75th–90th percentile) with 30–50% narrowings in three vessels. O'Keefe stresses that such lesions matter as sites of inflammation, not as blockages to stent.

• Exercise follows a reverse J-curve

If exercise were a drug it would be the best one we have for heart disease, dementia, osteoporosis, depression and diabetes, but the dose matters. In O'Keefe's 'Training for Longevity' review, 8 of 10 large studies showed mortality dropping steeply, plateauing, then 'fish-hooking' up at the highest volumes. Even 15 minutes of brisk walking a day cuts serious cardiovascular disease by about 30%.

• Chronic extreme endurance training can damage the heart

Sustained hours at high heart rates, often under heavy load, push cardiac output to 30–35 liters a minute, and 40 in elite cyclists. That strains the atria and right ventricle and can leave dilated chambers and scarring. O'Keefe cites atrial fibrillation rates up to about 700% higher in lifelong endurance athletes, and troponin and NT-proBNP rises after long efforts, especially after 45. Youth makes people resilient to this, but that resilience fades.

• Moderate running is the sweet spot

Copenhagen data showed moderate-dose runners lived longest, and O'Keefe suggests about 15 miles a week is enough for health. Beyond that, he says, you're doing it 'for some other reason.' He also cautions that the evidence is epidemiological and lifelong patterns can't be randomized. Peter says it took him about three years after first hearing O'Keefe (around 2011) to change his own training, by 2014.

• Social, playful sports added the most years

In the Copenhagen City Heart Study, about 10,000 Danes were followed for decades. After multivariable adjustment, tennis, badminton and soccer added roughly 6–10 years of life expectancy. Cycling, swimming and running added about 3–4, and health-club workouts only about 1.5. O'Keefe first thought it was nonsense, then concluded that sports that reduce stress, are fun, last a lifetime and build relationships matter. He cites Julianne Holt-Lunstad's work showing social connection as a top predictor of longevity.

• Train like a hunter-gatherer: mostly easy, some hard, plus strength

Tribes in the wild walk about 16,000–18,000 steps a day, mostly at a comfortable pace, often carrying loads. Elite endurance athletes train about 80% easy and 20% hard. O'Keefe suggests capping hard aerobic sessions at about 30–45 minutes and adding strength and balance work. In one study, about 8,000 steps a day cut mortality by about 50% over 12 years, with benefit peaking near 12,000.

• Resting heart rate is a useful feedback tool

O'Keefe's resting heart rate was in the mid-30s when he was very fit and is now in the 40s. He tracks it to tune training, sleep and stress. Some people simply run higher, but trends within one person are informative.

• SGLT2 and GLP-1 drugs protect the heart

After decades of failing to prove that lowering glucose prevents cardiovascular disease, about seven large trials of 3,000–17,000 patients showed SGLT2 inhibitors do. They cause about 100 g of sugar a day to be lost in urine. High-dose semaglutide (2.4 mg weekly) can cut body weight by around 10% even in non-diabetics.

EXAMPLES

• Micah True

The ultrarunner made famous by Born to Run often ran about 12 miles a day plus 50–100-mile desert races. He died suddenly on a run in his 50s, and the autopsy reportedly showed a dilated, scarred heart, especially the right ventricle and septum.

• O'Keefe's low-fat experiment

Years earlier, eating pizza crust without toppings and lots of white rice, his triglycerides rose from 80 to 300 and HDL fell from 50 to 33. He got skinnier, felt worse and raced slower. He now advocates a 'pesco-Mediterranean' diet with daily time-restricted eating of 12–16 hours.

• Omega-3 at prescription doses

In REDUCE-IT, 4 g a day of EPA in people with heart disease or diabetes and triglycerides above 150 cut cardiovascular events and mortality by roughly 25–30%. O'Keefe notes most Americans are low in omega-3s.

• Calcium score regression

O'Keefe says scores almost never fall, but he has seen one drop by 200–300 points from about 1,400 over a few years, more than the margin of error. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

OTHER RELEVANT

- **Use extra-virgin olive oil that burns**

  Good EVOO, as used in PREDIMED, leaves a peppery burn 10–20 seconds after swallowing, a sign of polyphenols. Buy carefully. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Take a 30–40-year view of risk**

  Like Allan Sniderman, O'Keefe looks beyond 10-year risk. A 40-year-old with a zero calcium score but apoB at the 80th percentile may still merit treatment, and he favors aggressive LDL and apoB lowering, including non-statin options such as PCSK9 inhibitors, ezetimibe and omega-3s.

- **Moderate sodium and add minerals**

  O'Keefe considers 2–3 g of sodium a day better than going below 1,500 mg. He emphasizes magnesium, potassium and collagen-rich foods, the 'bones' our ancestors ate. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#133 - Vinay Prasad, M.D., M.P.H: Hallmarks of successful cancer policy

Guest: Vinay Prasad
Date: 2020-10-19 · Duration: 2:12:04
URL: https://www.youtube.com/watch?v=1CO7Ya7FAMc

KEYPOINTS

• Medical reversal: widely used practices that turn out not to work

Prasad, a haematologist-oncologist and meta-researcher at UCSF and author of Ending Medical Reversal and Malignant, came to the idea as a resident. He noticed practices that ran against the best evidence. As a resident he managed stent patients after the procedure and saw the complications. Meanwhile the large COURAGE trial had found that stents in stable disease didn't reduce heart attacks or extend life. He and colleagues called this pattern 'medical reversal': plausible biology plus observational data, later overturned by randomised trials.

• Sham-controlled trials separate the procedure from the ritual

Arthroscopic knee surgery beats physical therapy or ibuprofen, but not a sham operation in which the surgeon inserts the scope and does nothing. The same holds for cement injections into osteoporotic vertebral fractures, some shoulder procedures and, Prasad believes, stenting for chronic stable angina (the ORBITA trial). Much of the benefit comes from reassurance and the patient's belief that something was fixed.

• Stents are 'seductive' because both patient and doctor feel rewarded

Patients come back grateful, convinced their life was saved and that shovelling the driveway hurts less. That feedback reinforces the procedure even when trials show no hard benefit. Prasad says this disconnect between what patients think a treatment does and what doctors know it does recurs across medicine.

• Structural problem 1: huge costs for small gains

In an analysis by Fojo and colleagues, 71 consecutive drugs approved for solid cancers improved survival by an average of 2.1 months. Prasad says two months can matter a great deal to someone, but the result should come with a lower price. Attia recalls a drug that added 0.7 months, about 20 days, at roughly $38,000. Compared with 1960 or 1970, someone with metastatic breast cancer in 2020 is not dramatically better off, Prasad argues, while surgical outcomes like the Whipple procedure and the move away from radical mastectomy have improved.

• Structural problem 2: approvals rest on weak surrogate endpoints

Progression-free survival and response rate often stand in for living longer or better. 'Progression' means the tumour has grown 20% from its smallest size. At 19% the disease is 'stable', at 21% it has progressed: an arbitrary cut-off that often doesn't track how patients feel. The 30% shrinkage needed to count as a 'response' goes back to a 1976 Mayo Clinic exercise in which doctors measured marbles through foam rubber. Prasad questions why so much weight is put on drugs with 10–20% response rates.

• Structural problem 3: the people choosing don't pay

Patients and doctors decide while insurers, governments and employers pay. Prasad compares it to a Saudi friend who left his air conditioning running all summer because energy was subsidised. When someone else pays, cost stops affecting choices. In the UK, NICE declined drugs above a cost-effectiveness threshold, which Attia recalls as about £100,000.

• Hallmark 1: independence from industry money

Patient advocacy groups are often heavily industry-funded. The most common employer for staff leaving the FDA is industry. Prasad calls expert oncologists, many of whom take payments, 'probably the biggest offender'. He thinks the profession won't police itself, because the most influential doctors receive the most payments. He would have guidelines written by experienced oncologists with no financial ties.

• Hallmarks 2–3: evidence and relevance

Drugs should prove they help patients live longer or better, against the right control group. Trials should also enrol patients who look like the people who will actually get the drug. Trial participants tend to be younger and fitter, so real-world success rates are lower because the drug is less tolerable and response is poorer.

• Hallmark 4: affordability

Prasad groups possible fixes into buckets. One he highlights is letting Medicare decline to pay for drugs. At the moment it must cover drugs recommended at level 2A or above by guidelines such as the NCCN's, whose authors are often industry-funded. He notes that some states asked HHS for permission to experiment with not covering every drug.

• Hallmarks 5–6: possibility and agenda

Possibility means funding more bold science. The NIH budget of about $30 billion a year is 'not nearly enough', grant cycles favour incremental work, and Prasad suggests running randomised experiments on how grants are awarded. Agenda means looking at the whole trial landscape. Many trials test 'Coke, Pepsi and 18 other Cokes', near-identical low-promise drugs, and at $p<0.05$ some will come out positive by chance.

EXAMPLES

• Hormone replacement and the Women's Health Initiative

Observational data from Harvard found that nurses on hormone therapy had less heart disease. Plausible biology and heavy promotion by Wyeth followed, and it became a multibillion-dollar treatment. The randomised Women's Health Initiative, around 2001–2002, was halted for more blood clots and cardiovascular events: the opposite of what was expected.

• The CAST antiarrhythmic trial

Antiarrhythmic drugs suppressed post-heart-attack arrhythmias, and cardiologists felt it was unethical to withhold them. When a randomised trial (CAST) was finally run, the drugs increased the risk of death, and class 1C agents were largely abandoned. Prasad's lesson: smart, well-meaning people with sound biology and observational data can still be wrong.

• POLO in pancreatic cancer

Patients whose disease was controlled on chemotherapy (FOLFIRINOX) stopped it and got either a targeted drug costing

about $12,000 a month or a placebo. Progression-free survival improved but overall survival did not. Prasad argues the control arm should have continued the chemotherapy that was working, not a placebo.

• Real wins exist

Gleevec for chronic myeloid leukaemia, which targets the single driver fusion, took median life expectancy from three to four years to near-normal in Swedish data. Prasad also calls treatments 'no-brainers' when the benefit is clear and the toxicity low or reversible. Attia notes that Avastin's first approval (around 2000–2002) was in colon cancer, at roughly $100,000 a year.

• Press release before data on dexamethasone

When the UK announced that dexamethasone helped hospitalised COVID patients needing oxygen, Prasad pointed out that the published protocol showed a well-run trial. He was willing to act on it before the full paper and took criticism for doing so. His point was that the quality of the trial matters more than its format.

OTHER RELEVANT

• Ask what a treatment does for survival and quality of life

With any new cancer drug, ask whether it helps people live longer or better, by how much, and compared with what. A hazard ratio of 0.7 in a press release says nothing about how long people lived or the side effects.

• Be skeptical without being contrarian

Prasad's clinical stance is to do everything that adds something for the patient in the room, while being honest about weak evidence. When asked about expensive add-ons like hyperbaric oxygen protocols, his first question is how much they cost.

• Watch for conflicts of interest

Ask whether an advocacy group or expert is funded by the companies whose products they recommend. Prasad admits that as a resident, sleep-deprived, he didn't see through drug-rep perks such as fancy branded pens.

• Be cautious about 'game changers'

CAR-T and checkpoint inhibitors produce real, sometimes dramatic responses in some people. The open question is how much they help across all the conditions they are now being tried in.

#130 - Carol Tavris, Ph.D. & Elliot Aronson, Ph.D.: Recognizing and overcoming cognitive dissonance

Guest: Carol Tavris and Elliot Aronson
Date: 2020-09-28 · Duration: 1:59:43
URL: https://www.youtube.com/watch?v=vrlIMuMQuvg

KEYPOINTS

• Cognitive dissonance is the discomfort of holding two contradictory thoughts, and we reduce it to protect our self-image

Carol Tavris and Elliot Aronson co-wrote 'Mistakes Were Made (But Not by Me)' (2007). Aronson trained with Leon Festinger at Stanford in the mid-1950s and is listed among the 100 most eminent psychologists of the 20th century. His contribution was to see that the most painful dissonance is with the belief that 'I am a good, kind, smart person.' We often justify a bad act rather than revise that self-concept.

• The theory began with frightening rumours after an earthquake in India

Festinger studied rumours after a major earthquake. At the epicentre, people spread comforting rumours that help was coming. In a city 15–20 miles away with only mild damage, people spread rumours of a coming typhoon and floods. Festinger concluded that people who felt very anxious with little visible reason adopted beliefs that justified their anxiety.

• Paying people less makes them believe their lie more

In Festinger's experiment, participants did a boring task, then told the next person it was interesting, for either $20 or $1. The behaviourist theory of reinforcement predicted the more you're paid, the more you'd like it. Dissonance theory predicted the opposite. Those paid $20 could think they'd sold their soul for a good price. Those paid $1 had to convince themselves the task wasn't so dull after all.

• The pyramid: small first steps drive people apart

Two people with nearly identical beliefs face a hard choice, such as whether to cheat on an exam. Each justifies their choice, and justification changes their attitude, so they slide down opposite sides of a pyramid until they barely recognise each other. Attia calls it path dependency. The hard part is climbing back up. A Stuyvesant High School student caught among 71 exchanging answers redefined cheating as 'taking a risk'.

• Smart, powerful people are the most dangerous dissonance reducers

Prosecutors who sent a man away for 25 years may reject DNA evidence of his innocence and keep him in prison, not because they're evil but because they see themselves as good. One prosecutor's theory shifted from 'he was the rapist' to an unnamed accomplice once the semen didn't match. The authors also discuss the Amanda Knox and Duke lacrosse cases, where about 80 faculty signed a newspaper ad before the facts were in.

• Outrage can override skepticism

In the 1980s McMartin preschool abuse case, Attia notes that this case really challenged Tavris. He quotes a line from their discussion of it: 'we sacrificed our skepticism at the altar of outrage.' The broader lesson is to withhold judgement in sensational cases. A related exercise: imagine a person you despise in 10 poses, and you'll find a negative story for every one.

• Ideology distorts science and memory

The recovered-memory era produced patients who emerged from therapy believing they had dozens or even hundreds of personalities. Tavris notes that events from 25 years ago that seemed benign at the time can be reinterpreted as traumatic. Attia, who trusted his detailed memory, was shaken to learn that memory is reconstructive.

• Certainty freezes the ability to change your mind

Anyone who is totally certain has almost certainly lost the ability to update. Attia argues for tying decisions to behaviour ('with these facts, I'll do this') rather than identity, so new evidence doesn't feel like a personal attack. The scientific habit of 'rooting for the null hypothesis' is hard but necessary.

• Institutional cultures entrench dissonance

Officers may justify planting evidence on suspects they 'know' are guilty. The authors say it may be understandable but is never justified. They cite the claim that 20–25% of US police officers come from the military, and the bystander culture that shields the most brutal cop. Attia points to Mark Fuhrman from the O.J. Simpson trial as where small justifications can lead years later.

• Brain-imaging studies seduce us

Tavris cites research showing the same lecture is judged more scientific when it includes fMRI images. She describes Drew Westen's studies of partisans facing damaging information about their own party's candidate. Bad behaviour from the other side is consonant, while from our own side it gets explained away.

EXAMPLES

• Wayne Hale and the Columbia disaster

NASA's Wayne Hale, who knew the crew and their families, began to defend the launch decision ('no launch is perfect'), then stopped mid-sentence. He said he wished he'd been more cautious, because the weight of the evidence had favoured aborting. The authors hold him up as a model of owning a mistake.

• Shimon Peres at Bitburg

When his friend Ronald Reagan agreed to lay a wreath at Bitburg cemetery, where 47 Nazi officers were buried, Peres said: 'When a friend makes a mistake, the friend remains a friend, and the mistake remains a mistake.' It separated the two dissonant thoughts.

• Aronson breaking his father's pattern

As a child, Aronson watched his mother list her complaints at dinner and his father explode within about 20 seconds. Early in his marriage, he stormed halfway down the stairs after an argument and realised he was copying the behaviour he detested. He went back and apologised. He was married for 65 years and counting.

- **Smokers justify themselves**
  Smokers who fail to quit tend to downplay the risks. A study of pregnant women who smoke shows the same pattern, even though they know the double harm.
- **The Semmelweis story**
  A doctor who had just done autopsies carrying something on his hands that killed mothers was rejected by colleagues who didn't want to believe it, a story repeated throughout history.

OTHER RELEVANT

- **Say 'I made a mistake, and here's how I'll make amends'**
  The authors' recommendation for a meaningful life: ask why you did it, what you'll learn, and how to repair the harm.
- **Separate your identity from your decisions**
  Hold beliefs as conclusions from the current evidence, not as who you are.
- **Hesitate before the first step down the pyramid**
  Small justifications compound. Notice them when the stakes are still low.
- **Withhold judgement on sensational stories**
  Wait for the facts, especially when outrage feels righteous.
- **Model it for children**
  Attia wants his 11-year-old to be comfortable sitting in discomfort. Showing children your own corrections teaches more than lectures do.

#129 - Tom Dayspring, M.D.: The latest insights into cardiovascular disease and lipidology

Guest: Tom Dayspring, M.D.
Date: 2020-09-21 · Duration: 2:00:04
URL: https://www.youtube.com/watch?v=svYYprvlL_U

KEYPOINTS

• ApoB-carrying particles are the core driver of atherosclerosis.

Dayspring, a lipidologist who practiced internal medicine in New Jersey for 37 years, describes a growing consensus. Attia lays out the model: smoking and high blood pressure injure the artery lining, and apoB particles act as the 'Trojan horse' that carries cholesterol into the artery wall. There it is retained and oxidized, setting off an inflammatory repair response that builds plaque. Each atherogenic particle carries exactly one apoB molecule: apoB-100 for liver-made particles, and the shorter apoB-48 for chylomicrons from the gut.

• ApoB is the preferred metric, and cost is no longer an excuse.

Because of their long half-life, 90–95% of apoB particles are LDLs, so apoB works essentially as a particle count that also captures VLDL remnants, IDL and Lp(a). Attia's practice switched from LDL-P after going through three particle-count technologies in eight years. Dayspring cites Allan Sniderman's work showing that even non-HDL cholesterol leaves roughly 20–30% of people misclassified compared with apoB.

• Lower is better, and physiological apoB is probably under 50 mg/dL.

Dayspring notes newborns have apoB under 50 mg/dL, and trials show the greatest risk reduction when it is pushed that low. Guidelines suggest at least a 50% reduction in higher-risk people. PCSK9 inhibitors now routinely bring apoB to 20–40 mg/dL. He stresses that halving plasma cholesterol (say 200 to 100 mg/dL) barely changes total-body cholesterol, because most cholesterol sits in cell membranes and tissues, not in circulating lipoproteins.

• HDL cholesterol is a poor target.

HDL cholesterol was adopted from 40- to 50-year-old epidemiology. Decades of trials that raised it have been neutral at best and harmful at worst, and Mendelian randomization studies of HDL genes are neutral too. Dayspring calls HDLs 'fire engines' of many types: an average particle carries about 45 cholesterol molecules and can carry some 150 different proteins. HDL function matters, but there is no good clinical test for it yet.

• Lp(a) is 'the most dangerous particle you've never heard of.'

Lp(a) is an LDL-like particle with apo(a) attached. Its level is genetic, so a single test is enough: if it isn't high at 18, it won't be at 68. For heart attacks before 60 in the family, Attia's rule is 'Lp(a) until proven otherwise.' Yet some people with high Lp(a) reach 80 with little plaque, which suggests risk depends on more than concentration. A recent study found Lp(a) particles carrying apoC3, a 'double whammy' that makes them harder to clear.

• Lp(a)-specific drugs are still in trials, and Lp(a) isn't yet a treatment target.

Second-generation antisense drugs that work in the liver are in development, and Novartis has acquired one that has entered phase 3. Dayspring explains why the first trial enrolls only people with very high Lp(a): Mendelian data suggest the drop has to be large to help, and a failed first trial would kill the drug. For now the target is apoB. Statins may nudge Lp(a) up slightly, but they lower other LDLs so much that net risk falls.

• Statin strategy: there's residual risk, and the dose debate is real.

Statins reduce events but leave plenty of residual risk. Trials suggest that if you decide to use one, you should pick the most potent (atorvastatin or rosuvastatin) at maximum dose. Dayspring personally prefers to start lower, depending on risk, rather than use the 'gorilla dose' on day one. Before starting, he urges a CAC scan, an Lp(a) test, family history and blood pressure.

• Ezetimibe and bempedoic acid add non-statin ways to lower apoB.

Mendelian randomization predicted that blocking gut absorption of cholesterol would cut events before ezetimibe's outcome trial confirmed it. On its own, ezetimibe lowers LDL-C about 10–18% and apoB a bit less. Bempedoic acid blocks ATP citrate lyase upstream of HMG-CoA reductase. It is a prodrug activated only in the liver and isn't taken up by muscle, so it should avoid the muscle aches that limit statins, which Dayspring thinks are more common than trials show.

• Omega-3s only lower triglycerides at serious doses: about 4 g/day.

Dayspring says 1–2 g won't do much for triglyceride-rich lipoproteins. With Bill Harris he questions whether EPA alone is uniquely beneficial or whether 4 g of combined EPA plus DHA would work too. It is also unclear whether people with triglycerides below 150 and residual apoB risk would benefit.

• Fibrates are underappreciated in the right patient.

Earlier fibrate trials were badly designed and often didn't target people with high triglycerides. A selective PPAR-alpha modulator is in big outcome trials. Niacin is 'a dead drug' that appears in no guideline, though a few Lp(a) specialists still use it selectively.

EXAMPLES

• The untreated patient with apoB 170

Attia describes a woman in her late 60s with total cholesterol in the 300s, LDL-C 220 and apoB 170 mg/dL, but a coronary calcium score of zero. Dayspring consulted, and the practice chose not to treat her, an example of individualized risk assessment.

• REDUCE-IT

High-risk patients on statins with LDL-C under 100 and triglycerides of about 150 or more (137 was allowed because of assay variability) took 2 g of prescription EPA twice daily with food. Residual risk fell by almost 30%, which Dayspring calls mind-boggling on top of a statin.

• The EPA+DHA trial that stopped

A similar trial of free EPA plus DHA in high-triglyceride patients was halted about two years in, in late 2019, for futility, and

was unpublished at the time. It caught both men off guard.

- **The 38-year-old on 'Alone'**
  Attia describes a superbly fit contestant on the survival show who had had a heart attack at about 38. His instant thought: Lp(a) until proven otherwise. He also points to New York Times reporter Anahad O'Connor, who wrote about discovering he carries high Lp(a).
- **Trilipix turnaround**
  In one patient with triglycerides around 400 and apoB around 200, fenofibric acid (Trilipix) dropped triglycerides to about 100 and apoB to roughly 80–100. Attia's practice has a few patients on it and calls it a 'world beater' for the right case.
- **LDL triglycerides**
  Dayspring says that if he could have only one lipid measurement, he'd choose LDL triglyceride over LDL cholesterol, because it tracks inflammation and poor HDL function. The assay is simple (Denka makes one) but hard to find.

OTHER RELEVANT

- **Pick one metric and stick with it**
  Both men favor apoB. Use the same assay, and ideally the same lab, over time, because NMR, ion mobility and apoB results aren't interchangeable.
- **Test Lp(a) once**
  Combine it with family history, a CAC scan and blood pressure before deciding on treatment.
- **Match the omega-3 dose to the goal**
  For triglyceride lowering, the speakers point to about 4 g/day. Typical over-the-counter doses won't do it. This is their view, not individual medical advice.
- **Context and caveats**
  Recorded September 2020: later trial results for Lp(a) drugs, bempedoic acid and omega-3s postdate it. Dayspring served as chief scientific officer at two cardiovascular biomarker labs from 2012 to 2019.

#128 – Irene Davis, Ph.D.: Evolution of the foot, running injuries, and minimalist shoes

Guest: Irene Davis
Date: 2020-09-14 · Duration: 1:53:06
URL: https://www.youtube.com/watch?v=L7iHfxOrqJI

KEYPOINTS

• Irene Davis moved from prescribing orthotics to minimising support

Davis, a physical therapist and biomechanist who moved from the University of Delaware to Harvard, used to match shoes and orthotics to foot type. Her early instinct came from rehab, where the goal was to remove bracing so patients could build their own strength. Her cousin, who had quadriplegia, had to move 100% of his body with about 25% of his muscle power. Her views on running shoes shifted after she met the evolutionary biologist Dan Lieberman and joined his 2010 Nature paper.

• Matching shoes to foot type doesn't prevent injuries

In Joseph Knapik's military studies of roughly 7,000 service members, people given shoes 'matched' to their arch type had the same injury rates as those who all got the same shoe. The arch types were motion-control shoes for flat, flexible feet, cushioned shoes for high, rigid arches and stability shoes for normal arches. Davis says that result made her question her own prescribing.

• Humans evolved as endurance runners

With 26 bones and many small muscles, the foot is well equipped to walk and run without support. Lieberman's argument is that over 24 hours no animal can cover more distance than a human, because we shed heat through sweat while big animals such as kudu overheat. For about two million years we ran barefoot or in minimal footwear, like 10,000-year-old sagebrush sandals found at Fort Rock, Oregon.

• Running injuries became a research topic only after cushioned shoes arrived

Olympic marathoners around 1900 ran in thin leather soles, and that remained broadly the case until the 1960s and 70s. Davis says the first running-injury articles appeared in the early 1970s, after cushioned, raised-heel shoes let people land on their heels without learning to cushion the landing. She concedes there's little good high-speed data from before cushioned shoes.

• The steepness of the impact matters, not just its peak

Heel striking creates a sharp impact spike before propulsion. The steeper its slope, the higher the rate of loading, which studies link to running injuries. Forces at the knee can reach about seven times body weight, or 1,400 lb for a 200-lb runner. Several studies show people hit harder in highly cushioned shoes such as Hoka. Her rule: if you stay a rearfoot striker, keep cushioning under your heel.

• Retraining runners to land softly cut injuries by 62%

In a study of 320 novice runners, half did eight treadmill sessions, building from 10 to 30 minutes, with visual feedback on their impact and the single instruction to land more softly. Over the following year, their injuries fell 62% compared with controls. They weren't told how to change their form.

• Orthotics weaken the foot, and minimal shoes strengthen it

A study under review fitted healthy feet with orthotics for 12 weeks: intrinsic foot muscle size fell 10–17%, with no change in controls. In Sarah Ridge's study at BYU, gradually walking in minimal shoes strengthened the foot almost as much as an eight-week 'foot core' exercise programme. The arch has about 10 muscles in four layers.

• Make the transition slowly

Davis's 'pre-gait' programme lasts one to three months, longer for older people, who are 'less plastic'. It includes foot strengthening, hip and knee work, teaching people to engage their foot muscles while moving, and hopping, lunging, plyometrics and skipping rope. Patients should be able to walk briskly for about 30 minutes in minimal shoes before adding running, or they'll load the foot faster than it can adapt.

• Knee valgus is the most common malalignment

In more than 700 patients at her running injury clinic, the two most common features are hard landings and the leg collapsing inwards: knees coming in, the kneecap rotating inwards and the pelvis dropping on the opposite side. Her prospective and retrospective studies of IT band syndrome found the same pattern, which pulls on the band's attachment near the knee. Weak hip muscles let the pelvis drop.

• Shin splints are often a heel-striking overuse problem

New runners who land on their heels must use the muscle at the front of the shin to lower the foot. Without conditioning, it becomes sore from overuse.

EXAMPLES

• La Sierra High School

From 1955, Marine Stan LeProtti ran a 30-year programme of daily 55-minute PE with boot-camp-style fitness at this school in Carmichael, California. It is featured in the documentary 'The Motivation Factor'. Only 21 of perhaps 20,000 students reached the top tier. Davis proposes studying the alumni, now aged roughly 55–79.

• Plantar fasciitis

Patients who 'just want to run again' get an approach Davis calls 180 degrees from what they've been told: anatomy lessons on the arch muscles, strengthening and a gradual move to minimal shoes, rather than more support.

• Shoe lifespan

Conventional shoes should be changed every 300–500 miles. Davis now wears Xero shoes for their wide toe box. Attia bought them for his young children.

• Attia learning to swim at 31

He relied on drills and short bursts of 50 yards with lots of rest so his technique wouldn't break down, and compares this to slowly rebuilding running form.

OTHER RELEVANT

- **Transition over months**
  Walk in minimal shoes first, strengthen your feet and hips, then add short runs gradually.
- **Land softly**
  Aim for quieter, lower-impact foot strikes. Treadmill feedback on impact works even without detailed form cues.
- **Don't rely on shoe-type matching**
  Arch-based shoe prescriptions didn't reduce injuries in large studies. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch for knees collapsing inwards**
  If they cave in or your hip drops, strengthen your hips and core, and consider a gait analysis.
- **Let children move**
  Running is an activity of daily living, not a skill to be taught. Minimal footwear lets young feet develop.

#126–Matthew Walker, Ph.D.: Sleep & immune function, chronotypes, hygiene tips, & his book

Guest: Matthew Walker
Date: 2020-08-31 · Duration: 1:41:52
URL: https://www.youtube.com/watch?v=5stcuh065Vk

KEYPOINTS

• The pandemic changed sleep in three ways: how much, when, and dreaming

Walker, a UC Berkeley neuroscientist, cites a sleep-tracking company's data on about 68,000 Americans claiming total sleep rose 20%. He is skeptical of that figure. More cautious peer-reviewed papers in Current Biology found a gain of about 15 minutes. On average, people went to bed about 30 minutes later and woke about 50 minutes later. He expects the data to split into two groups: people sleeping longer and better, and people sleeping less and worse because of job loss or anxiety.

• Lockdown shrank 'social jet lag'

Social jet lag is the gap between weekday and weekend sleep timing. Walker says sleeping until 10 or 11 a.m. on weekends and then dragging the clock back two or three hours on Sunday night is 'like flying back and forth from San Francisco to New York every weekend.' Without commutes and school runs, sleep times became more uniform across the week. He calls it the 'revenge of the night owls,' who could finally sleep in line with their chronotype.

• There are two likely reasons people dreamed more

First, sleeping in extends time in the late-night window where REM sleep is concentrated, so people get more REM cycles and vivid dreams. Second, Walker says REM sleep provides 'overnight therapy.' It isn't time that heals all wounds but 'time during REM sleep.' Because sleep responds to the day before, more emotionally difficult days can produce more REM. That may explain why Peter's dreams intensified even though his schedule didn't change.

• Alcohol can create an anxiety–REM spiral

Walker says alcohol sedates rather than producing natural sleep, fragments sleep by stimulating fight-or-flight activity, and suppresses REM in the later hours. If wine numbs anxiety but removes the REM that processes emotions, the next day starts more anxious, which invites another glass. He stresses he isn't judging. Both men agree responses vary: fast metabolizers may clear an early drink before bedtime, while for others even a glass with a late lunch could crush their REM.

• Short sleep weakens immune defenses and vaccine response

Walker cites a study finding that people sleeping under seven hours were almost three times as likely to be infected with a rhinovirus. In a prospective study of more than 70,000 women, those sleeping five hours or less were 70% more likely to develop pneumonia. Too little sleep in the week before a flu shot led to less than half the normal antibody response. Antibodies remained low 20–30 days later, so the response wasn't just delayed. He says whether this applies to COVID vaccines is unknown and should be tracked.

• Deep sleep depends on time awake; REM depends more on circadian timing

Deep non-REM sleep, front-loaded in the first cycles, is driven mainly by adenosine sleep pressure. Higher cortisol typically means less deep sleep, and melatonin plays a smaller role. REM depends less on how long you've been awake and more on the circadian clock. Walker admits 'we have no idea why' sleep is organized with deep sleep early and REM late.

• Naps are a double-edged sword

In Walker's studies, naps as short as 17 minutes improve learning and memory, and naps have shown cardiovascular benefits too. But naps release sleep pressure. His rule: if you struggle with sleep at night, avoid naps; if you sleep well, regular naps are fine. Some hunter-gatherer groups sleep six to six and a half hours at night plus a summer afternoon siesta. He calls this biphasic pattern different from the historical 'first and second sleep,' which he doesn't think reflects how our physiology is designed.

• Chronotype is largely genetic and shifts with age

About 25–30% of people are morning types, 25–30% are evening types, and the rest are in between. Data from 23andMe and UK Biobank point to about nine contributing genes, mostly clock genes. Teenagers' rhythms shift later, so a 15-year-old who can't fall asleep at 10:30 isn't at fault. Older adults shift earlier, hence Florida's early-bird specials. A validated morningness–eveningness questionnaire works without genetic testing.

• Walker publicly corrected errors in Why We Sleep

Examples he gives: a study described as 'over half a million' people actually analyzed 474,684. Another said to involve over 4,000 people analyzed 2,282 and measured 'cardiac events,' including angina requiring bypass, not 'cardiac arrests.' He also wrote that short sleep doubles cancer risk; he now says it is linked to doubling for specific cancers such as ovarian or lung, and calls the original phrasing 'poor judgment.' The figure of 30–40% of depressed patients responding to sleep deprivation was 45% in a later meta-analysis of prospective studies. Corrections went to a second edition, plus a blog post of more than 8,000 words.

EXAMPLES

• Peter's wearable data after alcohol

Peter says that whenever he reaches two drinks, heart rate variability is 'crushed,' resting heart rate rises 10 to 25 beats, respiratory rate rises two breaths a minute and core temperature rises half a degree. He admits drinking more during the pandemic. One drink around 6 p.m. doesn't seem to affect him.

• Long sleep and mortality, reinterpreted

Walker's book argued that long sleepers die sooner because undetected illness drives extra sleep. He has updated that view: poor-quality sleep, which itself predicts mortality, leads people to stay in bed longer, so it can look like 'long sleep'.

• The 'WHO vs IARC' correction

Critics said it was the IARC, not the WHO, that classified night shift work as a probable carcinogen in 2007, reaffirmed in 2019. Walker notes the IARC is part of the WHO, but says he should have named both.

• Night terrors in children

Night terrors usually arise from deep, dreamless non-REM sleep, so people recall little. Children have more intense deep sleep, which raises the odds. Walker stresses he isn't a pediatric sleep specialist or an MD.

OTHER RELEVANT

- **Build a wind-down routine**

  Sleep is 'not a light switch' but more like landing a plane. Give yourself 15–30 minutes of light stretching or meditation, with phones away. Keep the room cool, get daylight in the first half of the day, and if you've been awake 20 minutes, get up and return only when sleepy.

- **Consider CBT-I sleep restriction for insomnia**

  A six-hour window of solid sleep beats eight hours in bed with two spent tossing and turning. Walker notes he is a scientist, not a clinician, and suggests seeing a doctor if problems persist.

- **Use your chronotype, don't fight it**

  Knowing you are an owl explains the struggle of a 7:15 start on your fourth coffee. It helps couples with mismatched schedules and removes self-blame: 'it's not your fault.'

#125 - John Arnold: The most prolific philanthropist you may not have heard of

Guest: John Arnold
Date: 2020-08-24 · Duration: 2:28:25
URL: https://www.youtube.com/watch?v=TH5ttn3eF_M

KEYPOINTS

• John Arnold started trading as a teenager

At 12 he knocked on doors for lawn work. By around 14, during the 1988–90 boom, he was renting $30 tables at trade shows to sell baseball cards and learning arbitrage, buying cards in one market to sell in another. His father's Crohn's disease meant he got a driver's licence at 14 to help the family. He joined Enron in 1995, driving from Nashville to Houston the weekend after graduating.

• Enron's gas desk was built on deregulation and merit

Natural gas deregulation was completed in 1992, and Enron became a gas merchant and market-maker. In the winter of 1996, the first big price blowout after deregulation, Arnold was supposed to be on a six-month rotation but stayed on the trading desk. He was head trader on the largest gas-trading desk in the world at about 25. He describes the culture as very merit-focused and his own approach as total focus: you couldn't tell a best day from a worst day by watching him.

• He didn't see the fraud coming

Arnold says he doesn't have a full answer to how the trading desk could make so much money while the company went bankrupt in November 2001. The problems sat in the CFO's office, on the financing side. He was fixated on 'The Smartest Guys in the Room' when he read it years later.

• His hedge fund took over the middleman role

After Enron collapsed, many dealers left energy trading in the first half of 2002, and the market became very inefficient and willing to pay for intermediation. He launched his fund in mid-2002, initially letting investors put in only 25% of what they wanted. Early trades were mispriced on risk and reward, such as a bet on a cold winter in 2002, and returns were dramatic: he recalls up 36% in a month, and 150% in three months. He stresses that value at risk, not just value, is what matters.

• Amaranth versus the market, not versus Arnold

Brian Hunter made a fortune in 2005, the Hurricane Katrina year, with a long, bullish position. By 2006 supply was ample and the market bearish, but Hunter kept buying, propping up prices and distorting relative values. Arnold says the popular 'me versus him' story is wrong: it was the whole market versus one huge position, which collapsed as hurricane season began without storms.

• Fundamentals and probability drive his thinking

Arnold asks what the world looks like if weather is at the 90th, 99th or 10th percentile, and how the price compares with fair value. He brings the same discipline to philanthropy, asking what the evidence really shows.

• Why he quit trading at 38

He met his wife in early 2006, and his time on philanthropy grew from about 3% to 10–15%. Competitive markets demand 100% focus, and at 90% it got harder. Natural gas prices peaked around mid-2008 and volatility then declined. By 2012 he had shut down his fund, after about 24 months building the confidence to leave.

• Philanthropy is tiny compared with government

Arnold breaks the US economy down as roughly 60% private sector, 40% government and about 2% philanthropy. Excluding giving to museums, religion and the arts leaves about 1% of the economy. Arnold Ventures, with assets of a little over $2 billion, gives about $400 million a year and has about 120 staff, far more than they ever expected.

• He focuses on changing systems

They found that very few programmes rigorously work, and those that do (like K–12 schooling) are already funded by government. So they focus on changing rules and incentives. They merged their charitable (c3) and advocacy (c4) entities into an LLC, because the wall between them stopped experts from talking to legislators. That advocacy draws fire from both left and right.

• Criminal justice and drug prices are structural problems

Bipartisan tough-on-crime laws responded to violent crime that rose after World War II and peaked in the late 80s and early 90s. Why crime then fell is still debated. About 95% of cases end in plea deals, so an innocent person facing a 20% chance of a 20-year sentence may plead. On drugs, Arnold says the US is about 5% of the world's population but pays about 50% of global pharmaceutical revenue, often 2–3 times other countries' prices, with healthcare at 15–17% of GDP.

EXAMPLES

• The return on reducing recidivism

Arnold's hypothetical: if 80 of every 100 released prisoners would return within five years and a programme cut that to 20, it would almost pay for itself. But the payback takes five years, longer than political cycles, so good data is needed to persuade states.

• Policy is a 20-year game

He cites the advocate whose nearly 20-year campaign against 'Don't Ask, Don't Tell' counted tiny wins, such as a talk at a military academy, for a decade. Attia adds Rick Doblin, who has worked on legalising MDMA therapy since about 1986.

• Healthcare reform needs 20 changes, not one

There are many loopholes and bad incentives, and policymakers lose interest by item four, which is the frustration of the work.

• Debt and interest rates

Arnold warns that the US never really pays down its debt. A return to 2007-era rates of about 5% would hit stock prices and the budget badly.

OTHER RELEVANT

- **Climate and other issues need bipartisan support to last**
  Policy won on a party-line vote can be reversed when power changes hands.
- **Kids shouldn't grow up as checkbooks**
  Arnold doesn't want his children working at the foundation in their 20s and 30s, the decades for building their own lives.
- **For young philanthropists, give where the evidence is strong**
  He points to the Further Pledge, giving everything above roughly $30,000–50,000, as an example of high-impact giving.
- **Judge philanthropy by the theory of change**
  Ask what system or incentive a grant changes, not just how many people it reaches.

#123–Joan Mannick & Nir Barzilai: Rapamycin and metformin—longevity, immune enhancement, & COVID-19

Guest: Joan Mannick & Nir Barzilai
Date: 2020-08-10 · Duration: 2:16:12
URL: https://www.youtube.com/watch?v=XVA4v0R5PuI

KEYPOINTS

• Mannick moved into aging research at 50 to test mTOR inhibition in humans

Around 2012, at Novartis, Joan Mannick asked to work on aging. Colleagues questioned why she'd give the drug sold to suppress the immune system in the hope of enhancing it. Her reasoning was that inhibiting mTOR had extended life in every organism tested: yeast, worms, flies and, through the NIH's Interventions Testing Program (ITP), mice. A lifespan trial in humans was impossible, so she looked for a measurable human endpoint and carefully dosed the drug to minimise side effects.

• Turning mTOR down, not off, improved immune function in older people

Her 2014 study gave older adults a rapamycin analog (RAD001, everolimus) before a flu vaccine. The two lowest doses, 0.5 mg daily or 5 mg weekly, worked best, better than 20 mg weekly. These doses gave less mTOR inhibition. Exhausted T cells (PD-1 positive CD4 and CD8 cells, which accumulate with age) fell by about 25–30%. Attia calls the paper his '2014 Christmas gift'.

• Low intermittent doses mostly spare mTORC2

Mannick says the low doses mainly hit mTORC1. They caused no real hyperglycaemia or high blood lipids, which are the side effects linked to mTORC2. Her newer compound, RTB101, is catalytically selective and has a 4–6 hour half-life, so once-daily dosing inhibits mTORC1 for only part of the day. She compares it most closely to 0.5 mg of everolimus daily.

• RTB101 reduced respiratory infections in phase 2

In the first phase 2 study, six weeks of RTB101 combined with everolimus looked best. In the second, which lasted 16 weeks in a sicker population, RTB101 alone did better. In both, RTB101 reduced respiratory tract infections, and one phase 2b study showed 52% less severe disease. Mannick's interpretation is that mTOR inhibitors don't prevent infection. Instead, they produce a better immune response so symptoms are milder. Lab-confirmed infections were too few to analyse well.

• Barzilai chose metformin for strategy, not because it's the best drug

Barzilai says rapamycin may be the better drug. Metformin was chosen for TAME (Targeting Aging with Metformin) because it is cheap, safe and generic, and has decades of data, making it a tool to establish aging as a target the FDA can accept. He cites about 30 animal studies in which metformin extended lifespan. The ITP results for metformin alone are mixed. Metformin plus rapamycin produced some of the longest-lived mice in the programme.

• The diabetic-patient paradox

Attia highlights a frequently cited finding: people with type 2 diabetes on metformin lived longer than matched people without diabetes, despite the vascular damage diabetes causes. The guests frame metformin as acting on several interacting hallmarks of aging at once. Barzilai declines to name a single most important mechanism.

• TAME is designed to measure delay of multiple age-related diseases

The trial is powered on 3,000 participants, and the team may expand to 3,500. It runs across 14 centres and includes ancillary studies, some needing only 250 people. Participants take 1,500 mg of extended-release metformin a day, three 500 mg tablets. That is the dose Barzilai takes himself.

• Older people's COVID risk is about comorbidity as much as immunity

Barzilai says people aged 80 and over are about 180 times more likely to die of COVID than 20-year-olds. Attia argues that to make someone resistant you would reduce their comorbidities first, not just raise immunity by 10–20%. Both drugs might help on both fronts. Barzilai criticises ageism in leaving older people to quarantine.

• Commercial aging clocks can mislead

Barzilai points out that clocks combine methylation with blood markers such as glucose, insulin and vitamin D. Correcting a vitamin D level of 20 with 5,000 IU a day could 'improve' biological age, even though no trial has shown vitamin D extends life. He prefers proteomics: in 1,000 people aged 65–95, hundreds of proteins changed with age. In about 500 children of centenarians, around a third of those changes were slowed.

EXAMPLES

• Why Attia stopped metformin

He began metformin in May 2010 at 2,000 mg a day without titrating up, which caused about two months of nausea. Now he titrates patients up from 500 mg at night. In 2018, testing zone 2, defined as the most work he could do with lactate under 2 mmol, he found his resting lactate around 1.6 mmol, unusually high. That raised concern that metformin was hurting his mitochondrial performance, so he stopped.

• Metformin blunted exercise gains in older adults

In a study of people around 75, metformin blunted the improvements from exercise. Barzilai says the gene-expression data showed mTOR transcripts were higher with exercise alone and dampened by metformin. That is consistent with metformin lowering mTOR while exercise raises it.

• Early observational COVID data

Barzilai cited a not-yet-peer-reviewed University of Minnesota analysis of about 6,000 patients. Women on metformin had roughly 21–22% lower COVID mortality, along with lower TNF-alpha. He admits he couldn't tell from the paper whether the effect was limited to people with diabetes. For Chinese data he relied on indirect figures because exact data cost $3,500.

• Rapamycin for Attia since about 2018

Attia wanted to take rapamycin from 2011–2012 based on animal data, but his biggest fear was immune suppression. Mannick's 2014 paper made him bolder, and 5 mg once a week looked like a reasonable starting dose.

- **Centenarians' families**

  The intro cites Barzilai's Longevity Genes Project of more than 500 healthy people aged 95 to over 110, plus their offspring. Barzilai notes centenarians get the same diseases about 30 years later and behave physiologically like much younger people, rather than avoiding disease entirely.

OTHER RELEVANT

- **Separate dosing goals**

  Mannick and Attia discuss using low, intermittent rapalog doses to enhance immunity. High, immunosuppressive doses might help suppress the dangerous late immune overreaction in severe infection. A small Hong Kong influenza study and one hospitalised-COVID trial were the only data cited, so it remains unproven.

- **Titrate metformin**

  If metformin is prescribed, start low (500 mg at night) and build up to avoid GI side effects. Exercisers may want to weigh possible blunting of training adaptations.

- **Prefer trials to associations**

  Barzilai warns that if metformin delays death, observational data may show more people living longer with diseases like Alzheimer's, which is a misleading signal. Only randomised trials settle this.

- **Risk tolerance should update with the situation**

  Attia argues that the stakes in summer 2020 justified a different regulatory appetite for risk than in 2018. Mannick prefers generating data in trials before acting.

#122 - Lori Gottlieb: Understanding pain, therapeutic breakthroughs, and keys to emotional health

Guest: Lori Gottlieb
Date: 2020-08-03 · Duration: 1:30:12
URL: https://www.youtube.com/watch?v=biSHLJKli0k

KEYPOINTS

• Gottlieb's winding path shaped how she does therapy
After college she worked in film development, then at NBC the year ER and Friends premiered. The ER's physician consultant told her she seemed happier in the real emergency room than at her day job, and urged her to try medicine. She went to Stanford medical school, left to become a freelance journalist, and later retrained as a therapist while raising an infant. She says none of these moves were impulsive: she weighed leaving medicine for about two years.

• The sunk-cost argument rarely survives scrutiny
Attia left medicine around 2006, at 33, while people around him argued that ten years of training were too much to walk away from. His answer was that he still had about 40 years of work ahead, so the question was what he wanted to do for those years. A Hopkins attending, Peter Pronovost, gave him a Joseph Campbell book with a line about the hero having the courage to follow his bliss. Even so, the decision took him four months.

• 'We all have a terminal diagnosis'
A young patient diagnosed with breast cancer just after her honeymoon asked why people need a terminal diagnosis before they pay attention to what they want from life. Gottlieb's reflection is that life has a 100% mortality rate for everyone. Most of us drown out the quiet inner voice that knows what we want with outside noise about what's practical.

• Obnoxious behaviour is often armour around pain
John, the first patient in her book Maybe You Should Talk to Someone, arrives complaining of insomnia caused by the 'idiots' around him, calls her his 'mistress' and insults everyone. Gottlieb saw glimpses of the tender person underneath, starting with his story of losing his mother at six; she was hit by a car while trying to save a student. Attia notes that by the end of the book readers love him.

• The relationship matters more than the method
Gottlieb says research consistently finds the patient–therapist relationship is the biggest single predictor of success, ahead of the therapist's training, approach or years of experience, though those still matter. Her goal in every session with John was simply one moment of real connection.

• Breakthroughs come from a thousand small strikes
Attia compares it to a stonemason who strikes a stone a thousand times with no visible effect until the next blow splits it. Six months in, John was still mocking her shoes and ordering the same salad, yet the small moments of connection were what made the eventual 'breaking open' possible. Gottlieb contrasts breaking open with breaking down.

• The hardest step in change is maintenance
Gottlieb's chapter 'How Humans Change' describes stages people go through before they act at all. Taking action gets the attention, but she says the most important stage is the last one: keeping the change going. Quick fixes may work in the short term but rarely last.

• Asking about suicide doesn't plant the idea
Gottlieb says therapists must ask whenever someone is depressed, and parents of teenagers especially shouldn't hold back. Being asked often brings relief, and isolation is one of the biggest risk factors. She distinguishes two kinds of despair: people whose good life was derailed by a loss, and people who feel life has always been barren.

• Many people hand themselves a life sentence for being human
Gottlieb asks what the right 'sentence' is for past mistakes. Many people effectively choose the death sentence: alive but not living, because they believe they don't deserve joy, so they sabotage it. Learning to forgive yourself for being human is central to both John's and Rita's stories.

• We shake the bars instead of walking around them
Her own therapist, Wendell, once showed her a cartoon of a prisoner desperately shaking his cell bars while the sides are open. People often prefer the familiar role of the victim over the frightening freedom of change. When the bars open, Gottlieb says, people feel elated and frightened at the same time.

EXAMPLES

• Rita's 70th-birthday deadline
Rita, 69, estranged from her adult children and living alone after several failed marriages, told Gottlieb that if life didn't improve by her birthday she didn't want to live; she was giving therapy a year. Gottlieb assessed the risk and judged that Rita had come because she wanted change. Her goal was to get Rita 'to join the human race again'. Attia found Rita's letter to Myron, which reveals her shame, one of the most moving parts of the book.

• Pedicures and skin hunger
Rita got pedicures that no one would see because they were the only time anyone touched her. Gottlieb uses this to explain skin hunger: the many small daily touches, such as hugs, handshakes or brushing hands with a barista, that isolated people lose entirely.

• 'Just a few sessions' for a breakup
Gottlieb went to Wendell expecting a handful of sessions to get over a breakup. It became a much deeper reckoning. She believes the things we least want to happen often come just before real transformation.

• The Valentine's Day proposal deadline
A man called before the holidays wanting to know by Valentine's Day whether to propose. Gottlieb told him she could help

him get clarity but couldn't promise an answer on a schedule from someone she didn't yet know. She uses the story to describe our 'instant gratificationitis' around therapy.

OTHER RELEVANT

- **Think of therapy as a second opinion on your life**
  The people in your life are too close to see clearly. Gottlieb finds most people come for relational problems with a partner, parent, sibling, adult child or colleague, or with themselves, when life hasn't gone the way they expected.
- **Expect therapy to focus on the present**
  Endlessly rehashing childhood is a misconception. The past matters to the extent that an old story is still causing trouble now. Therapy also isn't meant to last forever: a good therapist keeps its purpose clear and works toward you leaving.
- **If you're worried about someone, ask directly**
  Ask about suicidal thoughts plainly, especially with a teenager who seems depressed, and treat isolation as a warning sign. Giving voice to those feelings often brings relief rather than risk.
- **Plan for maintenance, not just the start**
  When you make a change, decide in advance how you'll sustain it and what you'll do after a relapse, since keeping the change going is the step where most efforts fail.

#121 – Azra Raza, M.D.: Why we’re losing the war on cancer

Guest: Azra Raza
Date: 2020-07-28 · Duration: 1:54:55
URL: https://www.youtube.com/watch?v=3GcP75TXEfM

KEYPOINTS

• Raza argues that age-adjusted cancer mortality is essentially where it was in 1930

Peter usually says cancer mortality hasn't changed since about 1970. Raza goes further. She says the roughly 27–30% decline over the last 30 years followed a 30-year rise driven by smoking, so the fall mostly tracks the drop in smoking. In her words, 'otherwise we are really at square one.' She compares herself to Nietzsche's man with a lamp at noon, except she is 'looking for an adult in the room.'

• Most cures still come from 'slash, poison, burn,' and only in early disease

Raza's breakdown: of newly diagnosed cancers, about 68% are cured, overwhelmingly with surgery, chemotherapy and radiation. The 32% who present with advanced disease mostly can't be cured with those same tools. She takes this as the best evidence that the only reliable lever is catching cancer early. Some of the first chemotherapy agents came out of chemical weapons research, and she gave all three of the original drugs to her own husband.

• Real breakthroughs are real but rare

Gleevec for CML and GI stromal tumors proved targeted therapy can work, but those are rare cancers, and Peter doubts it has moved overall mortality even 1%. Melanoma survival is dramatically better with checkpoint inhibitors. Still, Raza estimates all such successes together account for under 10% of cancers. Her question is whether they reflect the 'quarter of a trillion dollars' invested. She is clear that this research should continue.

• 95% of experimental cancer drugs fail, and Raza says many of the 5% shouldn't have passed

In her account, the 'winners' often extend survival by a few months in only 20–30% of patients. Approvals often rest on progression-free survival: if the tumor isn't seen to grow for an extra two and a half months but the patient dies at the same time, the drug can still be approved and earn billions. Peter adds that a 'partial response' has a somewhat arbitrary definition and that durability is rarely discussed.

• The core scientific problem, in her view, is the preclinical model

Raza blames the failure rate on reductionist testing platforms such as cell lines, 2D and 3D cultures, and genetically engineered or immune-compromised mice. She says she supports animal research for biology, but not for drug development, because what a drug does in a mouse is only true for mice. She would not even rely on animals for safety. She points to the FDA's phase zero design, which starts humans at 1/500th of a dose and escalates.

• New drugs often cost far more for small gains, with ruinous consequences for patients

Her figures: 42% of newly diagnosed cancer patients will be financially ruined by the second year, and 50% of women with breast cancer are pursued by collection agencies. Peter recalls that Avastin in metastatic colorectal cancer added about four months of median survival at roughly $100,000, which led some publicly funded systems to rely on quality-adjusted life years. Peter flags that his Avastin details may not be exact.

• Good intentions slowly produced a broken system

Raza uses the frog-in-slowly-heating-water image: each step began with good intentions. Peter adds that publication as a promotion metric fuels a 'cottage industry' of low-quality journals and irreproducible studies. He also says that by his own analysis from about five years earlier, slightly more than half of global oncology research money ran through the NCI after Nixon's war on cancer, though he notes he could be a little wrong.

• Her proposed solution is aggressive early detection, monitored continuously

Raza argues that mammograms and PSA failing on their own doesn't prove early detection fails. She wants genomics, transcriptomics, proteomics, metabolomics and imaging combined with AI, with up to '50 tests if we have to,' read continuously rather than once a year. Peter frames it as three rules: don't get cancer, screen smartly, and treat when tumors are in the millions rather than billions of cells. He estimates lifestyle changes could cut cancer risk 30–50%, based on his reading of the literature.

• Powerful late-stage therapies should move earlier

She calls current treatment 'paleolithic,' quoting the line about beating a dog with a baseball bat to get rid of its fleas. She notes that whole industries exist just to manage CAR-T side effects. She says such therapies should be developed, but used when tumor burden is low.

EXAMPLES

• Andrew, 22, and the book The First Cell

Her daughter Shahzad's best friend developed arm weakness, was quadriplegic within hours, and had a 9 cm unresectable glioblastoma. His first words were 'just call Azra… she will cure me.' Their helplessness pushed her to write after years of turning down literary agent John Brockman.

• 'Seven and three' for AML since 1977

Raza still uses cytarabine plus daunorubicin. Five-year survival rose from about 10% to about 26%, which she credits to better antibiotics and transfusions, not new drugs. A liposomal version for patients aged 60–75 costs $45,000 versus $5,000, approved on a 3.7-month median survival gain in selected patients.

• Karachi in the early 1970s

Raza was born and raised in Pakistan and entered science through medicine. She saw patients arrive by donkey cart with fungating tumors. Her first patient, a young woman with AML and a large spleen, made her favor studying liquid tumors, which can be sampled repeatedly.

• Harvey Preisler's acceptance

Her husband, head of the Roswell Park leukemia program, died in 2002 after a five-year battle; their daughter was four at diagnosis. On hearing his diagnosis he said, 'I'm glad it's me and not you or Shahzad.' Raza admits kicking doors and crying

while he called it 'the luck of the draw.'

• A 60,000-sample tissue bank

Since 1984 Raza has collected serial blood, marrow and germline samples, doing every marrow herself. She hopes to trace pre-leukemia to leukemia, find early biomarkers, and find the 'first cell.'

OTHER RELEVANT

• Read 'approved' and 'progression-free survival' skeptically

When a new drug is touted, ask about median overall survival, what fraction of patients benefit, and whether the gain is weeks or months. Raza's 3.7-month example shows how far headlines can outrun benefit.

• Smarter screening beats single tests

Peter points to PSA velocity, PSA density and 4Kscore over PSA alone, citing his Ted Schaeffer episode, and to his Raj Attariwala episode on mammography's limits. Raza highlights an FDA-approved fingertip-blood PSA chip and Toshiba's claim of 13 cancers from one drop of blood for $180 in four hours.

• Treat liquid biopsies as promising but early

Both are optimistic about multi-cancer blood tests such as Grail, which Raza says was in phase 2 with about 30 cancers. Peter avoids predicting a timeframe and wants regulatory milestones first.

#119 – Terry Real: Breaking the cycle of shame, anger, and depression

Guest: Terry Real
Date: 2020-07-15 · Duration: 1:39:45
URL: https://www.youtube.com/watch?v=QbI4fm2cNz8

KEYPOINTS

• Terry Real became a family therapist to understand his father's violence

Real grew up poor in Camden, New Jersey, the 'scapegoat child' of a depressed, abusive father. He says he started his career at about age four, because he needed to make sense of his father so he wouldn't repeat him. At about 28 or 29, after years of gently pushing past his father's defences, he finally heard his father's story.

• Trauma is passed down

Real's father lost his mother at nine during the Depression. His own father, whom he called a 'passive loser', lost his candy store, and in a fit of depression tried to gas himself and his two sons in the family car. Real's father, then 11, kicked out a window, grabbed his younger brother and got out. He says that was the last real contact he had with his father. Afterwards he despised vulnerability in himself and in others.

• Relationships move through harmony, disharmony and repair

Real borrows this model from Ed Tronick's infant-observation research. Closeness, rupture and a return to closeness is the basic rhythm of healthy relationships. Everyone is shaped by their parents' imperfections, which form what Real calls the adaptive child. What matters is whether ruptures are followed by repair and accountability, or just more injury.

• Shame is about who you are; guilt is about what you did

Children who are neglected or mistreated take on shame and feel bad about themselves. Real says it is actually 'compassionate' for a child to blame himself, because a random, scary world is harder to accept than 'I'm bad.' Guilt, feeling bad about a behaviour, is healthy. He wants men going from inflated entitlement to deflated shame to land in the middle: accountable but not worthless.

• Grandiosity and shame are two sides of the same coin

Real describes a 'one-up/one-down' seesaw. Men in this culture tend to lead from overt grandiosity, with shame hidden underneath. The central move of traditional masculinity, he argues, is turning shame into grandiosity and helplessness into attack. Real, now 69, says that whereas he swung up and down as a teenager, these days he rarely goes one-up or one-down.

• Male depression is often covert

When his book 'I Don't Want to Talk About It' first came out in the late 1990s, depression was seen as a women's disease, diagnosed two to four times more often in women. Men hide it because being overwhelmed by feelings feels unmanly, and families and doctors collude: he cites studies suggesting family physicians miss depression in about 70% of cases. The defences are what show: radical isolation, anger, sexual acting out and self-medication with alcohol or drugs.

• Real self-esteem can't be earned

He describes three forms of false self-esteem: performance-based (what I can do), other-based (being loved or admired) and attribute-based (looks, wealth). He says the California self-esteem drive was misguided. True self-esteem is 'spiritual, ontological': you have worth because you exist, not more or less than anyone else, and nothing you do adds to it or subtracts from it.

• Narcissism is too little self-love, not too much

Narcissus was an addict to his reflection. Grandiosity covers an inner emptiness, which is why it needs constant feeding.

• Patriarchy hurts both men and women

Real, who has practised feminist family therapy for about 40 years, cites Carol Gilligan's 'In a Different Voice': girls at 13 or 14 fall prey to 'the tyranny of the nice and kind' and lose their voice. Patriarchy, he says, rests on despising vulnerability and on the delusion of dominance. He argues that relational growth, for both sexes, is the next step for feminism.

• Relational skills are a technology you can learn

Real's model, Relational Life Therapy, treats relating as a skill set, like learning to ski in your forties, play the piano or speak French. It takes about as long if you're diligent. The adaptation that protected you as a child, such as thick walls against an intrusive mother, can get you into trouble at 45 with an emotional spouse.

EXAMPLES

• Skates on the wrong feet

Real put his son Justin's skates on the wrong feet and pushed him to keep going despite his complaints, until he saw the red blisters forming. He admits he would have listened if it had been his daughter. 'I was the voice of patriarchy.'

• Witness abuse

Children have no boundaries, so screaming at your spouse in front of them lands as if you were screaming at them, at five or at 12. Real gives couples 30 days to stop. If they're still yelling after that, one of them moves out.

• Attia's Instacart rage

An order delayed again and again sent Attia into a spiral of contempt for the shopper. Remembering David Foster Wallace's 'This Is Water' ('I don't know her story'), he ended up almost inviting her to dinner. Real says he went from 'batting zero' to about .500 at this.

• A father's blessing

As his father lay dying of ALS, paralysed and cared for by Real's mother, a nurse, Real asked for his blessing. Amid a comic family squabble on the phone, his father said: 'May nothing I've said or done in your life prevent you from achieving your greatest potential.'

• Harry and the basement

A client who, as a child, locked his little sister in the basement to keep her out of their father's way was protecting her. Real worked to show him how the angry child's defences were now driving his adult behaviour.

OTHER RELEVANT

- **Prioritise repair over perfection**
  Ruptures are inevitable. Come back, take responsibility and reconnect.
- **Aim to be neither one-up nor one-down**
  Notice when you go grandiose or into shame, and come back to the middle.
- **Look for depression behind anger and withdrawal**
  In men it may show up as isolation, irritability, drinking or acting out, rather than sadness.
- **Never fight in front of the kids**
  If yelling continues, consider a physical separation.
- **Treat relational skills like any adult learning**
  Expect years of deliberate practice, not a single insight.

#118 – Lloyd Klickstein, M.D., Ph.D.: Rapamycin, mTOR inhibition, and the biology of aging

Guest: Lloyd Klickstein
Date: 2020-07-09 · Duration: 2:14:54
URL: https://www.youtube.com/watch?v=fIAM2YADBbg

KEYPOINTS

• Context: the phase 3 trial later failed

This interview was recorded in September 2019. Attia notes up front that resTORbio's phase 3 trial of RTB101, discussed throughout, was later published and did not meet its primary endpoint. Everything said about that programme should be read with that in mind. Lloyd Klickstein, a rheumatologist and immunologist, left Harvard academia in 2006 for the Novartis Institutes, partly because grant funding had become far more competitive than in the late 70s and early 80s.

• Translational medicine works in both directions

At Novartis, Klickstein set up a 'new indication discovery unit' around 2008–09. It chose projects with real medical need, scientific tractability, and no existing Novartis work (ideally no one else's either). Joan Mannick brought the idea of testing mTOR inhibition against ageing of the immune system and started the project around 2010. Klickstein stresses that observations can move from humans back to animals as well as forward.

• The 2009 mouse study made rapamycin a credible longevity drug

Rapamycin extended lifespan in mice that were already about 600 days old, an age at which caloric restriction no longer extends life. Klickstein cites gains of roughly 15% and 25%. TOR was identified in yeast by Michael Hall's work in 1991 and in mammals in 1994, including by Sabatini. Ilya Mechnikov's work on cells that engulf pathogens (phagocytosis) earned a share of the 1908 Nobel Prize.

• mTORC1 and mTORC2 behave differently

Rapamycin, bound to FKBP12, inhibits mTORC1 but acts unevenly on its targets, more weakly on 4E-BP1 and less still on ULK1, which helps start autophagy. It doesn't directly inhibit mTORC2. With sustained exposure, though, signs of mTORC2 inhibition appear within a week to a month: high blood sugar and high triglycerides. Klickstein says the exact mechanism isn't known.

• Dose and schedule determine whether it boosts or suppresses immunity

The 2014 trial gave adults over 65 the rapalog everolimus (RAD001) in one of three regimens. 0.5 mg daily gave partial, sustained mTORC1 inhibition. 5 mg weekly gave full inhibition for a couple of days. 20 mg weekly fully inhibited it throughout. High doses of rapalogs are immunosuppressive, which is why rapamycin (sirolimus, approved in 1999) is used in transplant patients.

• The 2014 result: a better flu-vaccine response at low doses

The pre-specified target was a 1.2-fold improvement in flu vaccine response for two of three strains, the threshold earlier work linked to fewer symptomatic infections. Both low doses reached it, but 20 mg weekly improved only one strain. Checkpoint proteins such as PD-1, markers of exhausted T cells, fell by about 10–20% on CD4 and CD8 T cells. Adverse events also listed fewer infections over the following year, although influenza alone was too rare to analyse.

• Side effects rose with dose

Attia remembers mouth ulcers as the classic side effect in transplant patients on 2–4 mg daily. In the trial, mouth ulcers affected about 4% of people on 0.5 mg daily or 5 mg weekly, compared with about 17% on 20 mg weekly. Total adverse events rose with dose, from about 35 to 46 to 109 across the three drug arms of roughly 53 people each. That supports the idea of a therapeutic window for low or intermittent dosing.

• The 2018 study added a catalytic inhibitor

In 264 older adults, BEZ235 (later RTB101), an inhibitor that blocks mTOR's catalytic site, and its combination with RAD001 reduced respiratory tract infections. The combination and RAD001 improved flu vaccine response, but RTB101 alone did not. Klickstein clarified that RTB101 is not everolimus combined with something else.

• The phase 2b refined the target population

With 652 patients across southern- and northern-hemisphere cold and flu seasons, 10 mg of RTB101 once daily again reduced respiratory infections. Benefits were seen in people over 85 and those with asthma or diabetes, but not in smokers or people with COPD. It was used to power phase 3, which included a fully enrolled study of 1,024 people aged 65 and over treated for 16 weeks.

• Fasting and rapalogs overlap but aren't the same

Klickstein mentions a mouse study in which 24 hours of fasting before an otherwise lethal ischaemia–reperfusion injury let most or all of the mice survive, while fed mice died. He doesn't know how to extrapolate that to humans, since the metabolic consequences of the fast may matter more than its length.

EXAMPLES

• A Cialis analogy for drug exposure

Attia compares 5 mg daily of Cialis (tadalafil) with 20 mg on demand. The daily dose keeps a narrow gap between peak and trough and causes fewer side effects. A single 20 mg dose overshoots, but lasts two to three days.

• Ketamine activates mTOR

Klickstein calls intravenous ketamine 'almost a miracle drug' for major depression, working in minutes to hours with a large effect size. Its mechanism is unclear, and ketamine has been linked to mTOR activation, the opposite of rapamycin.

• Rapamycin binds more than FKBP12

Attia was surprised to learn that rapamycin binds at least FKBP12 and FKBP51. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Metformin**
  Klickstein calls it a wonderful drug with excellent data in diabetes, plus some retrospective longevity signals in people with diabetes.

OTHER RELEVANT

- **Don't extrapolate from transplant doses**
  The doses that suppress immunity differ from the low, intermittent doses studied for ageing.
- **Watch metabolic markers on a rapalog**
  Rising glucose or triglycerides may signal mTORC2 effects. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Weigh promising phase 2 data cautiously**
  This programme looked strong in phase 2 and still failed its phase 3 primary endpoint.
- **Use vaccine response as one biomarker of immune ageing**
  Ageing immune systems respond weakly to vaccines, so a better response is a measurable outcome.

#114 – Eileen White, Ph.D.: Autophagy, fasting, and promising new cancer therapies

Guest: Eileen White
Date: 2020-07-09 · Duration: 1:58:54
URL: https://www.youtube.com/watch?v=93U__YRR-aU

KEYPOINTS

• Eileen White found autophagy by accident, through apoptosis

Eileen White, of the Rutgers Cancer Institute of New Jersey, did her postdoc with Bruce Stillman at Cold Spring Harbor. She was given an adenovirus oncogene and found it was a viral version of BCL-2, a human oncogene that blocks apoptosis (programmed cell death). Cells that couldn't commit suicide survived even in buffer with no nutrients. Explaining how led her lab, in the early 1990s, into autophagy, then barely studied in mammals.

• Apoptosis is a tidy, tumour-suppressing death

Unlike necrosis, where cells burst and inflame surrounding tissue, apoptosis breaks a cell down in a controlled way and packages it into apoptotic bodies. Macrophages clear these, which limits inflammation and may help antigen presentation. p53 activates apoptosis-promoting proteins such as PUMA and NOXA, which antagonise BCL-2. Common hotspot mutations of p53 can both disable it and actively promote cancer, so the old 'loss versus gain of function' teaching is too black-and-white.

• Autophagy is the cell's recycling system

Under stress such as starvation, cells engulf their own components in autophagosomes and send them to lysosomes to be broken down for fuel and building blocks. Exercise induces autophagy strongly, and muscle needs it because exercise damages muscle. White points out that much of a cell's mass is protein, a point David Sabatini has made, so recycling proteins is a major supply route.

• Autophagy is essential to life

Mice lacking the autophagy genes ATG5 or ATG7 are born but die in the newborn period. When White's lab deleted autophagy in adult mice, they died of neurodegeneration within two to three months. If those mice were fasted, they were all dead within 16 hours. The brain and liver depend on autophagy for long-term protection.

• Tumours depend on autophagy more than the host does

In mice with lung cancer driven by RAS, deleting an essential autophagy gene throughout the body killed the tumour before the mouse. A newer model from a former trainee and a UK lab can switch autophagy off and back on, and normal tissues show a remarkable capacity to recover. That suggests treatment could use a temporary window.

• Some cancers are especially autophagy-dependent

RAS-driven cancers, BRAF V600E lung cancers and melanomas, and homologous-recombination-deficient breast cancers appear particularly sensitive. Lung cancers that have lost LKB1, the tumour suppressor that activates AMPK, can't turn on this protective response to low energy, a mouse model made by Jessie Guo, now at Rutgers.

• The paradox: autophagy prevents cancer yet feeds established tumours

By clearing damaged components, autophagy buffers the stress that can lead to cancer. Once a tumour exists, it uses autophagy to survive. White cautions against equating caloric restriction with autophagy. Caloric restriction may limit tumours partly through other routes.

• No one knows the dose of fasting

Attia is sure that after about seven days of water-only fasting, autophagy is 'fully cranked', and that a 12-hour gap does nothing. Where between those it switches on is unknown. That leaves his own protocols (3 days monthly, 5 or 7 days quarterly) as guesses. Measuring autophagic flux requires blocking lysosomal breakdown with bafilomycin or hydroxychloroquine and tracking the conversion of LC3-I to LC3-II, so blood-cell measurements in fasting people only give clues. George Cahill's classic 40-day fasting study showed that the first, second and third 24 hours are metabolically very different. The open question is whether 48–72 hours gets you 80% of the benefit or only 20%.

• Metabolic tracing could answer this

White proposes labelling mice with carbon-13 or nitrogen-15 tracers to see how different tissues use nutrients during fasts of different lengths. That could define the roughly 50 metabolites or proteins that track autophagy, and later test them in humans. It's possible now, she says, in a way it wasn't 20 years ago.

• Delaying chronic disease is the real target

Attia argues that the animal and centenarian data point to delaying the onset of chronic disease, which by his analysis accounts for 82% of US deaths over 50. He notes that for solid tumours, median survival has improved by less than about a year since 1970.

EXAMPLES

• A Lynch syndrome patient on Keytruda

A friend of Attia's with Lynch syndrome developed unresectable pancreatic adenocarcinoma wrapped around his mesenteric vessels. A paper in the New England Journal of Medicine on mismatch-repair-deficient tumours led Attia to push for the anti-PD-1 drug Keytruda through a trial. Five years later he was disease-free.

• Mutation burden and immunotherapy

Melanoma responds well to CTLA-4 and PD-1 blockade because it carries so many mutations. Yet some high-mutation tumours don't respond. White's NIH grant builds mouse models with low, medium and high mutation burden to test how blocking autophagy affects the response.

• The 2016 Nobel

The Nobel Prize for autophagy went to work in yeast that White's field then extended to mammals.

• The Warburg debate

Attia cites the 2009 Science paper by Matt Vander Heiden, Lewis Cantley and Craig Thompson, which argued that cancer cells' heavy glucose use serves biosynthesis, not just energy.

OTHER RELEVANT

- **Exercise as an autophagy inducer**
  Exercise is a potent, low-risk trigger. White says it's less of a dosing problem than fasting, since most people just need more.
- **Treat fasting protocols as unproven**
  The duration and frequency of fasts are educated guesses until autophagy can be measured in humans. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Inherited risk still matters**
  Good health practices don't erase a BRCA mutation. Screening still matters. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Watch for autophagy-blocking cancer trials**
  Combining autophagy inhibition with targeted drugs or immunotherapy is an active research direction, but still experimental. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#117 – Stanley Perlman, M.D., Ph.D.: Insights from a coronavirus expert on COVID-19

Guest: Stanley Perlman
Date: 2020-07-09 · Duration: 1:43:55
URL: https://www.youtube.com/watch?v=YgY4svjn-M4

KEYPOINTS

• A coronavirus researcher since long before COVID

Perlman, a microbiology, immunology and paediatrics professor at the University of Iowa, has studied coronaviruses for nearly four decades. He trained as a paediatric infectious disease physician and was drawn to how viruses damage developing brains. A mouse coronavirus causes demyelination resembling multiple sclerosis, and he studied that model for about 20 years before SARS arrived. His lab now uses mouse models of SARS-CoV-1 and SARS-CoV-2. The conversation was released in late June 2020, so it reflects what was known then.

• What makes a virus a coronavirus

Coronaviruses are grouped by how they look under the electron microscope, how they replicate and, now, their genetic relatedness. Belonging to the family doesn't mean sharing hosts. Members infect mice, pigs, cows, cats, dogs and bats, and close relatives infect insects and snakes.

• Animal reservoirs make viruses hard to eliminate

Measles and smallpox infect only people, which is why eliminating them is possible in theory. Most coronaviruses can cross species: MERS is a camel virus, SARS-CoV-1 jumped between animals, and SARS-CoV-2 can infect animals. Attia notes a reservoir lets a virus 'hide' outside humans even when most people are immune, as West Nile does in birds.

• SARS-CoV-1 burned out for two reasons

It emerged from a live animal market in Guangzhou. Perlman says it was almost certainly a bat virus that spread to other animals, and up to a third of animal handlers had antibodies. It was declared eliminated in July 2003 after about 8,000 cases worldwide. It had no ongoing animal reservoir, and people weren't contagious until they were sick, so identifying and isolating cases worked.

• MERS: deadly but poorly transmissible

MERS, in a slightly different branch of the family, kills about 35% of those diagnosed, with roughly 2,500 confirmed cases. Camels probably carried it since at least 1983, though it was found in people only in 2012. Perlman attributes the limited spread to an R0 of about 0.3. Infected workers returning to poorer countries infected no one, yet in Korea a single patient infected 186 people, mostly in hospitals.

• SARS-CoV-2 combines a cold virus with a SARS-like lung disease

Perlman describes it as a common cold coronavirus in the upper airway plus SARS or MERS in the lungs. That combination gives it both transmissibility and severe disease. If only about one in five infected people develop pneumonia, its lethality among pneumonia cases may resemble SARS. He compares it to 1918 influenza: a few percent fatality across a huge denominator.

• Bad luck, not biology, protected us before

Attia asks whether deadly coronaviruses are somehow bound to transmit poorly. Perlman says nothing about the biology makes a virus with SARS-CoV-2's spread and MERS's lethality unlikely. Attia calls that potential combination a five-fold disaster.

• No evidence of meaningful drift so far

Unlike influenza, the human coronaviruses don't seem to change much, with the partial exception of OC43. Perlman said there was no evidence the new virus had changed in a way that would stop a vaccine or prior infection from protecting people.

• Immunity to coronaviruses wanes

Antibodies and protective IgA to common cold coronaviruses fade within a year or two, unlike smallpox antibodies still measurable decades later. Perlman says no one really knows why, and that this is a key unknown for reinfection, vaccines and herd immunity.

EXAMPLES

• One sick doctor in a Hong Kong hotel

SARS reached the world when a physician who had treated a sick animal handler traveled to a Hong Kong hotel while ill. He infected others on his floor, and they carried it home to several countries. Perlman cautions that SARS's average R0 of 2–3, versus 1–2 for cold coronaviruses, hides how much spread came from a few people.

• Herd immunity arithmetic

Measles needs about 95% immunity; a virus with an R0 of 2–3 needs roughly 60–70%. Perlman rejects the idea that widespread silent infection lowers the threshold to 20–30%. He says it may simply mean more people are already immune.

• Why MMR and BCG are unlikely explanations

A popular graph claimed MMR vaccination explained why deaths rise above age 50. Perlman notes most people his age actually caught measles and mumps, and that no one had shown any cross-protection. Attia doubts BCG for lack of specificity. Perlman adds that boosting immunity, for example with interferon, might help just before exposure but could harm at the wrong stage.

• Timing therapies to disease stage

Both men argue for antivirals early and immune modulators later, when the virus is gone and respiratory support matters. They also argue for biomarkers to find the subset who benefit, because treating everyone dilutes a drug that helps 20%. Perlman imagines serial cytokine testing feeding a model that flags who needs remdesivir, or ideally an oral version.

OTHER RELEVANT

• Long-term damage is uncertain

Perlman could never obtain follow-up data on MERS survivors. After SARS, he says, cognitive problems were attributed to long ventilation and corticosteroids, and only occasionally to virus in the brain. With no virus found in the brain, he thinks immune-mediated effects, like the rare Kawasaki-like illness in children, are more plausible than direct infection.

- **The question that matters for society**

A vaccine may prevent severe pneumonia even as immunity wanes. Perlman considers it more important, and still unknown, whether it reduces shedding enough to stop transmission. He suggests re-running 1980s-style challenge studies in volunteers given a cold coronavirus.

- **Coexisting with the virus**

Attia tells his five-year-old the virus is never going away, so the goal is learning to live with it.

#115–David Watkins, PhD: Immunology, monoclonal antibodies, & vaccine strategies for COVID-19

Guest: David Watkins
Date: 2020-07-09 · Duration: 1:37:32
URL: https://www.youtube.com/watch?v=jwpTQJVPxo8

KEYPOINTS

• The adaptive immune system is ancient and underpins vaccination

Watkins, an AIDS-vaccine researcher who spent decades on SIV in monkeys, separates the fast, nonspecific innate system from the adaptive system of T and B cells. The adaptive system creates memory and goes back at least to amphibians. He calls vaccination, which relies on that memory, the public-health measure that has saved more lives than any other.

• A positive antibody test doesn't mean you're protected

Only antibodies that cover the part of the spike that binds the human receptor neutralize the virus; antibodies elsewhere on the spike may not stop infection. IgM appears first and fades over about two to three months, IgG follows and carries the eventual neutralizing response, and IgA protects mucosal surfaces. Standard antibody (serology) tests detect IgG or IgM, not whether those antibodies neutralize.

• Responses vary hugely between people

Watkins cites a Rockefeller preprint of about 70 people with prior COVID-19 in which nearly 20% made no detectable neutralizing antibodies. A few people could neutralize the virus even when their serum was diluted 1 in 5,000, while most managed about 1 in 100. Whether low responders can be reinfected, and how soon, was unknown; common-cold coronaviruses do reinfect people repeatedly.

• Neutralization is hard to measure routinely

The test requires mixing a patient's serum with live virus, adding it to cells and watching for infection over two to six days. Labs do this for HIV, Zika and dengue, but there was no clinical version at the time, which is why ordinary antibody tests dominated the news.

• HIV shows what a vaccine-proof virus looks like

In the first weeks of infection, HIV reaches 10–100 million copies per milliliter, and almost every copy differs. Killer T cells and antibodies select for escape mutants over and over because the infection is chronic. Its envelope protein is sparse and covered in a sugar shield, and no vaccine has ever induced antibodies that neutralize it. Watkins can make monkeys produce huge amounts of binding antibodies, but none neutralize. HIV has infected about 75 million people and killed 32 million, and Watkins calls its vaccine challenges probably insurmountable.

• SARS-CoV-2 should be an easier target

It isn't chronic and shows far less escape, which Watkins puts at orders of magnitude less than HIV, so a protective antibody response is achievable. He cautions that he'd been wrong about every prediction about this virus since January. Asked by Attia, he estimated it at perhaps ten times worse than seasonal flu, depending on age, diabetes, obesity and initial viral dose. Attia's own reading of age-stratified infection fatality rates was two to eight times.

• Live attenuated vaccines work best but carry rare risks

The 17D yellow fever vaccine came from a virus taken from a patient in Africa and weakened by repeated passage in monkeys and lab culture. In Watkins's Brazilian collaboration, recipients' serum still neutralized it at a 1-in-5,000 dilution, though protection against wild virus taken straight from a monkey was weaker. About 1 in 300,000 recipients get sick from the vaccine, and some die.

• Monoclonal antibodies are Watkins's favourite strategy

Find the people who make the best neutralizing antibodies, clone the genes from their memory B cells, test the antibodies in animals, grow them in large vats and inject them. Engineered mutations can keep protective levels for three to six months. Attia frames it as giving people the product of B cells directly, ideal for nursing homes, high-risk patients and healthcare workers, perhaps two to four times a year. Watkins adds that a cheap vaccine is still the best route for most people.

EXAMPLES

• A truck fire destroyed 30 years of samples

Moving his lab to George Washington University, Watkins shipped over 100,000 frozen samples in a truck with freezers and liquid nitrogen tanks. It caught fire in North Carolina, destroying them.

• The attenuated SIV that turned dangerous

Ronald Desrosiers's SIV with the nef gene deleted protected monkeys strongly, yet years later some animals developed disease as the virus repaired itself. In Watkins's own challenge study, the incoming virus recombined with the vaccine strain into a new, highly pathogenic hybrid, a lesson in caution before giving any construct to millions.

• Antibodies against Ebola and yellow fever

Watkins says a monoclonal antibody given after Ebola infection cut deaths from about 50% to about 15%. His colleague Esper Kallás in São Paulo was treating yellow fever patients with about 40% mortality, and they wanted to test whether neutralizing antibodies could save them.

• Zika: protection in monkeys, but not for the fetus

With Dennis Burton, Watkins showed that a combination of antibodies gave monkeys complete (sterilizing) protection against Zika. But in a small number of pregnant monkeys already infected, antibody treatment didn't prevent transmission to the fetus. The right approach depends on each virus's biology.

• Hepatitis C went from feared to curable

Hep C varies as much as HIV and has no vaccine, yet antiviral drugs now cure it in about 30–60 days, albeit at high cost. Attia, who feared hep C more than HIV during surgical training, calls it possibly the greatest medical advance of the past decade.

OTHER RELEVANT

• A vaccine doesn't need to be perfect

Attia argues that cutting viral load at first exposure by 70–80% could lower severity, spread and the risk of an inflammatory 'cytokine storm'. That would be especially valuable in hospitals, where much early transmission happened. Flu vaccines are imperfect too but protect healthcare workers and the elderly every year.

• Interpret antibody results cautiously

A positive serology test shows exposure, not necessarily neutralizing protection. Don't treat it as an immunity passport until neutralization and its durability are better understood.

• Layer protection for the highest-risk people

The approach Watkins and Attia describe combines an affordable vaccine for the population with periodic monoclonal antibodies for people who may respond poorly, such as nursing-home residents.

#112 – Ned David, Ph.D.: How cellular senescence influences aging, and what we can do about it

Guest: Ned David
Date: 2020-07-08 · Duration: 2:15:33
URL: https://www.youtube.com/watch?v=BhayqoIg2Bc

KEYPOINTS

• David's framework: aging is flexible, nature has 'control knobs', and some can be turned

David, co-founder of Unity Biotechnology, points to similar creatures with very different lifespans. A hard clam lives about 40 years, while an ocean quahog has been aged at more than 500, roughly a 12-fold gap. Mammals range from shrews living under a year to bowhead whales, and rodents from field mice living two to three years to naked mole rats. Since the biochemistry is shared, he reasons that lifespan must be set by adjustable mechanisms.

• The first knobs discovered were insulin/IGF-1 signaling and calorie restriction

Cynthia Kenyon's daf-2 work in roughly one-millimeter C. elegans worms doubled lifespan by impairing one gene, a 'mind warp' when aging was seen as passive decay. David cautions that worms are a weak model; analogous receptor knockdowns in mice give far less longevity. Clive McCay at Cornell first extended rodent life with calorie restriction in the 1930s. David believes rapamycin and calorie restriction work through the same knob, mTOR.

• Other candidate knobs include young blood, mitochondria and the methylation clock

Experiments joining young and old animals date to the 1970s, which David notes is 'not exactly an optimal way to live.' He calls the methylation clock an area of intense debate. He uses the analogy of a vinyl LP, whose grooves wear down with each play, for how living itself might degrade the epigenetic record.

• Senescence is an anti-cancer emergency brake you don't want to remove

Mice engineered so they can't make senescent cells are born normal but are full of tumors before reproductive age. Unity's approach leaves the brake alone and clears cells only after they have permanently stopped dividing. Even in a single dish of identical irradiated cells, some die and about 99% of survivors become senescent, and nobody knows why cells choose one fate or the other.

• The damage comes from what senescent cells secrete

Senescent cells are only a small minority of cells, yet they can harm their neighbors through an inflammatory secretory profile, known as SASP, that co-founder Judy Campisi described in 2008. Campisi also found the first in-vivo marker of senescence around 1995. Leonard Hayflick overturned the dogma that cells divide forever in 1961, after earlier cultures had been contaminated by fresh cells in their feed.

• The company rested on four questions answered in parallel

The questions were: do senescent cells drive natural aging, can clearing them reverse a modeled human disease, can drugs selectively kill them, and will it work in humans. The 2011 Mayo Clinic paper from Jan van Deursen's lab got David to meet within 72 hours. A five-year natural-aging study published in 2016 was 'the trigger' to go public about Unity's work.

• Osteoarthritis became the first target

David calls osteoarthritis 'the primary reason it hurts to be old.' He says off-the-shelf pain models are irrelevant, so Unity used Jennifer Elisseeff's ACL-transection model at Johns Hopkins. Clearing senescent cells, genetically or with drug, reduced pain and regenerated cartilage in mice. In humans, senescent cells hover around 1–2% even in osteoarthritic knees, but their number scaled with disease and pain.

• Phase 1 knee data were striking but small

The trial enrolled 48 patients, randomized 3:1 to drug or placebo across six dose levels of about six patients each, with a single injection followed for three months. Pain fell in a dose-dependent way and hadn't returned at three months. At the top dose, pain dropped from about 6.2 to just over 1 on a 0–10 scale, mostly within two weeks. David stresses the small numbers and the large placebo effect seen with knee injections, and warns against comparing results across trials.

• Clearing senescent cells delayed cancer onset rather than changing its prevalence

In mice cleared from midlife until death, about 85% still died of lymphoma, but it appeared roughly 30% later in life, matching about a 30% lifespan extension. David calls this a phase shift of chronic disease and admits nobody knows why. The same mice kept 41% more intervertebral disc volume.

EXAMPLES

• Showing Hayflick the mice

David met Leonard Hayflick by chance at the Portland airport. He showed him photos of sibling mice with and without senescent cells, the phenomenon Hayflick had first described decades earlier, and watched him take it in.

• Lab mix-ups still happen

About a year before this conversation, Unity ordered what it thought were mouse cells from a cell bank. They turned out to be rat cells, which is why they weren't behaving properly. David cites it as a reminder of how the pre-Hayflick error could happen.

• The Phase 2 design

The study followed patients for 24 weeks, tested placebo plus 0.5, 2 and 4 mg doses with 45 patients per arm instead of six, and added MRI and X-ray to see whether pain relief comes with structural change.

• Kythera and Kybella

At David's earlier company, one of four clinical candidates worked: a molecule that makes fat cells burst. It became Kybella, for under-chin fat, and Allergan acquired the company. David says that experience taught him dispassionate decisions about drug-development risk.

OTHER RELEVANT

• Next frontiers: the eye, metabolism and the brain

Dry macular degeneration is about eight times as common as wet and has no treatment; only about one in eight macular degeneration patients has the treatable wet form. Unity planned injections into the eye, as with anti-VEGF drugs, using a different molecule than for knees, because senescent cells in different tissues have 'different Achilles heels.' Senescent astrocytes and microglia rise with age, and David finds it hard to imagine senescence plays no role in cognitive decline.

• Treat health span, not lifespan, as the realistic endpoint

Mortality is impractical to measure in trials, so diseases like osteoarthritis offer a path to approval while longevity effects are studied in animals.

• David's career advice

Slow down, because you have your whole life. Build around a single beautiful idea that gives you goosebumps. He compares an experiment finally working after 18–24 months to love for one's kids. And learn from people who are better and more patient than you.

#103 – Looking back on the first 99 episodes: Strong Convictions, Loosely Held

Date: 2020-07-08 · Duration: 1:17:22
URL: https://www.youtube.com/watch?v=CdfHFhpJqyc

KEYPOINTS

• 'Strong convictions, loosely held' means trying to shoot down your own hypotheses

For episode 100, Bob Kaplan interviews Attia about which of his views have changed since the podcast began in mid-2018. Kaplan quotes a blog by Richard Feinman, the SUNY biochemist (not the physicist Feynman), recounting a colleague's description of science: make a hypothesis, then try to shoot yourself down. Changing your mind is 'a feature, not a bug'.

• Attia stopped taking metformin

He had taken it since about 2011 for its possible longevity benefits, though few patients in his practice took it. In December 2018, when he started Zone 2 training and checking lactate again, his resting and low-effort lactate was surprisingly high. He concluded that metformin, a weak mitochondrial toxin, was probably blunting his mitochondrial output. He stopped, then spent months experimenting on and off it.

• Metformin's effect on training is still unclear

Studies of metformin's effects on muscle mass and training adaptation exist but seem suboptimal, because they often skip functional measures. Attia would like a large study using lactate, Zone 2 efficiency and muscle mass as proxies for whether the drug blunts the benefits of exercise in people without diabetes.

• Rapamycin took him years to act on

His interest dates to about 2012, peaked with the December 2014 everolimus paper by Joan Mannick and Lloyd Klickstein, and grew through 2017 interviews with David Sabatini and Matt Kaeberlein. Unlike most drugs, rapamycin has no biomarker to show you're taking enough or too much, beyond side effects such as mouth sores. It took him about four years to settle on a dosing approach, which happened around autumn 2018.

• Zone 2 came back into his training

After he stopped time-trial cycling around late 2014 or early 2015, he dropped low-intensity aerobic work entirely, something endurance athletes get without trying, even swimmers training for short events. Now it's a central part of his week. He enjoys it because it isn't hard, and there has never been a day he didn't want to do it.

• He now sees deadlifts as hugely valuable for longevity, if done properly

Starting dynamic neuromuscular stabilisation (DNS) about 18 months earlier changed his approach. He lifts lighter than before. He's rarely had 400 lb on the trap bar in the past year, tops out around 350–375 lb, and goes much lighter for slow tempo work. He films every rep of every set and sends it to his coach, Beth Lewis. His warm-up checklist of about 10 exercises takes 10–15 minutes.

• No more baby aspirin for flights

He used to assume that aspirin's antiplatelet effect prevented deep vein thrombosis on long flights. On digging, he found little evidence that it does. The gold standard, heparin, is impractical because it has to be injected, so he found supplement alternatives such as one sold as 'Flite Tabs'.

• Some generic drugs may not be equivalent

His default through medical school was that generics are identical and brand names a scam. But he has seen patients switched from Crestor to generic rosuvastatin show no change in their labs after two months, despite adherence they had no reason to lie about. Katherine Eban's episode (#71) on generic drug manufacturing shifted his view; he calls it one of the 10 most important episodes.

• He would push omega-3 levels higher

Before Bill Harris's episode, Attia targeted a red-blood-cell omega-3 index of about 8–10%. Afterwards he felt 12–14% could be reached without side effects and with more benefit. He says clinical trial data on EPA and DHA are still unclear, including a setback in a recent EPA-plus-DHA trial.

• Omega-6 associations are confounded

Foods high in omega-6 polyunsaturated fat are often 'crap', which makes associations hard to interpret. He calls it a polarising topic worth a deep dive. It matters little for his own diet but has big public-health implications.

EXAMPLES

• Archery as practice in stillness

At 20 yards an archer is expected to hit something the size of a quarter. A perfect round is 60 shots in the X ring. He uses a shot trainer for 20–40 practice draws a day in hotel rooms.

• A 1.44 GPA

Attia admits to a 1.44 high-school GPA while focused on sport. He contrasts it with his daughter's new self-driven studying.

• Getting a dog

After years of resisting, the family got a dog. A month in, it was far more work than expected, mostly for his wife and daughter.

• Learning to say no

He used to say yes to everything. Inspired partly by Jason Fried and Ric Elias, he's much better at declining, while avoiding the opposite extreme. He notes that Charlie Munger and Warren Buffett keep almost empty schedules.

• Reluctant podcaster

When the idea was first floated in about 2014, he called it the worst idea he'd ever heard, fearing the workload and that he'd run out of guests after 50 episodes.

• Books

He has reread Ryan Holiday's 'Stillness Is the Key' three times and recommends Siddhartha Mukherjee's 'The Emperor of All Maladies' and 'The Laws of Medicine'. He jokes that when you're writing a book, reading great ones makes you want to quit

writing yours.

OTHER RELEVANT

- **Re-test your convictions**
  Look for the data that would prove you wrong, as he did with metformin. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Check that a drug is working**
  With measurable drugs like statins, recheck labs. If nothing changes, suspect the formulation, not just adherence.
- **Don't assume aspirin protects you on flights**
  The evidence for aspirin preventing flight-related DVT is weak. Discuss real risk factors with a doctor.
- **Practise technique deliberately**
  Film your lifts, use a warm-up checklist and favour quality over load. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#94 – Mark Hyman, M.D.: The impact of the food system on our health and the environment

Guest: Mark Hyman
Date: 2020-07-08 · Duration: 1:50:28
URL: https://www.youtube.com/watch?v=DxbeLdVoYpU

KEYPOINTS

• Hyman frames ultra-processed food as a health, economic and climate problem at once

Hyman, a functional medicine physician, cites 11 million deaths a year worldwide from eating too much ultra-processed food and too little good food. He says 70% of US military recruits are rejected as unfit. He also cites a UN projection of 200 million to a billion climate refugees within the coming decades. In his view the food system connects chronic disease, healthcare costs, national security and the environment.

• Calories aren't biologically equivalent, he argues

Hyman's example: 750 calories of soda is a Big Gulp holding 46 teaspoons of sugar, while 750 calories of broccoli is 21 cups with 35 grams of fiber and no sugar. He says ultra-processed food now makes up about 60% of American calories, and that each additional 10% of calories from it raises death risk by 14%, as he reports the data. Peter adds that processed foods may hijack the body's normal appetite feedback loop.

• He says the food industry funds confusion

Hyman cites about $12 billion spent by the food industry on nutrition 'research.' He describes how Coca-Cola executive Rhona Applebaum set up the Global Energy Balance Network. He says it paid scientists including James Hill, with about $20 million in funding, to push 'all calories are the same' and 'exercise more, eat less.'

• Gut health sits at the center of his model of inflammation

Hyman says low-fiber, high-sugar diets feed harmful microbes, damage the gut lining ('leaky gut') and let food antigens trigger inflammation, noting that about 60% of the immune system is in the gut. He cites rodent experiments in which transferring stool from lean to obese animals changed their weight. He adds that stress alone can increase gut permeability.

• US health statistics he calls staggering

Hyman says 6 in 10 Americans have a chronic disease and 4 in 10 have two or more. One in two has prediabetes or type 2 diabetes, about 75% are overweight, and most states are near 40% obesity, whereas no state had 20% when he finished medical school. He says 80% of the world's type 2 diabetics now live in developing countries, and some ethnic groups face higher risk at lower body weights.

• Policy works, and the tobacco playbook is being reused

Hyman points to Chile, where a senator who was also a doctor pushed through warning labels on unhealthy foods, marketing limits and a soda tax. He says marketing restrictions and labels had about four times the impact of the tax. Peter recalls that requiring anti-smoking ads alongside cigarette ads led tobacco companies to pull their TV ads. US adult smoking fell from about 50–55% in the mid-1960s to about 18%.

• Fertilizer and tillage degrade soil, Hyman argues

Hyman says global fertilizer use is 400 billion pounds, sevenfold higher than 40 years ago yet two-thirds as effective. It is made from fracked natural gas, emits nitrous oxide, which he calls about 300 times more potent than CO2, and runs off into roughly 400 ocean dead zones, including one the size of New Jersey in the Gulf of Mexico. He claims a third to 40% of excess atmospheric carbon comes from lost soil.

• Regenerative agriculture is his proposed fix

Regenerative farming means cover crops, rotation, minimal tillage and animals or legumes for nitrogen. He says it rebuilds organic matter, holds water and can match yields. Peter notes that US corn yields were flat at about 20 bushels per acre from the Civil War to World War II, then climbed to about 200 before GMOs arrived. GMOs, added perhaps about 10% more, a figure Peter says may be debatable.

• Glyphosate: Hyman is alarmed and Peter isn't convinced

Hyman says glyphosate is 70% of agrochemicals used, weeds are becoming resistant, there are about 14,000 lawsuits, and animal studies show microbiome and epigenetic effects. He says his own urine glyphosate was at the 50th percentile on a Great Plains Lab test. Peter eats similarly but says he is far less confident that glyphosate causes human disease than that tobacco causes lung cancer, because the data haven't convinced him.

EXAMPLES

• Gabe Brown's North Dakota farm

Hyman says this farmer, battered by hail and bad weather and close to bankruptcy, switched his roughly 5,000 acres to regenerative methods and says he has built 29 inches of soil. He uses no chemical inputs and is profitable, while the average farmer loses money and relies on subsidies.

• Impossible Burger versus regenerative beef

Hyman cites a Quantis life-cycle analysis: the Impossible Burger beat a factory-farm burger but still added about 3.5 kg of carbon per burger. A regeneratively raised beef burger removed carbon on net. He objects to scaling GMO soy monocrops sprayed with glyphosate.

• SNAP and soda

Hyman says food stamps can buy a two-liter soda but not a rotisserie chicken. By his estimate, 75% of SNAP purchases are junk food or soda. That includes about $7 billion a year, roughly 30 billion servings, on soda alone, in a $75-billion-a-year program feeding 46 million Americans. He says this contradicts the Dietary Guidelines.

• Why bread feels different in Europe

Peter noticed European bread and pasta didn't affect him the same way. Hyman's reasons include modern dwarf wheat bred under Norman Borlaug, which he says is more disruptive to the gut, and pre-harvest glyphosate spraying of non-GMO wheat. He

suggests heirloom grains like einkorn as an alternative.

OTHER RELEVANT

- **Hyman's 'Five R's' for gut repair**
  Remove triggers (gluten, dairy or grains for some people; parasites; yeast overgrowth); replace missing fiber, prebiotics and enzymes; reinoculate with probiotics, which he admits is 'still sort of a Wild West'; repair with nutrients like glutamine, vitamin A, fish oil, butyrate and polyphenols; and rebalance stress and lifestyle.
- **Buy organic where it matters most**
  Organic certification bans synthetic pesticides, hormones and antibiotics but allows 'industrial organic' monocrops. Use contamination lists to prioritize organic strawberries and celery and save on bananas and avocados. A regenerative organic certification has been proposed.
- **Hyman's top three changes if he were 'food czar'**
  Pay for food as medicine, including produce prescriptions and healthy government food purchasing. Reform SNAP, school lunches and the Dietary Guidelines. Back regenerative agriculture with policy and investment.

#113: Normative errors — a conversation with my daughter about current events

Guest: Olivia Attia
Date: 2020-07-08 · Duration: 0:22:08
URL: https://www.youtube.com/watch?v=QC5BBW1MUsk

KEYPOINTS

• Attia speaks from what he knows: how doctors are trained

Recorded after dinner in the days following George Floyd's death, this 20-minute conversation with his daughter Olivia, who was in the middle of finals and lockdown, is explicitly limited in scope. Attia says he is not an expert in law enforcement, racism or the history of police brutality. His one contribution is a framework from medical training, which he offers for parents struggling to explain events to their children.

• Racism is systemic and centuries deep, not just individual

When Olivia asks why skin colour should matter more than eye colour, Attia says the answer goes back hundreds of years, to how Black people were brought to the country and the conditions of racism that kept it going. He hopes that when she studies history she'll see it as understanding the systemic nature of racism, not just passing tests or writing essays.

• Video has exposed what was always happening

Olivia notes that this case is known only because it was filmed, and that there must be many others no one knows about. Attia agrees and imagines the era before phone cameras: 'you would need scientific notation to count the number of times this has happened'.

• White and Black people have completely different encounters with the law

Olivia mentions an online comment: a white person who tried to use a fake $20 bill at Home Depot was handed it back and allowed to leave. Attia says there is no question that white and Black people have completely different interactions with law enforcement and the criminal justice system. He tells her he is glad it upsets her, because it should.

• 'Mostly good' isn't good enough when the stakes are this high

Attia acknowledges the argument that most protesters don't loot and most officers wouldn't do what this officer did. But he asks whether law enforcement should have zero tolerance. He cites Chris Rock's analogy: you wouldn't fly with airlines where 99% of pilots are good and 1% horrible. He then argues doctors are a better comparison than pilots, because both jobs involve constant face-to-face encounters and medicine has its own abusers, such as the former US gymnastics team doctor.

• Medicine recognises three kinds of error

Technical errors are mistakes in carrying out a procedure, such as cutting too much or too little. Judgment errors are wrong calls about whether to operate, change a medication, admit a patient or bring in a consultant. Normative errors are errors of character: lying, covering up, or putting your own interests ahead of the patient's.

• Technical and judgment errors are forgivable, with two conditions

You must own the mistake immediately, never covering it up or denying it, and you must learn from it. Attia admits he made many technical errors in residency, including cutting a bile duct by accident. A trainee who keeps making the same error, such as puncturing a lung when placing a central line, may simply not be capable of the job, even if they admit it every time.

• Normative errors should end a career in medicine

A good training system encourages open discussion of technical and judgment errors but removes people who commit normative errors, not just from one programme but from medicine. Otherwise they are picked up elsewhere. Attia's reasoning is that people who commit these errors at all tend to commit bigger and bigger versions of them.

EXAMPLES

• Attia was pulled off his bike by a police officer in 1995

In college, in an almost entirely white town, Attia, who notes his skin is somewhat darker, was riding on the sidewalk to avoid water and snow. An officer pulled up, yanked him off his bike and threw him onto the grass outside his gym. The officer switched between the sidewalk rule and hints about an older woman mugged nearby, and let him go only after people came out of the gym. Attia says racism played a role, and calls it 'one one-millionth' of what Black Americans face daily.

• The falsified allergy record

Attia's firsthand example of a normative error: a doctor gives an ER patient an antibiotic without asking about allergies. When the patient reacts, the doctor alters the chart to say they had a penicillin allergy. Even if the reaction is treated with Benadryl or epinephrine and the patient is fine, the lie is unacceptable.

• Choosing a drug for profit

Another normative error Attia has seen: a doctor prescribes the more expensive of two drugs because they have a financial interest in it.

• Nearly nine minutes is not a first offence

Attia argues that an officer who kneels on a Black man's neck for nearly nine minutes for no apparent reason has almost certainly acted in racist ways before. Olivia compares it to a surgeon who is 'so far down the road' that he cuts off the wrong leg. Attia's question is why the earlier warning signs weren't caught.

OTHER RELEVANT

• Treat racism as a normative error with zero tolerance

Attia's proposal is for people with more expertise to define what early, small 'normative' signs of racism look like in policing and to remove those people quickly. He frames it as the difference between admitting racism may never be fully eradicated and tolerating racist officers. He notes self-policing is weak in many professions, including medicine and teaching, and that racism exists in all of them.

• Channel anger into changing the system

Attia plans to show Olivia Killer Mike's press-conference speech. Its message, as he describes it: rioting and looting aren't

productive, nor is just marching or sending fist emojis. Vote out the people who allow racism to proliferate.

- **Talk about it at home if school won't**

  Olivia says her teachers haven't addressed it while her group chats are 'blowing up'. Attia is surprised and says he's glad they get to talk about it together.

#109 – John Dudley: The beauty in archery, the love of practice, and a model system for life

Guest: John Dudley
Date: 2020-07-08 · Duration: 2:16:34
URL: https://www.youtube.com/watch?v=Z_symF-3qx4

KEYPOINTS

• Dudley turned down a Division I football scholarship to build arrows

A 6'5" quarterback recruit, he walked away one week into school to work in an archery shop for $4.10 an hour. Attia calls it one of the craziest decisions a college athlete could make. Dudley says he never looked back. Even in moments of rage when he broke arrows and threw his bow, his self-talk was that something had beaten him that day and wouldn't tomorrow.

• He loves archery because it's hard

Dudley learned archery at 9 and first bowhunted at 10. When he struggled to explain why he loved it, his friend Andy Stumpf, a retired Navy SEAL, told him the answer was all over his personality: some days you're good at it and some days you aren't. The sport keeps offering a next level, which is what keeps him coming back after burning out.

• The only arrows you control are the ones still in your quiver

An early coach asked whether anyone could pull a bad arrow back from the five ring to the shooting line. Since no one can, he told Dudley to let it go. Dudley began literally talking to the arrows in his quiver, asking which one would shoot a 12 to make up the points. Attia calls it a metaphor for life: you can't turn back time, only shape the next shot.

• Every world-class performer Attia has met loves practice

Attia lists Lance Armstrong, who teammates say wanted more at the end of a six-hour ride; Apolo Ohno, whose appetite for training continued ten years after the Olympics; and Ayrton Senna. The common thread is loving to practise deliberately and correctly, which Attia doesn't think anyone reaches an exceptional level without. Dudley trained at all hours, sometimes because insomnia gave him a reason to get up.

• Compound and recurve bows load energy differently

Olympic recurves get heavier through the whole draw, so a strong recurve archer holds about 50 pounds at full draw. A compound's cams make the weight peak early, around 70 pounds on Dudley's bow, and then drop off. That makes it easier to hold steady at full draw and stores more energy. His bow shoots about 292 feet per second, close to 100 mph, so an arrow takes about half a second to travel 50 yards.

• Elite accuracy over a football field's length

At 90 meters, roughly from one goal line to the opposite one-yard line, Dudley estimates most professional archers would land about eight of ten arrows inside the 10 ring, which is roughly the diameter of a large coffee mug (about three to four inches).

• Hyperfocus and flow may be linked to attention differences

Dudley describes ADD-like traits: he's easily distracted, yet he can lock in so completely that a song played on repeat for an hour and a half without him noticing. Near the end of his competitive career he began reading sports psychology to see whether such hyperfocus helps athletes reach flow. He offers this as a personal question, not an established finding.

• Great performers are rarely great teachers, and Dudley is both

Attia notes how little overlap there is between the top 1% of doers and the top 1% of teachers. Dudley credits former Mr. Olympia Frank Zane, who had worked as a teacher and who coached him on presentation. The key technique is relating a skill to something the student already knows, such as Formula 1 for Attia or SEAL training for Jocko Willink. Attia believes someone could get 60–70% of a coach's benefit from Dudley's videos alone.

• Honest selling is rare and valuable

Attia says he can buy anything Dudley recommends without wondering about kickbacks, which he considers hard for anyone to manage, since incentives work even subconsciously. Dudley, who runs the education side of a business while his wife runs the e-commerce side, says he can spot ventures run without that integrity fail quickly.

• Hunting raised the stakes of every shot

Attia took up archery only to shoot paper, a skill where you can spend a lifetime chasing the last 20% of improvement. Once he began hunting, a miss on paper hurt more, because the same miss in the field could wound an animal and make it suffer. Dudley argues that ethical hunting means knowing exactly where your meat came from, funding conservation through tags and not relying on commercial farming.

EXAMPLES

• The house fire at nine

As a self-described 'Beavis and Butt-Head' troublemaker, Dudley stayed home sick, played with matches and started a fire. The extinguisher was empty because he'd secretly used it months earlier after a firecracker accident. The house burned down; the family kept only what was in his parents' two cars. He traces his shift from troublemaker to committed athlete back to that event.

• 'What are you going to do with your moment?'

At a University of Illinois recruiting camp, a coach tossed Dudley the ball and asked that question. Dudley stood up and threw it from about the nine-yard line into the far end zone. He had built that arm alone, using a gym key from his coach to throw at laundry baskets.

• The 3D shoot that started it all

Recovering from a knee injury the summer before college, he saw an 'archery shoot' sign, joined a 3D target course and missed so badly he ran out of arrows. Furious, he drove to a Gander Mountain in Wilmot, Wisconsin, bought another dozen and came back to finish, vowing never to be that bad again.

• An elk earned over 250 miles

Dudley and his friend hunted from August 24 until they took a bull on September 11, logging roughly 200–250 miles on GPS, followed by a three-mile pack-out in multiple trips. He prepares for that moment all year with lifting and shooting, which is why he won't waste the meat.

OTHER RELEVANT

- **Train for the next shot, not the last one**

  Use Dudley's quiver rule after any mistake: say what went wrong, then shift your attention to the next repetition, which is the only thing you can still affect.

- **Try archery even if you never plan to hunt**

  Attia and Dudley pitch it as a lifelong sport, like tennis, that trains focus, patience and emotional control and that parents can share with children. Good coaching or well-structured videos can speed up early progress.

- **Teach through the learner's world**

  When coaching anyone, connect the skill to something they already understand. That's how Dudley got students he'd worked with fewer than a dozen times shooting at levels few competitors reached in his era.

#95–Luke Bennett, M.D.: Emotional, cognitive, & physical demands that make Formula 1 a special sport

Guest: Luke Bennett
Date: 2020-07-08 · Duration: 1:38:31
URL: https://www.youtube.com/watch?v=jhTGGp88uu0

KEYPOINTS

• F1 drivers resist 5–6 G with their necks

In the fastest constant-radius corners, a driver's roughly four-kilo head plus helmet effectively weighs five or six times as much. Attia says the most he has felt in a race car is about 2 G. Bennett, who rode as a passenger in a two-seater F1 car in Mexico, says he couldn't have managed five or six laps. He likens a race to two hours of intense CrossFit with five-to-ten-second breaks, while someone tries to push you off your equipment.

• The cognitive load is as extreme as the physical load

While hitting millimetre-perfect apexes, drivers take engineering instructions over the radio ('solve maths equations') in front of 200–300 million viewers, sometimes without a contract for next season. Cockpits sit so high that drivers can barely see the tops of their tyres or the ends of the front wing, yet they race wheel to wheel. That's why Bennett has sympathy for mistakes like the near-collisions at Monza that fans criticised.

• A weight rule ended a culture of starving drivers

Drivers used to be told to lose as much weight as possible, which led to overtraining, undereating and disordered eating that worried Bennett. After he raised it with the FIA and technical leader Charlie Whiting, the sport set an 80-kilo minimum for driver plus helmet, suit and seat, with ballast added below that. Drivers can now carry a kilo or more of extra muscle, and nutrition is 'not the daily misery it used to be'.

• Singapore is the toughest race physically

Bennett calls it a street circuit with more corners than any other (about 23–25 ninety-degree turns) in tropical heat and humidity. Drivers often lose three to four kilos, and on a race like Singapore may carry a 1.2–1.5-litre drink bottle, about twice the usual amount.

• Drivers are getting younger

Damon Hill was about 30 in his rookie year. Today a 30-year-old couldn't break into the sport. Max Verstappen arrived just after turning 17, followed by teenagers like Lance Stroll and Esteban Ocon. Bennett credits a cultural shift once it was shown to be possible, gaming and simulators, and cars that demand less raw muscle than the brutal V10 era.

• Safety rests on asking why drivers die, not why they crash

Attia recalls Max Mosley saying after Ayrton Senna's death that at the limit of human and mechanical capability crashes will happen, but nobody should die in them. Bennett, initially skeptical of the halo cockpit protection device, counts at least four incidents in F1 and F2 where it prevented a serious head impact. The seven-kilo titanium halo must withstand a load of roughly 10–12 tonnes, about a bus parked on top of it.

• The sport is still dangerous

In the 1960s and 70s, many drivers didn't live to retire; Jochen Rindt is the only posthumous world champion. Bennett notes that side-on impacts with a stationary car remain a major vulnerability, as shown by Anthoine Hubert's death in Formula 2 at Spa after being hit at more than 200 km/h (about 170 mph).

• Women face a pipeline problem, not an F1 ceiling

Only two or three women have raced in F1; one scored half a point in the 1970s. Bennett thinks a woman can absolutely succeed in F1, but the grassroots pipeline is tiny and the junior categories are physically harsh. They also put women up against teenage males whose risk-taking, and as Attia jokes, underdeveloped prefrontal cortex, can be a competitive advantage. He sees the all-female W Series, which his team supports, as a good first step toward finding the outliers.

• Hintsa's model pairs every driver with a coach

Hintsa Performance, where Bennett is medical and sports performance director, looks after about 14 drivers with at least one in every team. A performance coach, usually a sports scientist, travels to every race and trains with the driver in between, covering physical preparation, nutrition and sleep. Bennett calls the medical services 'the glue' that cements those relationships.

EXAMPLES

• Diagnosing his own cancer with a portable ultrasound

Working with Australia's Royal Flying Doctor Service in a remote area, Bennett found his own non-seminoma testicular cancer, which had already spread to his lungs. He notes that this cancer has survival rates above 90%. Treatment brought a cancer-related clotting tendency; his chemotherapy catheter clotted off and caused superior vena cava syndrome, which he spotted in the mirror one morning. He says that being a patient, with the needles, fatigue and parking, made him a more empathetic doctor.

• The Flying Doctor's territory

Western Australia is about the size of Western Europe, with roughly two million people, most of them in Perth. A doctor, nurse and pilot fly patients to the city, and many are half a day to a day from specialist care. Funding planes is cheaper than building hospitals across the state.

• More telemetry than Apollo 11, but no heart rate

Attia points out that an F1 car sends back more data on tyre pressure than mission control received from Apollo 11, yet teams don't know the driver's heart rate, heart-rate variability, electrolytes or fluid status. Bennett says new monitoring devices compatible with the regulations were being trialled.

• Learning a new circuit

Good drivers are close to race pace within about six laps of a new track, then find another tenth or two over the weekend. Before each race they spend a day or half-day on the team simulator, partly to relearn even familiar tracks in this year's car.

OTHER RELEVANT

- **Protect sleep and health against brutal travel**

  With 21 races in 2019, more planned and around 40 nights a year in his own bed, Bennett says he could only sustain the job because he loves the sport. Coaches manage drivers' jet lag and recovery individually.

- **Emotional control is a performance skill**

  Anger rarely helps in the car or in front of the media. Bennett and Attia treat emotional regulation as part of driver preparation, alongside physical and cognitive training.

- **Basic endurance training gives a coach empathy**

  Bennett, who started triathlon in 1988 and struggled through a couple of Ironmans, says knowing the chore of a hard morning session and the difference between aerobic and anaerobic work helps him, while he leaves the technical coaching to his coaching director.

#96–David Epstein: How range of experience leads to better performance in a highly specialized world

Guest: David Epstein
Date: 2020-07-08 · Duration: 2:37:10
URL: https://www.youtube.com/watch?v=uwSYROsue5o

KEYPOINTS

• The '10,000-hour rule' rests on thin data and hides huge variation

The famous study looked at 30 violinists at a Berlin music academy, split into three groups. The top group averaged about 10,000 hours of practice by age 20. Its author, Anders Ericsson, wouldn't call it a rule. David Epstein, author of 'The Sports Gene' and 'Range', says the average conceals the spread. When the researcher Tim Lightfoot asked about the variance, he was told it didn't matter.

• Chess shows how wide the range is

Reaching international master status takes an average of 11,053 hours, but some players got there in about 3,000 hours and others still hadn't after 25,000. Epstein would put a 90% confidence interval for mastery somewhere between 1,000 and 40,000 hours. In many sports, elite athletes logged far fewer, often 4,000–6,000. The deliberate-practice framework assumes 'monotonic benefits', that more practice always means more skill for everyone, which ignores individual differences.

• Some 'genetic' talents are learned perception

Epstein expected that hitting a fastball at about 100 mph needed exceptional reflexes, but it doesn't. The ball arrives too fast for any human reaction, even in the top 0.01%. Elite hitters instead learn to read cues before the pitch is released. Muhammad Ali's measured reaction time, about 150 ms, was very fast but not unique.

• Kind and wicked learning environments

Psychologist Robin Hogarth coined the terms. In a kind environment, goals are clear, patterns repeat and feedback is immediate and accurate, as in golf, where the ball is always static. In a wicked environment, the rules are unclear, feedback is delayed or misleading, and narrow experience can make people more confident without making them better. Most of life, including medicine and business, is more wicked than golf.

• Short-term success can undermine long-term learning

At the US Air Force Academy, cadets are randomly assigned to calculus professors for three years in a row and all sit the same committee-written exams. Over a decade, with about 100 professors and 10,000 students, the professors whose students did best in Calculus I had students who did worse in the next two courses. Teaching to the test boosts quick performance but undermines deep understanding.

• Struggle beats procedure

Students drilled in procedures would check 500 + 200 = 700 only by computing 700 " 200, never 700 " 500. Interleaved, 'desirable difficulty' practice feels slower and students don't feel they're learning, but in one randomised study it improved results by 0.83 standard deviations, moving a 50th-percentile student to roughly the 80th.

• Tiger Woods is the exception; Roger Federer is the rule

Tiger was given a putter at seven months, showed off his swing on 'The Mike Douglas Show' at two and was the world's best at 21. Federer played basketball, badminton, skateboarding, swimming, wrestling and football, and declined to move up levels so he could stay with friends. His mother, a tennis coach, refused to coach him. Epstein says Federer's 'sampling period' is the more common route to elite success.

• Early specialisation may burn out the desire

Tennis academies can produce players who are great at 16 but have lost the will to keep going, an 'above-the-neck' effect as much as a physical one. Even Tiger said in 2000 that his father never asked him to play; Tiger always asked.

• Match quality matters more than an early start

Herminia Ibarra studies 'match quality', the fit between your interests, abilities and work, which predicts performance and burnout. Her finding: 'We learn who we are in practice, not in theory.' Testing and switching careers is a feature, not a failure.

• Know when to drop your tools

Firefighters who died fleeing wildfires were often found still carrying chainsaws, drip torches and packs, sometimes 100 feet from safety. Their tools were central to their identity. Epstein urges experts to ask which habits help 99% of the time but could kill them the other 1%.

• Bad science thrives on uncritical dogma

Attia argues that 90–95% of the roughly 100,000 papers added to PubMed each month serve no purpose. He cites John Ioannidis's 2005 paper 'Why Most Published Research Findings Are False' and quotes a senior scientist who said 19 of 20 people who test hypotheses for a living can't really do it. Both men see the 10,000-hour story as an example of a catchy claim outrunning its evidence.

EXAMPLES

• The Challenger decision

NASA had launched in temperatures as low as 53°F. On the morning of the January 1986 launch it was in the 30s. Morton Thiokol's initial 'don't launch below 53' recommendation rested on 'we've done 53 before', which backfired when NASA pushed for quantitative data. Engineers used to having data didn't know how to argue from qualitative evidence.

• Frances Hesselbein

She took her first professional job at 54, with one semester of junior college, and became CEO of the Girl Scouts during a late-1960s collapse in membership and turned it around. She now has 23 honorary degrees and still works weekdays in Manhattan at 103.

• The 10,000-hour golfer

Dan McLaughlin quit his job to follow the 'rule' and became a pro golfer with Ericsson consulting. He got about 7,000 hours in, improving a lot at first, but never turned pro. Epstein notes that he never predicted an exact number of hours, only huge individual variation.

- **Ayrton Senna at Monaco**
  Both men call Senna's 1988 Monaco qualifying lap, 1.5 seconds clear of the field, inexplicable. Attia likens it to winning the Olympic 100 m by a second and a half.

OTHER RELEVANT

- **Sample broadly before specialising**
  Give children a sampling period and let their desire, not a parent's plan, lead.
- **Choose desirable difficulty**
  Mix up practice and test yourself, even though it feels slower.
- **Experiment to find your match**
  Short trials of work tell you more than personality quizzes.
- **Audit the tools you won't drop**
  Identify the habits and frameworks you rely on that could fail you in a new situation.

#87—Rick Johnson, MD: Fructose—the common link in hypertension, insulin resistance, T2D, & obesity?

Guest: Rick Johnson
Date: 2020-07-07 · Duration: 1:50:46
URL: https://www.youtube.com/watch?v=LbSic4Oo8ME

KEYPOINTS

• Uric acid led Johnson from blood pressure to fructose

Johnson, a nephrologist at the University of Colorado with roughly 700–800 publications, first studied uric acid as a cause of high blood pressure. Raising uric acid in animals with a uricase inhibitor raised their blood pressure, and lowering it brought pressure down. Expecting crystals in the kidney, his team instead found inflammatory changes. Uric acid, long thought to be an inert end product or even an antioxidant, was having pro-inflammatory effects. Since fructose raises uric acid, in 2002 they asked whether sugar could drive blood pressure.

• Fructose plus allopurinol: one intervention, many effects

Rats fed fructose developed high blood pressure, and allopurinol, which lowers uric acid, brought it back to normal. They also developed insulin resistance, high triglycerides and fatty liver, and lowering uric acid improved all of those. Johnson calls it a big discovery that linked sugar, uric acid and metabolic disease.

• Fructose drains cellular energy and flips a metabolic switch

Fructokinase uses ATP without the brakes that govern glucose metabolism. A big fructose load can drop ATP in the cell by 40–50%, which Johnson describes as a 'mayday' signal. Phosphate gets tied up in fructose-1-phosphate. The falling phosphate pushes AMP down the AMP deaminase pathway, which stores fat, generates uric acid and promotes insulin resistance, rather than the AMPK pathway, which burns fat and is what metformin activates.

• Fructose is nature's fat-storage signal

Animals use fruit to fatten before winter or before food runs short. Bears and other hibernators gorge on ripe fruit in the autumn, and orangutans eat large amounts at once to gain fat. Johnson notes that most people don't get fat from a few pieces of tart fruit, but large amounts of fruit juice can increase fat.

• An ape mutation made humans sensitive to sugar

As the climate cooled, fruit trees (including figs) disappeared from European forests, and by about 12 million years ago European apes were starving. Johnson argues that a mutation that disabled uricase, which raises uric acid, helped them store fat and survive. The surviving ape returned to Africa and Asia and became the ancestor of the great apes and of humans. His team even resurrected the ancestral uricase. Attia notes that evolution wasn't anticipating a world awash in fructose.

• Salt raises blood pressure through a spike in serum sodium

A very salty soup can raise serum sodium from 140 to 142–143 mmol/L, which raises blood pressure acutely, by about 6 mmHg for a 2 mmol/L rise, for a couple of hours. In Johnson's study, giving the same salty soup with water so that serum sodium didn't rise prevented the blood pressure rise. He thinks sugar also plays a role in salt-sensitive hypertension.

• Blood pressure risk climbs from 120/80, then steeply

Above about 160–180 mmHg, arteries can no longer constrict enough to protect themselves (autoregulation fails), and stroke risk shoots up almost vertically. But epidemiology also shows a stepwise rise in risk from 120/80 to 140/90, which is why 120/80 is treated as the target.

• Speed and dose determine how harmful fructose is

The same 25 g of fructose does more harm when it arrives quickly in liquid form on an empty stomach than when it is eaten with fibre. Johnson says a beverage company could make soda look harmless by having people sip it over three hours. About 20% of fructose is handled by the intestine and perhaps 40% by the liver, with at least 10–20% escaping into the circulation, more at higher doses.

• The body makes its own fructose from glucose

High glucose reaching the liver induces aldose reductase, which converts glucose into fructose. Mice given glucose in their drinking water became fat and insulin resistant, even though they ate less chow. Johnson uses this to explain why starchy foods such as French fries can be fattening even though they contain no fructose.

EXAMPLES

• Same weight, different livers

In an animal study with calories cut by 10%, both groups slowed their metabolism and kept their weight. But the group getting 20% of calories from fructose still developed severe fatty liver and all became diabetic. They looked the same on the outside.

• Gout, sugar and history

Gout was linked to the sugar-loving English upper classes of the 1600s–1800s. William Osler wrote in the 1890s that sugar and very sweet fruits were major risk factors. Purines from DNA and RNA also matter: anchovies, other small fish and beer (brewer's yeast) can trigger attacks. Men have higher uric acid than women until menopause, because oestrogen helps excrete it.

• Johnson's uric acid thresholds

He sees risk of prediabetes, insulin resistance, hypertension and kidney disease rise once serum uric acid passes 5.5 mg/dL. Most labs don't flag it until about 6.5 (intermediate) or 7.5 (high), cut-offs set with gout in mind. He has no doubt a level of 9–10 is harmful. Because every drug has side effects, he would want to be sure before prescribing allopurinol, and would consider HLA-B*58 testing.

• Diet versus regular soda

Animals with their taste buds genetically knocked out still prefer sugar but not artificial sweeteners, because sugar stimulates dopamine independently of taste. Rodents given artificial sweeteners don't gain weight. Johnson says regular Coke is more dangerous than Diet Coke, while acknowledging that the long-term safety of aspartame and sucralose isn't fully known and that dose matters.

OTHER RELEVANT

• Keep fructose low for fatty liver

For patients with fatty liver, Johnson's group limits fructose to about 10 g a day, only as whole fruit. Whole fruit brings vitamin C, flavanols, epicatechin and potassium, which counteract some of fructose's effects. Dried fruit loses many of those benefits.

• Avoid liquid and concentrated sugar

Soft drinks, juice and candy on an empty stomach deliver fructose fastest. Johnson notes about 70% of packaged foods contain added sugar.

• Drink water with salty food

Because the problem is the rise in serum sodium, having water alongside a salty meal blunts the blood pressure spike. Kidney patients need to be careful about fluid volume.

• Check your uric acid

Ask for the actual number rather than relying on the lab's 'normal' flag. Johnson treats levels above about 5.5 mg/dL as a metabolic warning sign.

#86 – Damon Hill: Overcoming loss, achieving success, and finding one’s identity

Guest: Damon Hill
Date: 2020-07-07 · Duration: 2:26:59
URL: https://www.youtube.com/watch?v=F2bxnVD1I1E

KEYPOINTS

• This is a human story told through racing

Attia frames the conversation around Hill's autobiography Watching the Wheels, a roughly 360-page book with only one chapter on his 1996 world championship. The rest deals with loss, depression and identity. Hill wrote it partly for readers who have struggled. He wanted to show that success in sport or anywhere else is 'never plain sailing', and not to gloss over the difficult parts.

• Drivers of his father's era raced against stark odds

Graham Hill, a two-time world champion, raced when grids had about 26 drivers and losing two in a season was not unusual. Hill calls that roughly a 12-to-1 chance of not surviving each year, compounded year after year. His christening was attended by racing figures including Stirling Moss and Bruce McLaren. That shows how much of the sport's world made up his childhood.

• Losing his father at 15 left lasting, unresolved trauma

In November 1975 Graham Hill died flying his own plane, about six months after retiring, when he was 46. Damon was 15, his sisters 16 and about 11. He still vividly remembers his mother screaming. He says going back to that moment brings back the same physical sensations, so he chooses not to replay it in detail. He didn't recognise these as unresolved issues until a couple of years after he stopped racing.

• He felt a quiet dread of matching his father's lifespan

Hill describes a 'creeping anxiety' of following a pattern. If he was different from his father, he had to live longer than him, which meant past 46. That fear sat in the background of his career and his choices.

• Motorbikes came first, and cars were a pragmatic switch

Shortly after his father's death, a family friend invited him to watch bikes at Brands Hatch. His mother let him race, and he started winning around 1983–84. Money was always short. Only Barry Sheene really made a living from bikes, and the alternative was risking the Isle of Man, so cars became the practical route. He preferred bikes because the rider is 'the projectile' and 'the acrobat'.

• He became an F1 rookie at 32 against the odds

At 29 he had lost his racing drive. He had just bought a house as mortgage rates hit 17%, and his first child, Oliver, was born with Down syndrome. He kept going anyway. He became the Williams test driver in 1991–92, learning the active-suspension cars. When Mansell left after winning in 1992, he stepped into a race seat for 1993 alongside Prost.

• Imola 1994: the weekend Senna died

After years of relative safety with carbon-fibre cars, Rubens Barrichello crashed badly and Roland Ratzenberger was killed in qualifying. Then Senna, Hill's teammate, died. Hill had driven past the scene of Ratzenberger's crash and knew 'that was not a good one'. Afterwards he went through the data with engineers. He says Senna chose a bumpier inside line through Tamburello than he would have. Hill also says Senna had talked to his wife about wanting a family. In Brazil the country stopped for three days, and over a million people lined the streets.

• Depression is a signal to change direction

Hill sees depression as 'a way of telling us we're going the wrong direction'. It is a drain of energy that starts to drag you down, telling you to reorient. He had a 'half-cooked' identity. He was racing partly for the family name, and he had to separate that from what he wanted for himself. Therapy and that reframe helped him.

• He worked to break the cycle for his own children

Attia's summary: Hill lost his father to death, but his children risked losing theirs emotionally if he didn't deal with it. Hill says you can't rebuild a family that died, but you can choose what you pass on.

EXAMPLES

• Suzuka 1994: an out-of-body lap

Going into the penultimate race, Hill had to beat Schumacher to keep the title fight alive. Exhausted in the wet, he called out to Senna for help. He describes the next lap as an out-of-body experience. Attia compares it to Senna's description of his 1988 Monaco qualifying, when he felt the car was driving itself.

• Adelaide 1994: losing the title by a point

Hill tried to pass a damaged Schumacher on the inside. They touched, and Schumacher crashed out, but Hill's suspension was broken and Schumacher won the championship. Hill still calls his own move clumsy and has never complained publicly. He notes he didn't know Schumacher's car was already probably terminally damaged. The lowest low and the highest high had been about a foot apart.

• Uncomfortable with praise

Attia found a clip of Hill on the TV show This Is Your Life and says his discomfort at being praised is 'palpable'. He asks whether that is simply Hill's manner or something deeper, tied to the inadequacy Hill writes about.

• Quitting at Suzuka 1999

By 38, racing in the wet was mentally and physically exhausting. He wanted to stop at the British Grand Prix, but Eddie Jordan had a contract to keep. In his final race he decided he was finished and retired the car. When the team asked what was wrong with it, he told them nothing.

• Hazard versus risk

An engineer reminds him that the hazard is what can happen, while the risk is how likely it is. Flying wheels have killed very

few people, but the halo removed that hazard altogether. Hill argues that a fluke can kill even when 99 out of 100 drivers would survive the same crash, as with Senna.

OTHER RELEVANT

- **Unprocessed loss can resurface years later**
  Hill's experience suggests grief pushed aside by a demanding career often shows up once that career ends. Getting help can be a gift to your family as well as to you.
- **Untangle whose goals you are chasing**
  Separate what you pursue for a parent, family name or image from what you actually want. Hill sees that confusion as central to the identity crisis that followed his retirement.
- **Treat low energy and depression as information**
  Hill's view is that depression signals a need to change direction. Read it as a prompt to reorient, with professional support, rather than something to grind through.
- **Persistence through bad timing**
  At 29 he was out of a drive, under financial strain and facing a new family challenge, yet he became world champion. Attia sees it as chance favouring a prepared mind.

#107 – John Barry: 1918 Spanish flu pandemic—historical account, parallels to today, and lessons

Guest: John Barry
Date: 2020-04-22 · Duration: 1:22:02
URL: https://www.youtube.com/watch?v=fnkOcG3HGl8

KEYPOINTS

• Most of the 1918 deaths came in a 14–15-week window

Barry, author of The Great Influenza, puts the death toll at roughly 50–100 million, the equivalent of 220–440 million people today. About two-thirds of those deaths came in roughly 14–15 weeks starting in late 1918, and influenza typically burned through any one community in six to ten weeks. In absolute numbers it's the deadliest pandemic in history, though the medieval plague killed a far larger share of the population, an estimated quarter to a third of Europe.

• Even 'swine flu' is a misnomer

Seven of the virus's eight gene segments look avian and one mammalian, and Barry cites good evidence that humans gave it to pigs rather than the reverse. Barry has also backed away from his own theory that it began in Haskell County, Kansas, because New York's spring outbreak was hard to reconcile with that route.

• The deadly second wave was probably the same virus

Barry calls the evidence overwhelming that the mild spring virus and the lethal autumn virus were the same, having adapted dramatically. Both waves had the same unusual age pattern, and spring exposure protected against the fall wave. Neither, however, protected against a third wave that began in February 1919. Attia likens the size of the autumn peak next to the spring one to Everest beside Kilimanjaro.

• It killed young adults, with a peak age of death of 28

Influenza usually kills the very young and the old, but 1918 produced a 'W' curve. Barry links this to the virus binding deep in the lungs as well as the upper airway, and to strong immune responses causing what we now call ARDS. According to Metropolitan Life data he cites, over 3% of young factory workers and over 6% of young miners died, and studies of pregnant women report case-fatality rates of 21–71%.

• The war sped up the spread but didn't cause the pandemic

With a reproductive number close to two, Barry argues, one index case catches up quickly with ten or twenty. Troopships only changed the timing. The bigger effect of the war was a government more determined to control American thinking than at any time in its history, he says, with a press that went along.

• In the West, case fatality was about 2%

That was far higher in developing regions with populations that had never been exposed. Barry attributes the difference to Westerners' partial cross-protection from earlier flu viruses, not to better medicine. India alone lost around 20 million people, and the American Medical Association's 1927 global estimate of 21.7 million deaths was far too low because it applied Western death rates to the rest of the world.

• Telling the truth is the most important public-health tool

Officials told the public it was 'ordinary influenza by another name' while people died within 24 hours of symptoms. When Philadelphia finally closed schools, saloons and churches, a newspaper claimed it was 'not a public health measure'. Barry argues that losing trust fuelled terror and social breakdown. In pandemic-planning groups with D.A. Henderson, nobody disagreed on transparency, and the panels agreed the spokesperson shouldn't be a politician.

• COVID death rates must compare like with like

Recording in April 2020, Attia described Sweden's bet that the true infection fatality rate (IFR) might be close to flu's, about 0.1–0.3%, rather than case fatality rates of 1–2%. Barry stressed that flu's familiar ~0.1% is a case rate, and blood-antibody (serology) studies would push it lower still. A fair comparison needs antibody-based IFRs for both.

• 2009 H1N1 was almost two different diseases

Most people had mild flu, but in severe cases the virus also bound deep in the lung and behaved like 1918, with a similarly young average age at death. Barry adds that most of those who died had other health conditions.

EXAMPLES

• Philadelphia's Liberty Loan parade, September 28, 1918

Doctors unanimously urged cancellation, reporters wrote the story and editors killed it, and a public health commissioner tied to a corrupt political machine let the parade go ahead. Within 48–72 hours influenza exploded. About 4,500 died within three weeks and roughly 14,500 over the pandemic.

• St. Louis as a counterpoint

St. Louis closed things early and fared far better per capita. Barry cautions that not all of the difference is proven to come from social distancing; a city's experience in the spring wave may also have mattered, and that hasn't been fully researched.

• 'Like influenza in the bones'

Christopher Isherwood used the phrase to describe Nazis arriving in Berlin in 1933, expecting readers to recognise the dread. Yet the pandemic left surprisingly little mark on literature: John Dos Passos caught it on a troopship and barely mentioned it.

• US toll in context

The spring wave killed fewer than a tenth of the roughly 675,000 Americans who would eventually die. That is why the autumn surge caught cities so off guard.

OTHER RELEVANT

• Expect waves, and don't assume immunity carries over

1918 had three peaks, and protection from the first wave didn't extend to the third. Plan for repeated surges rather than a single event.

• Judge leaders on honesty

Barry contrasts Germany, Singapore, Taiwan and South Korea with the US in 2020, and wanted scientists such as Anthony Fauci, not politicians, as the public voice. When officials play down what people can see for themselves, compliance and trust fall apart.

• Read fatality statistics carefully

Before comparing a new pathogen with flu, check whether the figures are case or infection fatality rates and whether they come from antibody testing. Mixing them up can mislead you in either direction.

• Invest in surveillance between pandemics

Barry's silver lining is that people no longer need to remember 1918, because they'll remember 2020. He expects lasting investment in monitoring emerging diseases.

#106-Amesh Adalja, MD: COVID-19 vs. past pandemics, preparing for the future, & reasons for optimism

Guest: Amesh Adalja
Date: 2020-04-13 · Duration: 0:44:23
URL: https://www.youtube.com/watch?v=v9uY9UPctno

KEYPOINTS

• This is an April 2020 snapshot
This 40-minute conversation was recorded early in the pandemic. Amesh Adalja, an infectious-disease physician at the Johns Hopkins Center for Health Security since about 2008, works on pandemic prediction, H1N1, Ebola and bioterrorism agents. His estimates reflect what was known then, and some were later revised. Read it as expert reasoning under uncertainty, not as final numbers.

• He knew early that it couldn't be contained
When 41 patients in Wuhan were linked to one market, he found it worrying even before human-to-human spread or deaths had been confirmed. Once human-to-human transmission was confirmed, he expected the virus to reach the US, as H1N1 did after it surfaced in Mexico in 2009. He thought it possible the virus was in the US before 31 December 2019, which was controversial. He credits China with publishing the viral sequence very quickly, which let work on diagnostic tests and vaccines start almost immediately.

• Comparing it with 1957, 1968 and 1918
The 1957 and 1968 flu pandemics each killed roughly 100,000 Americans. The worst recent flu season, 2017–18, killed about 80,000, and a typical year kills 30,000–60,000. COVID deaths would come on top of flu deaths, not instead of them. A shutdown of society on this scale last happened in 1918, beyond living memory. He also stresses that pandemics hit cities very differently. H1N1 in 2009 infected about 61 million Americans and strained hospitals, but its fatality rate was lower than seasonal flu, so people took it in stride.

• It will likely become a fifth endemic coronavirus
Four common coronaviruses cause about 25% of colds. Adalja expected SARS-CoV-2 to join them, with intermediate severity: milder than SARS (about 10% case fatality) but harsher than the other four. Unlike SARS and MERS, it would never go away. He didn't expect full seasonality at first, since so many people were susceptible. Instead he expected successive waves that would ebb and flow as social distancing changed, until a vaccine arrived.

• His estimate of the fatality rate
Testing was biased towards severe cases, so the true denominator was unknown. He placed the overall fatality rate at about 0.3–0.66%, citing Imperial College's 0.66% and Germany's roughly 0.37%, and said it could drift either way as antibody surveys arrived. Risk is steeply age-dependent: perhaps around 15% for those over 80, and very low for children.

• Early models overshot
February models projecting 200 million US infections and 2–4 million deaths didn't account for undercounted mild cases. Adalja believed cases were undercounted by at least tenfold. Westchester County, which tested heavily after the New Rochelle outbreak, had a hospitalisation rate just under 5%, compared with the 15–20% often assumed. That changes ICU and ventilator planning dramatically.

• In the US, public health is largely local
Most public health powers sit with states and localities, not the CDC, NIH or HHS. Rigid early testing criteria, such as travel to China in the previous 14 days, missed spread. New York's virus came mainly from Europe.

• Testing failures set back the response
Adalja believes case finding and contact tracing would have been much better with early, broad diagnostic testing. Patients with symptoms overlapping colds and flu went untested. He looked forward to new rapid tests helping to define a 'new normal'.

• Mass gatherings may drive spread
Density and prolonged contact at stadiums and similar events make them powerful amplifiers. He expected them to be hard to hold until a vaccine arrived, while acknowledging that lockdown policy might reasonably differ between New York City and less-affected areas.

• Masks were an early messaging problem
Early guidance told the public not to wear masks because they wouldn't protect the wearer. N95s were in short supply and uncomfortable to wear for long periods. The guidance was shifting at the time of recording.

EXAMPLES

• Coronaviruses we missed
After SARS in 2003, Hong Kong University researchers identified HKU1, a coronavirus that later turned up disproportionately in hospitalised and ventilated patients in Cleveland. It had gone unnoticed because respiratory viruses are rarely tested for.

• H1N1 bred complacency
About 12,000 Americans died in 2009, and many concluded that the response had been an overreaction. COVID, Adalja argued, touched people personally in a way that H1N1, Ebola and Zika didn't.

• Surges are uneven
New York, New Orleans, Detroit and Chicago were in crisis. Other hospitals that prepared for a surge were reducing their nursing staff, and states shared ventilators. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• A string of warnings
Anthrax in 2001, bird flu in 2005, H1N1 in 2009, Ebola in 2013–14 and Zika: Adalja hopes the economic shock of COVID prevents the usual cycle of panic and neglect.

OTHER RELEVANT

• Influenza is still the bigger threat

Adalja thinks flu is taken for granted and remains the biggest pandemic threat. Avian strains such as H7N9 have case fatality rates around 65% (in his words). If one learned to spread efficiently between humans, it would be a far worse pandemic. That comparison is partly why he sounds more optimistic than most.

• Read pandemic numbers carefully

Early fatality rates are skewed by who gets tested. Look for antibody and population data. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Plan locally

Hospital capacity and policy should follow local epidemiology, not just national averages. Adalja thought places nowhere near New York's density could begin relaxing some restrictions, and that elective surgery and hospital clinics already needed to reopen.

• Make preparedness a voting issue

Adalja hoped people would remember how disruptive this was when they vote, and would ask policymakers about their plans so that pandemic preparedness becomes a 'platform issue' rather than being forgotten within 18 months.

#105-Paul Conti, MD: The psychological toll of a pandemic & the societal problems it has highlighted

Guest: Paul Conti
Date: 2020-04-12 · Duration: 1:26:52
URL: https://www.youtube.com/watch?v=ly1QIlkfxFM

KEYPOINTS

• Conti views the pandemic as a societal trauma that was largely predictable.
Drawing on a psychotherapy principle he summarizes as 'everything is as it should be' (meaning predictable, not morally right), he argues society walked 19 steps down a 20-step path and then acted surprised at step 20. In his view, the way we used new technology and built our systems paved the way for trauma that is both medical and socioeconomic.

• Pandemics isolate people instead of uniting them, unlike wars or terrorist attacks.
Attia cites Sebastian Junger's book Tribe, which describes suicide rates falling after 9/11 as people rallied against a common enemy, and notes that research on pandemics does not show the same effect. Conti explains that an invisible threat brings loss of control, vulnerability and suspicion: a stranger on the street might accidentally kill you, and you can't read safety the way you normally would. That makes people more isolated and more distrustful of each other.

• A vulnerable society goes looking for an enemy, and it often picks the wrong one.
Conti says the feeling of losing control looks for someone to blame, and he sees this coming out as xenophobia and racism. He fears we lose that sense of shared suffering across China, Iran, America, Europe, Africa and South America, which deepens divisions that were already dangerous.

• Global cooperation is possible but much harder without a plotting enemy.
Asked whether world leaders could have pooled testing, data and medicine starting January 12, once the virus had been sequenced, Conti says we can do it but don't right now. 'My enemy's enemy is my friend' comes easily. Uniting against a virus that 'isn't plotting against us' takes the deeper parts of the brain, beyond reflexive 'traumatic aggression', and a recognition of our shared humanity.

• The pandemic hit hardest the large group already on a financial precipice.
Conti sees an extreme gap between his patients. Indigent people in drug and alcohol treatment, where he is medical director, face 'desperation on top of desperation'. Patients with more resources mostly find some relief in hunkering down. He is most worried about the huge middle that can't absorb a roughly $500 surprise expense, people who don't know what they will be going back to. When medical, social and economic stresses combine, he argues, they amplify one another into a threat to society as a whole.

• Society has written off part of the population, and Conti says some shame is warranted.
Most of his work is about fighting the shame that trauma creates, yet he says there are things a society should feel ashamed of. Over his roughly 20 years in practice, he describes a dramatic shift: people who can't navigate complex systems, or who hit a couple of bad breaks, get written off en masse while institutions 'check a few boxes'.

• Fear has become a false strategy for staying safe.
Conti has never seen anything supercharge the belief that 'if I fear enough then I'll be safe' the way this crisis has. He describes a threat-detection drive, evolved to keep us alive long enough to pass on our genes, that has mutated into constant hyper-vigilant discomfort.

• Attia's joyless, irritable restlessness has a name: demoralization.
Attia describes days spent hustling between calls, with exercise squeezed into the gaps, while feeling no interest in anything and no joy even at the thought of the virus vanishing tomorrow. Conti calls this demoralization: a sense that personal effort is futile because you can't fully protect the people around you or change the world. He compares it to 2008–2009, when people who did everything right still ended up underwater on their mortgages.

• Healthcare workers face pervasive and possibly generational trauma.
Attia points to frontline exposure, possibly higher viral loads, and colleagues becoming patients. Conti expects the trauma to reach these workers' children too. He blames 'compounded ignorance' in a system run for profit and cost-cutting, which leaves staff feeling expendable, as disposable as a mask or a gown. Without acknowledgment and real change, he predicts more alcoholism, domestic violence and suicide years from now.

• 'I don't know' is a strength, not a failure.
Attia admits he is tired of saying 'I don't know' a hundred times a day, whether to his daughter or to his patients. Conti calls it 'a beautiful answer': it brings humility, caution and collaboration, the opposite of the medical-school myth that a doctor should never admit ignorance. He sees hubris and false certainty as reckless. He also notes that anger turns questions like whether hydroxychloroquine works into tests of political allegiance.

EXAMPLES

• Conti's presumed case of COVID-19
His wife and two-year-old had mild malaise and his six-year-old was significantly ill. Conti then got very sick quickly: alternating fever and severe chills, a bad headache, deep nausea and shortness of breath with no congestion. He stood shivering with goosebumps under water hot enough to scald, which gave him a sense of how lethal the illness could be for someone older or with other conditions.

• His father's 500-person event
About three weeks before the interview, his father and his father's girlfriend, both in their 80s, planned to attend an event with roughly 500 people because New Jersey had 'no cases', even though little testing was being done. Conti uses this as an example of the 'middle school playground' mindset of 'I don't have the cooties'.

• Absolute truth versus personal truth
Conti says that believing Ayrton Senna is the greatest Formula One driver, or that F1 is the best sport, is a personal truth

driven by emotion. Absolute truths are tested logically, and science is the toolkit for doing that. Attia adds a third category: probabilistic claims, such as whether hydroxychloroquine helps high-risk patients or how big climate risk is, which require talking in terms of error bars.

• Balloons and 'spring inside of me'

Conti describes tossing six balloons around with his six- and two-year-old children and feeling that everything was okay. His daughter, about to turn six, told him that having him home more felt 'like spring has come but inside of me'.

OTHER RELEVANT

• Return to the 'lowest common denominator' of what matters.

Conti's way of looking after himself is to focus on connection with people he loves. If you're alone, nurturing a pet, a garden or a poem can serve the same need to create something. This won't fix broken systems, but he believes it counteracts trauma at home and makes demoralization easier to bear.

• Acknowledge trauma before trying to move past it.

People instinctively push trauma down out of shame. Conti argues that healing, for individuals and for society, requires validating what happened and visibly working to change the systems that caused it. Pretending everything is fine just lets it fester.

• Expect anxiety to persist after lockdowns end.

Conti predicts more anxiety, obsessiveness, panic and agoraphobia when quarantines lift, along with more drinking, drug use, depression and accidents. A period of clear danger can make people feel unsafe long afterward, so this is worth watching for in yourself and in others.

• Hold strong opinions with humility.

If you face 20 open questions and feel strongly about 15 of them without logical grounds, Conti suggests saying so openly. He describes himself as 'pessimistic but not nihilistic' and urges people to help in uncomfortable ways too, beyond what comes easily to them.

#104 - COVID-19 for kids with Olivia Attia

Guest: Olivia Attia
Date: 2020-04-12 · Duration: 0:34:15
URL: https://www.youtube.com/watch?v=g7JlP6cz5Cg

KEYPOINTS

• A kid-level Q&A recorded early in the pandemic

Recorded in April 2020, this short episode has Attia's daughter Olivia asking her own questions and those of other kids. He says up front that he is 'pretty much a newb' on viruses, despite months of reading. His answers reflect what was known at the time. Several, such as surface transmission and when school would return, were openly uncertain.

• Viruses can't copy themselves without a host

Growing taller or growing longer hair comes from your own cells dividing. Viruses lack the machinery to divide on their own, so they infect a host and use its cells to make copies. Many viruses do this without causing much harm.

• Coronaviruses are astonishingly small

A virus is about 100 nanometres wide, and a nanometre is a billionth of a metre. Olivia guesses hundreds could fit across the cut tip of one of her hairs. Attia says it is about a thousand, which is why they can only be seen with special microscopes.

• SARS-CoV-2 probably jumped from bats via pangolins

Attia explains that the virus is called SARS-CoV-2 and the disease COVID-19. Based on the genetic analysis available then, he says it probably went from bats to pangolins and then to people. Pangolins are small, scaly, endangered anteater-like mammals, illegally poached in China, partly for their scales. The first human case was probably in Wuhan around November 2019. He was describing the leading view at the time, not a settled conclusion.

• Earlier coronaviruses were deadlier but spread less

SARS killed about 10% of those infected (one in ten) and MERS about 30% (one in three), but neither spread very far. Other coronaviruses cause nothing worse than a miserable cold. SARS-CoV-2 is harder to contain because it spreads more aggressively than flu.

• The US response was late and underprepared

Attia admits this topic 'gets my blood a little bit boiling'. There was no adequate national stockpile of protective equipment. The US could have doubled down on developing tests or used tests others had made. It was also slow to work out how to handle infected people. South Korea had its first case at about the same time, yet the US already had more than five times as many deaths per million.

• Earlier quarantines would probably have helped, especially in dense cities

Attia believes earlier action would have helped in New York, New Orleans and probably Florida. In New York, people sit close together on the subway, which amplifies spread from a virus passed on by breathing. He thinks New York did the best it could but started later than ideal.

• Herd immunity by deliberate infection is risky

Olivia had been vaccinated against chickenpox, while Attia had the disease as a child, before the vaccine. Either way you're unlikely to get it again, apart from shingles later in life. With COVID, he says, nobody yet knew what immunity looked like or how long it lasted. And even if at least 80% (perhaps 95%) of people recover, some are at high enough risk that letting them get infected isn't acceptable.

• Kids are at very low risk, but they can pass it on

At the time, not one person Olivia's age had died of it in the US. Risk rises with age and with conditions like high blood pressure or diabetes. Her real risk is giving it to a grandparent or someone vulnerable.

EXAMPLES

• Virus on cardboard

Attia cites a study published about three weeks earlier that put the virus on cardboard, plastic, steel and copper. It could survive about a day or two on cardboard. He cautions that the study didn't show you could get infected that way. His advice was to assume anything you touch might carry some virus, and to wash your hands thoroughly for 20 seconds.

• Paying the fiddler

Attia uses the pandemic as a teaching point about long-term trade-offs. Life balances enjoying the moment against preparing for when things go wrong. Here, he says, 'the adults screwed this up': they didn't do their homework, save their allowance or eat their vegetables. They failed to invest time, money, infrastructure and science, and innocent people are now suffering.

• The freeway analogy

If someone cuts you off, that is their fault. But if you were speeding, had been drinking, weren't wearing a seatbelt and were texting, the outcome is partly yours. Likewise, the virus came from China, probably partly because of food-handling practices, but the US still has to own how unprepared it was.

• Olivia's lockdown

When her dad kept her home before the school closed, she thought he was 'out of his mind', until classmates began dropping out and school shut. The hardest parts were missing friends and basketball season. Online classes were chaotic, with everyone talking over each other and no chance to ask questions afterwards. She now realises how amazing school was. The upside was her dad being home and making crêpes.

• Zone 2 at the Attia house

Olivia does zone 2 rides at about 65–70 watts. Her last lactate reading was around 2.1–2.3 mmol at 70 watts, and her dad tests her lactate, which her friends don't really know about.

OTHER RELEVANT

• Explain uncertainty honestly to kids

Attia repeatedly says 'it's too soon to say', for instance about when school would reopen and whether this virus would come back. He still gives his best guess: he didn't expect school to return that school year.

- **Focus on what you can control**

  The freeway lesson is about personal preparedness. You can't stop other people's mistakes, but you can be ready for them. That applies to health habits as much as to pandemics.

- **Protect vulnerable people even when you're low-risk**

  Children's own risk was tiny, but distancing and hand-washing protect grandparents and people with chronic conditions.

- **Invest before you need it**

  Pandemic preparedness, like saving or exercising, looks boring until the moment it's needed. Attia's broader message is that society should fund it in advance.

#102–Michael Osterholm, PhD: COVID-19—Challenges ahead & reasons for optimism and concern

Guest: Michael Osterholm
Date: 2020-03-31 · Duration: 1:22:30
URL: https://www.youtube.com/watch?v=caaY-NixY3s

KEYPOINTS

• This is a snapshot from 30 March 2020

Michael Osterholm, the epidemiologist who directs the University of Minnesota's Center for Infectious Disease Research and Policy and worked on SARS in 2003 and MERS, was speaking as US cases surged. On 20 January his centre had published that this would be a worldwide pandemic, almost two months before it was declared one. Several of his figures were projections and have since been overtaken. Read them as reasoning, not results.

• Transmission would continue until much of the population was infected

With each case infecting about 2–2.4 others, numbers double rapidly (1, 2, 4, 8, 16, 32…). Osterholm had 'every reason to believe' transmission wouldn't stop in any meaningful way until 50–70% of people were infected, unless it was suppressed. He also noted that past flu pandemics peaked about six months after the first cases.

• The scale arithmetic was sobering

Sixty percent of a little over 300 million Americans is about 170–175 million infections. If 80% are mild, the remaining 20% have illness serious enough that many could need hospital care. Even 'only' 100,000 deaths would be a staggering, non-linear burden. New York was then averaging about 150 COVID deaths a day, against roughly 100 deaths a day from all causes in the past.

• Fatality rates are very sensitive to undercounted deaths

His worked example: one death in 100 cases is 1%. Add 100 uncounted mild cases and it falls to 0.5%. But if those 100 extra cases come with 10 uncounted deaths, it becomes 11 in 200, over 5%. Missing deaths move the rate more than missing cases.

• Risk factors went beyond age

Early Chinese data showed higher risk in men over 65, but about 70% of Chinese men over 65 smoke, compared with under 2% of women. New York was seeing more severe illness and deaths in people aged 25–50. Obesity, diabetes, kidney disease (about 700,000 Americans live with end-stage renal disease) and immunosuppression were concerns in a population he called highly vulnerable.

• Healthcare workers lacked protection

Close to 4,000 health workers were infected in China and over 5,600 in Italy. 3M could make about 35 million N95 respirators a month. One New York hospital had used 2 million in a month, and Osterholm estimated the US would need 400 million or more for the first couple of months. When the CDC said to use surgical masks if N95s ran out, he warned many workers would risk their lives without proper protection.

• Supply chains were the hidden weakness

Of 156 critical drugs used in intensive care, all are generic and about 85% are made outside the US. In 2003, China wasn't central to global manufacturing. By 2020, PCR machines and test reagents were impossible to buy because demand everywhere had soared. About 800,000 US tests had been done by then.

• A safe, effective vaccine would take time

'I could make a vaccine tonight,' he said. The question is whether it is safe and effective. He expected one might work, perhaps needing boosters, but not before 2021. How T-cell and B-cell immunity work against coronaviruses was still uncertain.

• New antivirals are historically rare

A review he cited found roughly 5,000 antiviral inhibitors proposed in the literature since about 1963, but only 90 approved over 55–60 years, about 40 of them for HIV. He was sceptical that repurposed drugs would be a quick fix.

• Some cautious good news on immunity

He knew of no clear cases of reinfection after recovery, which hinted at some protection. He warned that it didn't prove durable immunity.

• Who gets infected shapes national fatality rates

Korea's case fatality rate had just risen above 1%. Its large outbreak in a religious group with a median age of 43 kept the rate low at first. In Italy, Osterholm said, a large share of cases were in people over 80 with underlying health problems. Comparing countries without looking at who was infected is misleading.

• Long-term harm to survivors was unknown

Attia raised the possibility of lingering myocarditis, kidney damage and lung fibrosis among survivors. Osterholm said those analyses hadn't been done yet. He likened the response to a boxer hit so hard he can only think about not getting hit again, not about counter-punching.

EXAMPLES

• Indirect signals

Osterholm watched indicators like the NYPD's report that more than 900 officers were out sick to gauge spread beyond what testing showed.

• Not 1918

He didn't expect a repeat of 1918, which uniquely killed 18–30-year-olds. But he called 1918 instructive for public-health methods such as knowing when the virus is in your community.

• The MERS outbreaks

He described standing outside a hospital in Abu Dhabi in 110-degree heat during MERS, as a reminder that coronavirus outbreaks happen in hot climates too.

- **Checkers, not chess**
  He compared the federal response to playing checkers with his 10-year-old grandson, reacting one move at a time. FEMA can't be in all 50 states at once.

OTHER RELEVANT

- **Plan for months, not weeks**
  Hospitals and families should prepare for sustained waves, not a single peak. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prioritise protection for health workers**
  If N95s are short, cohort patients into large wards. Attia suggested moving health workers to the hardest-hit cities, but that only makes sense if they have proper protective equipment, or you lose them unnecessarily.
- **Treat early numbers cautiously**
  Case and death counts lag reality. Look at hospital load and indirect indicators. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Reduce your own risk factors**
  Metabolic health, smoking and kidney health shaped outcomes beyond age. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#101 – Ryan Holiday: Finding stillness amidst chaos

Guest: Ryan Holiday
Date: 2020-03-31 · Duration: 1:22:51
URL: https://www.youtube.com/watch?v=JWpGztbtDnA

KEYPOINTS

• Adversity is a chance to audit how your life is set up

Ryan Holiday, author of 'The Obstacle Is the Way', 'Ego Is the Enemy' and 'Stillness Is the Key', spoke with Attia at the start of the COVID lockdowns in March 2020. Both noted that if someone had told them in January they couldn't fly from March until perhaps July, they'd have been horrified. Now that it was happening, the question was what to do with it: what would you do on the 17th floor of a 600-square-foot New York apartment?

• Humans have always faced plagues

Marcus Aurelius, the central figure in most of Holiday's books, ruled during the Antonine Plague, which struck Rome, lasted about 15 years and, Holiday says, likely killed Marcus himself in 180 AD. Holiday finds perspective in history. Attia adds that the gap between a virus killing 1% or 0.1% of those infected 'makes all the difference', alongside an undeniable economic tragedy like 2008–09.

• Shared crises can unite people

Holiday cites Sebastian Junger's 'Tribe': after 9/11, New York's suicide rate went down as people were united by urgency and a sense of having been wronged, and pettiness fell away. But he notes that a pandemic isolates people and affects the whole world at once, unlike 9/11, or even World War II, which spared large parts of the planet.

• Crises reveal what leaders are for

From Doris Kearns Goodwin's 'Leadership in Turbulent Times', Holiday retells LBJ's analogy from his ranching youth. When cattle get stuck in a ravine or mud, the foreman has to charge in and lead them out with confidence and clarity. Holiday argues we too often choose leaders to 'juice the stock market' or cut taxes, then discover that their real job is to show up in a crisis.

• Stoicism is about what you control

Holiday describes the central precept of Stoicism: we don't control what has happened or is happening, only how we respond. That means letting go of much of what we'd like to control and focusing on what is in our immediate purview. It isn't the same as being reactionary. He links it to unbreakable figures such as James Stockdale and David Goggins ('can't hurt me'), whose endurance under crisis comes from that internal locus.

• Churchill's 'wilderness years' were alive time

Churchill was born early enough to witness, as a young war correspondent, the British Empire's last cavalry charge, and lived into the jet age. He was taken prisoner at about 22 and escaped. In the 1930s he was a political pariah warning about Hitler. Instead of the equivalent of watching Netflix, he read everything he could about Hitler, wrote prolifically, and was ready when called.

• Churchill used routine to find stillness

At his country home he visited his goldfish pond every day, fed the swans, painted daily in a studio attached to the house, and laid the bricks for his estate's wall himself. Holiday argues that these rituals let him get into the flow state needed for enormous work. Attia notes the war lasted years, whereas the Cuban Missile Crisis was over in 13 days.

• Make room for detachment every day

Holiday says moments of detachment are non-negotiable, or you'll spend the whole day buried in the news. Attia asks whether there's any harm in watching 'Breaking Bad' for a fourth time. Holiday's answer is about choice. Some rest is fine, but ask when else you'll have this time with little expected of you.

• Structure protects you from constant reacting

Routines, exercise outdoors every day where it's safe, and a project to work on give shape to formless days. Holiday has felt 'on fire' as a writer, since writing is where he works out his thoughts. Both treat journaling and goals as ways to come out of the crisis with something that lasts.

• The US federal system adapts best to local disasters

Holiday describes the American design of 50 strong states backed by a stronger central government as resilient for local disasters, such as a hurricane in New Orleans or Florida. That model strains when every state is hit at once and the federal government can't be everywhere.

EXAMPLES

• Attia's favourite book

Attia had read 'Stillness Is the Key' three or four times and calls it his favourite of Holiday's books.

• Holiday's hopes

For the coming months, Holiday hoped the crisis would redefine the role of the presidency and the importance of international alliances.

• We saw the train coming and froze

Holiday spent a month trying to persuade his sister to leave her Park Slope apartment. He sees a lesson in how passive people were, carrying on as normal as if they had no agency, while still following health authorities. Attia notes the many people suddenly filing for unemployment and homeschooling, hardly conditions for stillness.

• A reluctant adopter

Holiday jokes that it took a global pandemic to get some people to try Instagram Live, since people suddenly have a minute.

• Social media's pull

Both men worry about social media's manipulative, anxiety-inducing features during isolation. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

OTHER RELEVANT

- **Separate alive time from dead time**
  Use enforced downtime to read, learn or build something, as Churchill did. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Build daily rituals**
  Exercise, a hobby you do with your hands, and fixed work hours anchor you when external structure disappears.
- **Ration the news**
  Check the news at set times rather than refreshing all day. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Look for perspective in history**
  Every generation has faced plagues and crises. Reading about them steadies your judgement.

#100 – Sam Harris, Ph.D.: COVID-19—Comprehending the crisis and managing our emotions

Guest: Sam Harris
Date: 2020-03-24 · Duration: 1:32:33
URL: https://www.youtube.com/watch?v=6KS5Fl6CId4

KEYPOINTS

• Recorded on March 23, 2020, the conversation captures how hard it was to make the threat feel real

Sam contrasts COVID with climate change, which still feels abstract and model-based. With COVID, people could watch the wave hit European hospitals. Even so, he found that showing smart friends the article that alarmed him often didn't work, because different information diets and politics set their 'confirmation bias knobs' differently. He notes how quickly yesterday's 'pessimistic hot take' started to look merely rational, or even late.

• Peter argues public projections need error bars

Peter describes a calibration game: give 95% confidence ranges for 20 factual questions, and you should capture 19. He says he has never seen anyone get close. Binary claims like 'on this date New York hospitals will be overrun' alienate natural skeptics. He thinks stating 90–95% ranges would communicate better. Sam suggests betting and prediction markets sharpen people's sense of probability.

• The flu comparison misses the exponential part

Flu kills tens of thousands of Americans a year in a predictable seasonal pattern. COVID was still in nonlinear growth, so its total toll was unknown. Peter's analogy: a $100,000 salary versus a $10,000 startup salary plus equity, where the equity could be worth far more. He adds that a frozen snapshot might eventually make COVID look smaller than flu, 'but we can't say that.'

• Treat each city as its own country

Peter says Italy wasn't uniform. By his figures, per-capita mortality in Milan was about 40 times higher than in Rome and 300 times higher than in Sicily, depending on which areas got a head start. He suspected New York would resemble Milan more than South Korea, citing density, subways, a late start and some cultural bravado.

• Is the cure worse than the disease? Sam takes the economic risk seriously

Sam worries about depression and lost social cohesion and hopes for a well-targeted stimulus. He points out that nobody offers economic 'happy talk', saying businesses fail all the time and there's no real wealth destruction, yet people offer the equivalent reassurance about the virus. Peter notes markets were down about 30% for the year. He asks how future outbreaks could be handled locally without a global economic calamity, and floats a short, total lockdown of about four weeks.

• Overwhelmed hospitals harm non-COVID patients too

Both expect collateral damage: delayed cancer surgeries, and people avoiding hospitals during heart attacks and strokes. Peter says he now treats any risk of physical injury as if the family were in the wilderness, far from a hospital.

• Mindfulness means clearly feeling anxiety as sensation

Sam says the goal isn't to banish emotions but to get more agile, shortening how long they last. If you feel the energy of anxiety without judgment, contraction or justification, it 'loses its psychological content,' like indigestion or an itch. Fear is useful when it's appropriate. He says 95–99% of moments of fear, shame or regret are 'wasted,' driving us to no good purpose.

• Even a blow-up is the next screen of the game

After losing your temper, shame is just more backward-looking thought. Sam says that moment is as much an opportunity to see through the illusion of self as any other: 'this is the next boss fight.' He describes letting his older daughter hold him to account when she's right that he was in the wrong.

• Peter and Sam held tempered expectations for a vaccine

Peter relays virologists' caution: coronaviruses can behave somewhat like RSV, where getting enough immunity has historically involved a less favorable risk–reward trade-off. He asks whether people would accept a vaccine with 0.1% mortality, offered as a thought experiment. He separates legitimate trial-based safety discussions from discredited claims such as vaccines causing autism. He was more hopeful about therapies targeting parts shared across the coronavirus family.

EXAMPLES

• Sam's friend's ski group

Of a group of five fit, roughly 50-year-old non-smokers among about 13 skiers back from Italy, two, 40%, were ventilated in induced comas. Sam admits it isn't a statistical sample. He compares it to drawing two black marbles in five from an urn that's either 1% or 50% black, which made the flu analogy sound 'delusional' to him.

• Peter's New York ICU math

Peter starts from about 11,000 confirmed cases and the most conservative multiplier of 5x for unknown infections, against estimates of 5–40x, giving about 50,000 infected. At roughly 4–5% needing ICU care, as in Italy, that's over 2,000 ICU patients. New York's capacity is about 1,000 ICU beds at baseline, perhaps 2,000 with repurposing, and about 25% are needed for non-COVID patients. Even assuming no further spread, beds would be full.

• The lights and the Lego

Peter berated his daughter for leaving hallway lights on, then exploded at his five-year-old who kept interrupting calls on his birthday. That was two blow-ups in 14 hours. His 'kryptonite' afterward is withdrawing in shame. Days later, rebuilding a smashed 500-piece Lego train, he got another chance to practice.

• 9/11 versus traffic deaths

Peter compares 'flu kills more' to the argument that traffic killed more people than the roughly 3,000 who died on 9/11. In his view, both miss the nonlinear potential of the threat.

OTHER RELEVANT

- **Talk to kids honestly without unloading everything**

  Sam's family rule is never to lie to their daughters, but that doesn't mean telling them everything. His 11-year-old is old enough to worry, yet he didn't sense the situation was making her anxious.

- **Write down your silver linings**

  Sam encourages noting what people discovered in lockdown, like more family time and a calmer pace, and deliberately keeping whatever is worth holding onto.

- **Watch where politics distorts the picture**

  Sam says people must hold seemingly incompatible thoughts at once. China's authoritarian government concealed the outbreak, which was a real failure, and political tribalism still muddies every other judgment.

#99 – Peter Hotez, M.D., Ph.D.: Continuing the conversation on COVID-19

Guest: Peter Hotez
Date: 2020-03-21 · Duration: 1:06:26
URL: https://www.youtube.com/watch?v=6OX8wo6Mfxk

KEYPOINTS

• A snapshot from March 19, 2020

This follow-up with vaccine scientist Peter Hotez was recorded when the US had a little over 13,000 confirmed cases, up from just under 10,000 that morning. Both warn that pandemic podcasts become 'obsolete pretty quickly'. Hotez says what they say 'may look totally ridiculous in a few days or a week'. Treat the specifics as a record of what was believed at the time.

• Confirmed cases badly undercount real infections

With so little testing, the US was 'just picking it up'. Models suggested 20 to 50 true infections for every confirmed case. Attia's team built its own model, based on the time from infection to death and an assumed infection fatality rate. Their conservative multiplier was about 25, while others argued for no less than 45–50. Attia notes the result is highly sensitive to both assumptions.

• Think in local waves, not national averages

Even 125,000–200,000 real cases wouldn't be spread evenly. New York might have 30,000–40,000 of them, with Seattle and other hot spots also emerging. National averages mislead. The fear was 'a New York situation' appearing in city after city, with hospital capacity the limiting factor.

• Protect frontline health workers first

Hotez says the US was 'not doing all we can, even close' to protect healthcare professionals. Hospitals in Philadelphia, Baltimore and New York already felt overwhelmed. Weeks earlier he had warned Congress about nursing homes after about 25 deaths at the Kirkland, Washington facility, calling it 'the angel of death' to get attention. He wanted a White House task force focused on frontline protection.

• Ideas for surge staffing

Moving rural doctors is unrealistic, since areas like western Nebraska are already underserved, and young physicians are already stretched. Hotez floated a large expansion of the commissioned corps of the US Public Health Service, or using the military, to train medic-level helpers to manage ventilators. He acknowledged Congress would be hard to persuade.

• Young adults were landing in hospital

US data suggested roughly a quarter to a third of hospitalised patients were 20–44, and about half were under 54, which differed from China. Possible explanations, such as smoking (which can upregulate the ACE2 receptor), vaping or genetics, were unknown. Attia read out the ages of one London hospital's ICU admissions that day, many in their 20s and 30s, including a 34-year-old whose chest X-ray was 'a complete whiteout'.

• Long-term damage is a concern even among survivors

Attia cited a 10-year follow-up of SARS-1 survivors showing non-trivial heart and lung disease. Hotez noted early Chinese reports of 'acute heart injury' whose cause wasn't clear.

• Immunity probably follows infection, but an 18-month vaccine is unrealistic

Hotez pointed to a non-human primate preprint showing that infected animals resisted reinfection. He would work on the premise that infection confers immunity, unlike flu with its antigenic drift. He suspected the federal 18-month projection came from Imperial College models, with the virus dipping in summer and returning in the fall. He repeatedly lowered expectations of a safe, rapidly deployable vaccine within 18 months.

• Repurposed drugs: interesting, not proven

Hydroxychloroquine inhibits the virus in vitro and has anti-inflammatory effects. Hotez knows Didier Raoult and calls him an excellent microbiologist, but says his small study was over-hyped and much larger trials were needed. Evidence on ACE inhibitors and ARBs was mixed. Some argued they might block viral attachment, others that they upregulate the receptor.

EXAMPLES

• Convalescent plasma as treatment and prevention

Antibodies from recovered patients could treat the sick in large doses. A small 5 ml dose might protect exposed health workers for a couple of weeks. Hotez noted an informal academic network had formed but hadn't been linked to the White House or FDA announcements.

• Blood type and risk

A Chinese study found people with type A blood had higher infection risk and type O lower. Attia thought the protective O signal, possibly from anti-A antibodies, was stronger. Neither knew whether it mattered in practice, and it is not immunity.

• Mail, takeout and produce

Hotez said he wasn't worried about mail and wasn't doing anything special with packages, though wiping them with Clorox or alcohol wipes does no harm. WHO data on SARS-1 suggested 56°C for 15 minutes killed the virus, so they suggested making sure hot food is above about 140–150°F. Produce like lettuce and strawberries seemed more concerning. Hotez simply washed it more with water.

• Why a bioweapon makes little sense

Hotez's team had long tracked SARS-like bat coronaviruses and tested whether its vaccine cross-protected against them. 'Mother nature is one of the best bioweapons producers there is.' Attia added that two decades of the best bioengineering can barely improve crop yields, which makes engineering a virus this effective implausible.

• Cuomo's op-ed

Both praised Governor Andrew Cuomo's New York Times op-ed calling for the Army Corps of Engineers to build capacity. They also credited officials such as Deborah Birx, Anthony Fauci and Brett Giroir.

OTHER RELEVANT

- **Read COVID numbers locally**

  National totals hide hot spots. Watch your own region's hospital capacity and trends. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Prioritise protecting people who protect others**

  Protective equipment and prophylaxis for health workers and nursing-home staff were Hotez's top priorities, because losing them collapses care.

- **Watch the mental-health toll**

  Hotez worried about suicide and economic devastation that could rival the damage from the infection itself. He was getting three to four hours of sleep while pushing his vaccine towards trials. He urged officials to explain that an '18-month pandemic' doesn't mean 18 months of lockdown.

- **Open science is speeding things up**

  JAMA, NEJM and The Lancet were releasing work quickly into the public domain. Hotez says science publishing still runs on rules from 1850s Germany, and this could change it.

#97 – Peter Hotez, M.D., Ph.D.: COVID-19: transmissibility, vaccines, risk reduction, and treatment

Guest: Peter Hotez
Date: 2020-03-14 · Duration: 0:57:06
URL: https://www.youtube.com/watch?v=hG80O4_YLlo

KEYPOINTS

• This is a snapshot from mid-March 2020

The conversation was recorded around March 13, 2020, when the US had run roughly 75,000 tests and had about 1,600 known cases. Hotez, a vaccine scientist at Baylor College of Medicine and Texas Children's Hospital, repeatedly says how much was still unknown. Treat the numbers as early estimates, not settled facts.

• Third major coronavirus outbreak this century

SARS in 2003 and MERS in 2012 preceded SARS-CoV-2. Hotez notes that when he trained, coronaviruses were considered minor causes of colds in children. Having had a serious coronavirus outbreak each decade is his argument for prioritising coronavirus vaccines from now on.

• Moderate lethality plus high transmission made SARS-CoV-2 dangerous

SARS-1 made people so sick that they ended up in hospital rather than spreading it in the community, so it burned out. SARS-CoV-2 leaves many children, adolescents and young adults mildly ill while they shed virus. Severe disease concentrates in people over 70 and in those with diabetes, hypertension or heart disease. Hotez's working reproductive number was about 2.2–3.6, compared with roughly 1.2–1.3 for seasonal flu and 12–18 for measles.

• Early fatality estimates ranged widely

Hotez cited a case fatality rate of 0.6–3.4%, which he called four to twenty times higher than influenza, and 10–20% among older people. He pointed to the nursing home in Kirkland, Washington, where about 13 of roughly 100 residents died. Attia relayed Marc Lipsitch's scenario of half the world infected within two years at a 0.5% fatality rate. Hotez called it plausible, but noted that small changes in a model's assumptions can shift its outputs by orders of magnitude.

• Losing healthcare workers hurts more than their numbers suggest

In Wuhan at least 1,000 healthcare workers were infected, and about 15% became seriously ill or needed intensive care, more than their ages would predict, possibly because of larger viral exposures. Attia points out that losing 10–15% of physicians, nurses and respiratory therapists reduces care by far more than 10–15%. First responders forced into quarantine compound the problem.

• Catching spread early decided how hard cities were hit

Hotez cites work by his colleague Marc Lipsitch's group: Wuhan, where transmission went unchecked for about six weeks, was overwhelmed. Guangdong detected it within roughly a week and had about 20 people in intensive care. Given US testing delays, Hotez expected case counts to rise as much as tenfold in a week as testing moved to Quest, LabCorp and Roche.

• Convalescent plasma was the treatment available immediately

Hotez publicly backed the idea, promoted by Johns Hopkins' Arturo Casadevall, of collecting antibodies from recovered patients to use both as treatment (large doses) and as prevention for healthcare workers (small doses). He drew on precedent from the 1918 flu, SARS and MERS. Attia flagged the bottleneck that collection requires plasmapheresis. Remdesivir, Gilead's Ebola drug then in compassionate use, still needed clinical trials.

• Vaccines carry a specific coronavirus safety risk

In the 1960s, an inactivated RSV vaccine made vaccinated children sicker when they later caught the virus, with more hospitalizations and two deaths. After SARS in 2003, killed-virus vaccines and whole-spike vaccines caused similar 'immune enhancement' damage in animals, in the lungs or liver. Because vaccines are given to healthy people, trials normally run through three phases over years, so Hotez didn't expect a vaccine within 12 months.

• ACE2 receptors throughout the body may explain the varied symptoms

The receptor occurs in the intestine, the heart and the lining of blood vessels as well as the lungs. Many critically ill patients had acute heart injury, and it was unclear whether that was myocarditis, heart attack or a consequence of ARDS and shock. At least 10% of some Wuhan patients first had GI symptoms, were sent to surgery and infected staff. Paul Offit speculated that cruise-ship outbreaks pointed to gastrointestinal spread, as with norovirus.

EXAMPLES

• A ready-made vaccine nobody would fund

After SARS, Hotez's team and New York Blood Center colleagues found that using only the spike's receptor-binding domain protected animals without immune enhancement. They manufactured an NIH-funded vaccine, then saw interest disappear. SARS-CoV-2 was about 80% genetically similar and used the same receptor, yet he still hadn't raised the money to move it into trials.

• How long the virus lasted on surfaces

A New England Journal of Medicine study discussed in the episode found the virus survived up to roughly 72 hours on plastic, 48 on cardboard, 24 on steel and 8–24 on copper. Attia used it to rebut social-media claims that copper door fittings would stop transmission.

• The 90-year-old in the nursing home

Hotez voiced the question families were asking him: should a 90-year-old mother in a Brookline, Massachusetts facility be confined to her room, with no cafeteria visits with friends and no visits from grandchildren? Hotez said such choices, which trade isolation and mental decline against infection risk, go beyond a vaccine scientist's expertise and need federal guidance.

• China's data sharing

Pushing back on the prevailing view, Hotez said Chinese researchers were very transparent in posting data to preprint servers like bioRxiv and medRxiv. That openness is what let his team spot the similarity to SARS-1 quickly.

OTHER RELEVANT

- **Protect older people living together first**

  Hotez's top priority was older adults in group settings, where attack and death rates were highest. Weigh the risks of isolation openly rather than ignoring them.

- **Reduce contact and surface transmission**

  With virus surviving on surfaces for a day or more and people infecting themselves by touching their faces, hand hygiene and cleaning plastic and steel surfaces made sense. Copper isn't a shortcut.

- **Buy time**

  Because so much was uncertain, slowing spread at the federal, local and individual level buys time for testing, treatments and clearer evidence. Attia stressed that how wrong the grim models turn out to be is partly up to us.

#70–David Sinclair, PhD: How cellular reprogramming could slow our aging clock, & the latest on NAD

Guest: David Sinclair
Date: 2020-01-14 · Duration: 2:10:15
URL: https://www.youtube.com/watch?v=IgosGWLVUrU

KEYPOINTS

• Sinclair's 'information theory of aging'

Sinclair, a Harvard geneticist, discussing his book Lifespan, borrows from Claude Shannon's 1940s work on preserving information in noisy communication. He proposes that aging is mainly a loss of epigenetic information, meaning which genes should be on or off in a cell, rather than a loss of the DNA sequence itself. His analogy: the genome is a DVD, and aging is scratches that stop it being read correctly.

• Sirtuins began as yeast 'silent information regulators'

SIR stands for silent information regulator. In yeast, the SIR2 gene responds to dietary restriction, heat and starvation. Adding an extra copy extended yeast lifespan by about 30%, an experiment done by then graduate student Matt Kaeberlein. These proteins keep certain genes silent but leave their posts to repair broken DNA. Sinclair argues repeated repair calls gradually scramble the cell's program, and aging yeast lose cellular identity and become sterile.

• Methylation is the deepest, most stable layer

Cells mark genes to stay silent for decades by attaching methyl groups to DNA. Sinclair describes histone modifications as more changeable layers above it. The pattern of methylation at a few hundred sites shifts predictably with age, and he says it is very hard to reverse; the only way he knows is the Yamanaka stem cell reprogramming factors.

• The Horvath clock measures how fast you're aging

UCLA mathematician Steve Horvath trained algorithms on methylation sites to estimate age, about 95% accurate for chronological age. Sinclair says the clock starts ticking from conception, runs faster with smoking and sedentary living, and is slowed by exercise and calorie restriction. Universal clocks now work across tissues in humans and, from a Harvard group, in mice.

• Partial reprogramming aims to restore youth without erasing identity

Fully turning on the Yamanaka factors can be dangerous: Juan Carlos Izpisua Belmonte's Salk lab showed it can cause tumors in mice or kill them within about two days. Sinclair's lab leaves out the fourth factor, MYC, a known cancer gene. It delivers the other three, OCT4, SOX2 and KLF4, in an adeno-associated virus that switches on with the antibiotic doxycycline.

• Reprogrammed mouse eyes regained vision

With Bruce Ksander's lab, Sinclair's team tested three models: a crushed optic nerve, raised eye pressure mimicking glaucoma, and naturally aged mice around 12 months old, which they compare to roughly 40-year-old humans. They report regenerated nerves in all three and restored vision in the glaucoma and old mice, measured by whether mice turn their heads to track moving lines. Treated retinal cells had a younger methylation age, with Horvath's help.

• Peter presses on whether boosters touch the deep clock

Sinclair says early data suggest rapamycin, NAD boosters and metformin have relatively little effect on the methylation clock and at best slow it, whereas reprogramming appears to reverse it. Peter wonders whether a week-long fast or pulsed rapamycin, which he takes, might shift it. The two imagine a future clock test read from interstitial fluid, much like today's continuous glucose monitors.

• NAD and the oral-precursor debate

Sirtuins need NAD as fuel, with resveratrol acting as the 'accelerator.' The body converts NR to NMN to NAD and keeps recycling it. Peter cites Joshua Rabinowitz's Princeton tracer study showing oral NR in mice was mostly converted in the liver, raising blood nicotinamide more than NR. A later human trial using 1,000 mg of NR raised muscle NAD but was not yet peer-reviewed. Sinclair suspects gut microbes strip nicotinamide off NR and NMN.

• The benefits may be greatest in the least healthy

Both men note a recurring pattern with metformin, resveratrol and NAD boosters: benefits are clearest in obese or sick mice and people. Peter worries that the health-obsessed people most likely to take these molecules may benefit least. Sinclair agrees the human evidence is incomplete.

EXAMPLES

• Smoking history written in DNA

Peter recalls Sinclair's story that the methylation clock predicted how much people had smoked better than their own recollection. It matched medical records rather than self-reports.

• A small ALS trial

A tiny study of high-dose NR plus pterostilbene (1,000 mg and 200 mg) in ALS patients reported better forced vital capacity than placebo. It had many dropouts and no hard endpoints. Peter suggests effects may show up mainly in severely stressed patients.

• The resveratrol mechanism dispute

Sinclair says a mutation in SIRT1, a 'stiff elbow,' blocks resveratrol's activation. He says repeating his 2006 high-fat-diet mouse study in mutant mice showed resveratrol's benefit depends on SIRT1. He says he takes a gram each morning with homemade yogurt.

• First human target: the eye

The eye is a protected organ where roughly half of optic nerve cells can be reached by the virus. Sinclair hoped to start a glaucoma trial within about 18 months. He suggests the prostate as another possible target, saying about 40% of 50-year-old men already have prostate cancer, though most of it won't kill them.

OTHER RELEVANT

- **Pulse your stressors**

  Sinclair skips metformin on days he exercises because it may blunt mitochondrial gains, taking it when traveling instead, and only when his stomach tolerates it. He avoids rapamycin around training and stops supplements during fasts longer than a day, admitting there is no direct evidence behind this.

- **Pterostilbene isn't proven superior**

  Pterostilbene is a methylated relative of resveratrol. Sinclair says he has seen no data supporting marketing claims that it beats resveratrol, and nobody knows whether the two match milligram for milligram.

- **Next-generation NAD boosters**

  His lab's NAD prodrugs are designed to absorb better, resist gut bacteria and stay stable. The most advanced was in a phase 1 study in healthy volunteers at Brigham and Women's Hospital.

#69 – Ronesh Sinha, M.D.: Insights from a patient population predisposed to metabolic syndrome

Guest: Ronesh Sinha
Date: 2020-01-14 · Duration: 1:59:15
URL: https://www.youtube.com/watch?v=_J8gFRxJVY0

KEYPOINTS

• A cluster of stubborn cases brought Attia to Sinha

Attia had two South Asian patients with unusually stubborn insulin resistance and a striking degree of inflammation, which led him to Sinha's book. Mark Sisson had introduced them about five years earlier. Sinha, an internist at the Palo Alto Medical Foundation, created a South Asian medical consultation service in Silicon Valley after seeing large numbers of Indian and East Asian tech workers with metabolic disease.

• Sinha's own numbers made him feel like a fraud

When local companies asked him to explain these conditions to Indian employees, he was giving advice while his own triglycerides were above 300 and his HDL in the 20s. Fixing his own metabolism shaped how he treats patients.

• Carbohydrate load is huge, even in vegetarians

At least half of Sinha's South Asian patients were vegetarian, and some had the worst lipoprotein abnormalities. His average South Asian patient ate 300–400+ g of carbohydrate a day, and some East Asian patients 500–600 g. Cutting carbohydrate dropped triglycerides by 150 points within three to four weeks.

• Thin doesn't mean metabolically healthy

Sinha describes couples in which the wife is 30–40 pounds overweight with flawless triglycerides and HDL, while the 'rail skinny' husband with a BMI of 21 has triglycerides 'through the roof'. The heavier person often stores fat subcutaneously and has more leg muscle. The thin one stores it viscerally, so BMI misclassifies risk.

• Visceral fat, not total fat, drives dysfunction

Sinha cites a New England Journal of Medicine liposuction study, with Sam Klein as one of the authors. Removing about 30 pounds of subcutaneous fat produced no metabolic improvement, pointing to the visceral compartment as the problem.

• Several factors may explain Asian susceptibility

A 2013 genetic study found lower beta-cell density in East and South Asians. Overfeeding for 24–48 hours depresses beta-cell function. Populations that migrated to colder climates have more brown fat, which can account for 15–18% of resting calorie burn. Within India, prevalence is higher further south toward the equator, reaching up to about 20% in Kerala. Sinha also cites studies in which mitochondrial ATP output rose only about 5% in offspring with a family history of diabetes, compared with about 90% in those without, before any insulin resistance was visible.

• Thrifty gene versus thrifty phenotype

James Neel's 1960s 'thrifty gene' idea was that famine cycles selected for fat storage, but no gene was found. Sinha says experts doubt there were enough famines to explain it. The Barker hypothesis instead points to the womb. In about 100,000 UK records, lower birth weight predicted higher heart-disease mortality, a pattern since reproduced on every continent.

• A1c often misleads; CGMs reveal more

Comparing 90 days of continuous glucose monitoring with A1c, Attia finds only about 25% of patients are concordant. The other 75% are off in either direction. He argues that the 6.5% A1c cut-off has no fidelity between 5 and 6, and misses people with normal fasting glucose but post-meal spikes of 200. He notes that the gap between a glucose of 100 and the diabetic 200 is about one extra teaspoon of glucose in the bloodstream.

• Night-time glucose may reflect cortisol

CGMs show very high overnight glucose in some people who eat well. Morning readings of 110 can occur in otherwise healthy people. Sinha noticed the pattern before CGMs and began prescribing calmer evening routines, no devices and brief meditation. They note that stress alone can push glucose from 90 to 120 within about two minutes.

EXAMPLES

• Fitness as an early marker

At matched age and BMI, insulin-resistant people, especially South Asians, have lower VO2 at submaximal effort. Attia prefers a zone 2 test, the most power sustained with lactate below about 1.8–2 mmol. For example, 200 watts versus 140 watts at the same lactate separates two people more sensitively than VO2 max, which shifts with body weight.

• PCOS as 'insulin-resistant ovarian syndrome'

Endocrinologists in Fremont estimate that 25–30% of Asian women there show some manifestation of PCOS. Sinha thinks the name should reflect its root in hyperinsulinemia. He also sees eczema and other inflammatory conditions that make insulin resistance harder to treat.

• A 47-year-old with a heart attack

A woman who read his book came in after a first heart attack at 47, with her parents and her child. Her Lp(a) was elevated. Sinha checks Lp(a) widely because many of his patients with a family history of coronary disease have normal LDL, and he sees Lp(a) as an independent risk factor.

• Vitamin D

Sinha aims for roughly 30–40 ng/mL and doesn't see the point of pushing to 80–90. Anecdotally, he sees CRP improve when deficient patients are corrected.

• Sleep tracking

Reviewing a patient's monthly averages, Sinha found 6 hours 12 minutes a night. He says moving someone like that to eight hours is among the most impactful changes he can make.

OTHER RELEVANT

- **Build movement into the workday**

  For busy executives who won't add time, Sinha treats leg strength as a vital sign, for example 'this many squats by 12 p.m.', plus balance and stretching breaks. Weak legs at 50–60 predict slower walking, canes and decline.

- **Breathing as 'meditation in meetings'**

  Using an Apple Watch or Fitbit, patients notice when their heart rate is 20 points above resting and breathe it back down. Sinha teaches this to people who refuse to meditate.

- **Look past BMI and A1c**

  Ask for triglycerides, HDL, fasting insulin and, where possible, a CGM. These matter most for lean South and East Asians, whose risk is often hidden.

- **Protect kids' sleep and limit devices**

  Sinha's family doesn't compromise on bedtimes. They delayed devices until about 7th or 8th grade and set no-device rules for gatherings. He worries about classmates studying or watching TV until 1–2 a.m.

#83 – Bill Harris, Ph.D.: Omega-3 fatty acids

Guest: Bill Harris
Date: 2020-01-14 · Duration: 2:02:25
URL: https://www.youtube.com/watch?v=2Nz7nFlvx9M

KEYPOINTS

• Harris has studied omega-3s for over 40 years

After a PhD in nutrition in 1978, Harris did his postdoc with Bill Connor in Portland, Oregon. He has published over 300 papers on EPA and DHA, and founded OmegaQuant about 10 years before this conversation. Attia was introduced to him in 2011 through Tom Dayspring. Keep his testing company in mind when weighing his advice on testing.

• How fatty acids are named

The notation gives the number of carbons and double bonds: palmitic acid is 16:0 (saturated), oleic acid is 18:1. 'Omega' (or n-) tells you where the first double bond sits, counted from the tail end, so oleic is omega-9. Linoleic acid (LA, 18:2) is the main omega-6. EPA has 20 carbons and five double bonds, and DHA has 22 carbons and six. Fish oils are rich in omega-3s, and vegetable oils such as safflower, corn and sunflower in omega-6s.

• The 1980 salmon-oil study found an unexpected effect

Participants drank salmon oil straight, about 25 g of EPA plus DHA a day. Triglycerides fell from about 100 to 75 mg/dL, and cholesterol dropped modestly (around 250 to 230). Nobody had known fish oil lowered triglycerides, and the paper came out just as the US was entering its 15–20-year era of fat phobia. In patients with extremely high triglycerides, 18–20 g a day took levels from around 2,000 down to 250. In some people, LDL rose (for example from 120 to 140–150).

• Typical intake is tiny compared with traditional fish-eating diets

The average American gets about 100–250 mg (roughly 0.15 g) of EPA plus DHA a day, out of 80–100 g of total fat. When Bang and Dyerberg studied Greenland Inuit in the 1970s, they documented about 6–7 g a day. The body converts little plant omega-3 (ALA) into EPA and DHA: even 12 g of ALA barely raises EPA.

• The omega-3 index tracks status better than plasma

The index measures EPA plus DHA as a percentage of red blood cell membrane fatty acids. It reflects most tissues, including the heart, which Harris validated using biopsies from heart-transplant patients, though it reflects the adult brain less well. Harris targets 8–12%. The average American is around 4–5%, and some non-supplementers are at 2%. Attia's own index was about 10–11% (EPA 2.2%, DHA 8%). Harris has seen no clear adverse effects at higher levels. International bodies consider up to 5–6 g a day of EPA plus DHA safe.

• REDUCE-IT: 4 g a day of purified EPA cut cardiovascular events by about 25%

The trial included about 8,000 statin-treated patients with triglycerides of roughly 150–500 and other risk factors. They received 4 g a day of EPA ethyl ester (Vascepa) or a mineral-oil placebo. Events fell by about 25%. Attia notes that was a bigger effect than in the PCSK9-inhibitor trials, though REDUCE-IT also ran longer, about five years against roughly 2.2 for FOURIER and 2.4 for ODYSSEY. Critics question whether mineral oil was a truly neutral placebo. Japan's JELIS trial, published in 2007, had also used an EPA drug.

• VITAL found little effect at a low dose in low-risk people

Reported at the same meeting as REDUCE-IT, VITAL gave about 20,000–25,000 relatively healthy Americans one Lovaza capsule a day (about 850 mg EPA plus DHA). It missed its primary endpoint but showed roughly 20% fewer heart attacks, including fatal ones. Harris says that with low-risk participants and about a fifth of the REDUCE-IT dose, the two trials can't be directly compared.

• Harris doesn't think omega-6 is the villain

He dislikes the omega-6 to omega-3 ratio, because the same ratio can mean very high or very low levels of both, and it assumes omega-6 is bad. Americans eat about 15 g of LA a day but only about 0.1 g of arachidonic acid. Tissue arachidonic acid barely shifts with intake, which Attia calls a buffer or 'capacitor'. Harris is sorry to see oils bred to be low in LA (safflower went from 77% to about 15%) because evidence suggests higher LA is linked to lower risk. Attia pushes back, pointing out that humans ate little seed oil for most of history.

EXAMPLES

• '1,000 mg fish oil' is not 1,000 mg of omega-3

Prescription Lovaza is a 1 g capsule containing about 850 mg (85%) of EPA plus DHA as ethyl esters. It was approved at 4 g a day for triglycerides over 500. Raw fish oil may be only about 30% EPA plus DHA. Modern processing concentrates it, so check how much EPA and DHA a capsule actually contains.

• Three NEJM studies in May 1985

That month the New England Journal of Medicine published three omega-3 studies back to back. Harris calls 1985 a turning point for the field.

• Some people reach 8% from diet alone

Even among non-supplementers eating roughly one fish meal a week, some had an index of 8%. Genetics and absorption vary, so intake alone doesn't predict status.

• STRENGTH trial pending

AstraZeneca's Epanova trial (4 g of EPA plus DHA, about 13,000 patients, similar criteria to REDUCE-IT) was due to finish around October 2020. Attia and Harris planned to discuss it once results were out.

OTHER RELEVANT

• Measure, don't guess

Harris wants omega-3 status checked as routinely as cholesterol. The finger-prick test costs about $50. Aim for an omega-3 index of about 8–12%.

- **Prefer fish, supplement if needed**
  Eating fish is preferable, but taste, cost and ecological concerns make that hard for many people. EPA plus DHA supplements can get you there. Because there is no pure EPA supplement equivalent to Vascepa, the prescription drug may even be cheaper if insurance covers it.
- **Read the label for EPA plus DHA content**
  A typical good supplement has EPA and DHA in roughly a 60:40 or 40:60 ratio. Count the actual milligrams, not the 'fish oil' weight.
- **Don't rely on flax or ALA**
  Plant ALA converts poorly to EPA and DHA, so it can't replace marine sources.

#76 – Kyle Kingsbury: Finding meaning, depression, and psychedelics

Guest: Kyle Kingsbury
Date: 2020-01-14 · Duration: 1:41:31
URL: https://www.youtube.com/watch?v=Dbh-mLrIBr4

KEYPOINTS

• This conversation deals frankly with suicide and drug use

Peter opens with two disclaimers. Anyone having thoughts of self-harm should seek medical help immediately. And discussing performance-enhancing drugs and psychedelics isn't an endorsement. Kingsbury, a former UFC fighter, describes suicidal thoughts that began around age seven, including picturing his father's guns and wondering if jumping off a mountain would kill him.

• Football gave him a path, but he stalled in the NFL funnel

Academically 'garbage' in his own words, Kingsbury went through two junior colleges to walk on at Arizona State. There he mostly rode the bench. He realized NFL hopes were unrealistic after watching a teammate who started every game for four years on the defensive line go undrafted. Peter notes the median NFL career is only about three to five years.

• He used anabolic steroids from high school onward

He started testosterone in his senior year of high school (he names 250 mg), and it gave 'only' about 10 pounds but taught him to care about sleep and food. Later came growth hormone and IGF-1, then nandrolone ('deca') with testosterone once he knew he wouldn't go pro. Growth hormone alone cost about $1,000 a month and, he hints, was 'sponsored.' He says he felt better, not angrier, and read a pharmacology textbook to understand the drugs.

• Peter: steroids amplify existing traits; long-term data are missing

Peter says the most he has prescribed for low testosterone is about 140–160 mg a week, while athletes may take ten times normal levels. Short studies of 12–16 weeks at such doses don't find bad outcomes, but longer use is unstudied, which is his main reason not to endorse it. His analogy: like money, steroids amplify an aggressive person rather than create one. He suggests that people who use them non-medically may already be filling a void, which could raise depression risk independently.

• After football, pills and partying filled the void

ASU was then the top party school; he lost friends to overdoses. For a year in junior college he started each morning with a bong hit. After football he mixed alcohol, cocaine, pressed ecstasy pills and Xanax, often awake until 5 a.m. He says the comedown always left the 'unworked-through stuff' waiting.

• A parking-garage ledge brought his first spiritual experience

After a fight with his girlfriend and the thought 'I will never be loved,' he swallowed his remaining pills and climbed to the top of an ASU parking structure at about 2 a.m. Standing at the edge, he felt a wash of warmth, the most peace of his life, and a voice saying 'not yet, it's okay.' A security guard talked him down, and he woke in the hospital with family who had flown in from California.

• MMA gave structure, but self-belief cracked in the UFC

He won about six straight fights in smaller promotions before an underprepared loss at King of the Cage in Laughlin, Nevada. He compares it to Tyson and Buster Douglas. A coach sent him to join a full team, and he entered the UFC as a jiu-jitsu white belt. Among equals, his 'negative monkey-mind chatter' got louder. He says chin-to-chest contact from a knee was the one blow that truly hurt him in the Octagon.

• Psilocybin, then ayahuasca, changed his direction

A coach introduced guided psilocybin work. After his third straight loss, in Nottingham, England, with a torn labrum and a fractured eyebrow, he began ayahuasca. His UFC record was 4–4, and the Reebok deal had removed personal sponsors, so he lived in his mom's detached garage. By this conversation he had done 26 ayahuasca ceremonies and called each one a new layer of the 'infinite onion.'

• Covert depression in men often looks like achievement or addiction

Drawing on therapist Terry Real, Peter contrasts overt depression (can't get out of bed, weepy) with covert depression, which hides behind workaholism, substance use and violence. He notes men are about 93% of the US prison population and about three times as likely to abuse alcohol. Kingsbury lived both extremes: 'a perfect little angel' in fight camp and countless nights of excess between camps.

EXAMPLES

• Peter's patient with normal LH and FSH

Peter describes a patient on testosterone whose LH and FSH stayed normal, as if he weren't taking it, a pattern Peter then reproduced in a couple of other patients. He uses it to show how individualized dosing is.

• The hardest ayahuasca night

One night in Colombia, Kingsbury had no visions and only purging. Another time he relived his father's rages from the first-person view of his six- or seven-year-old self and his 15-year-old self, with the same fear, rather than watching like a movie.

• Machu Picchu or ayahuasca?

A friend in Peru phoned to ask whether to spend five days hiking Machu Picchu or doing ayahuasca. Kingsbury found trip reports calling it the 'apex of teacher plants,' and they later found practitioners locally.

• Has he lost his edge?

Kingsbury says the chip on his shoulder that once made him want to hurt people is 'washed away.' He now wants to avoid the injuries fighters often leave with so he can read to his son and chase his kids around.

OTHER RELEVANT

• Create rites of passage for young men

Kingsbury points to Tim Corcoran's father–son wilderness survival camps and traditional cultures where children leave to

learn from elders. Peter worries how hard that is when eight-year-olds have cellphones.

• Forgiveness is for the forgiver

His relationship with his parents came full circle after ceremonies at Soltara in Costa Rica. He says forgiveness is about taking off his own 'weighted vest,' and that loved ones, like his wife, can see blind spots we can't.

• Use psychedelics with intention, space and supervision

Kingsbury spaces ceremonies and arrives with a reason to be there. Peter frames this as one person's experience, not a protocol, especially with suicidal history or legal risk.

#81 – Debra Kimless, M.D. & Steve Goldner, J.D.: Cannabis – the latest science on CBD & THC

Guest: Debra Kimless & Steve Goldner
Date: 2020-01-14 · Duration: 2:11:35
URL: https://www.youtube.com/watch?v=aaPnZKbkf10

KEYPOINTS

• Both guests have a commercial stake, and Attia flags it up front

Goldner is founder and CEO of Pure Green, and Kimless, an anesthesiologist, is its chief medical officer. Attia tells listeners to take everything with a grain of salt, while saying that after hours on and off mic he believes their intentions go beyond business. He expects the field to change enough that he'll need to revisit it within a year.

• THC and CBD act on the endocannabinoid system in different ways

THC binds the CB1 receptors that produce intoxication. According to the guests, CBD doesn't sit directly on CB1 or CB2. Instead it works indirectly, for example by slowing the breakdown of the body's own endocannabinoids, or through other receptors altogether. In the raw plant both exist as acid forms and only become active after time and heat remove the carboxyl group, which is why eating raw cannabis won't get you high.

• 'Hemp' is a legal category, not a separate plant

Under US law, hemp is cannabis with less than 0.3% THC. Growers crossbreed cannabis to stay under that line, so modern hemp is very different from the industrial hemp of the Constitution era. Hemp-derived CBD now shows up in lotions, teas, ice cream and vape cartridges, many sold through a large gray or black market.

• Cannabis is a botanical mixture, not a single molecule

Kimless cites more than 100 cannabinoids, more than 80 terpenes, plus flavonoids and other compounds that may act together. Their argument is that formulations combining ingredients can work at lower doses than a purified isolate. Attia frames this as the opposite of the reductionist, one-drug-one-target view he was trained in.

• THC's risks are mostly individual and depend on dose

Some people feel calm on a small dose. Others get panic, anxiety, a racing heart or a spike in blood pressure, sometimes even at low doses. Kimless agrees high-dose THC can worsen schizophrenia, but argues CBD with little or no THC may still help such patients. On teenagers, she says she wouldn't advocate any chemical substance for a developing brain unless it's medically needed, such as for a seizure disorder.

• Acute lethality is extraordinarily low

The guests cite a DEA attorney, writing in support of descheduling, who estimated that a 75-kilogram man would have to smoke about 1,500 pounds of cannabis flower in 15 minutes to die, and that the cause would probably be carbon monoxide, not cannabis itself. That says nothing about chronic, psychiatric or developmental risks, which the episode treats separately.

• The guests argue cannabis is not a gateway drug

Kimless says NIDA no longer calls cannabis a gateway and that Colorado didn't see increased youth use after legalization. She also cites lower opioid prescribing in states with dispensary access and trials using CBD to help people come off methadone or heroin, which is why she calls it a possible 'exit drug'. These are the guests' readings of the evidence; Attia notes he doesn't know that literature himself.

• Vaping risks include additives never tested for inhalation

Thinning agents such as propylene glycol and vitamin E acetate are 'generally recognized as safe' (GRAS) for eating, not for heating and inhaling. Heating propylene glycol can create formaldehyde. Goldner explains that the FDA's GRAS status covers specific uses, and that many cannabis products weren't tested for safety before they shipped.

• Edibles are unpredictable

Swallowed cannabis goes through first-pass metabolism in the liver. Kimless puts onset at 60–90 minutes, with only about 8% bioavailability in the best case, and effects lasting 8–10 hours. A full or empty stomach and time of day change absorption, so even an accurately labeled edible won't give a repeatable dose. That's why people stack doses and get far more intoxicated than they meant to.

• THC tolerance is real but may plateau

Heavy use down-regulates receptors, which Kimless says reset after a couple of days off. She contrasts it with opioids, where tolerance escalates and can flip into increased pain sensitivity. She cites Dutch medical-program data in which the average patient stabilized at about 750 milligrams of cannabis a day rather than continuing to increase.

EXAMPLES

• A 16-patient CBD pain pilot

Kimless gave a 5 mg water-soluble CBD tablet with terpenes for two weeks to 16 people treating mild-to-moderate pain with over-the-counter drugs, and reports a statistically significant reduction in pain. When Attia asked about a control group, she acknowledged there was no placebo arm; it was a proof-of-concept study.

• Epidiolex as the purified benchmark

GW Pharma's plant-derived CBD is purified to over 99% and approved for two rare, treatment-resistant seizure disorders in children. Kimless cites roughly a 30% reduction in seizures, with GI and liver side effects. She uses it as a contrast to lower-dose combination formulations.

• Under-the-tongue tablets for sleep

Their tablets dissolve in about 15 seconds under the tongue, bypass the liver and reportedly work within 8–10 minutes. The guests cite safety-monitoring data from several hundred thousand people reporting good sleep without grogginess, and suggests GABA activation as one mechanism. When Attia asked about sleep architecture, Kimless said she hadn't seen polysomnography data.

- **The road to FDA approval**

  Attia notes that a new drug takes about a decade and roughly a billion dollars to bring to market. The guests say they hold themselves to that standard, while pointing out that Schedule I status blocks standardized testing. State labs don't all use the same methods.

OTHER RELEVANT

- **Buy only from regulated sources**

  Kimless advises against buying online or on the street ('we tell our children don't take candy from strangers'). If you live where it's legal, register as a patient, get guidance from a clinician and use a licensed dispensary. The Society of Cannabis Clinicians lists experienced physicians by state.

- **Start low and wait with edibles**

  With onset of up to 90 minutes and effects lasting hours, take one measured dose at a consistent time. Capsules or tablets are preferable to foods, and don't re-dose because nothing has happened yet.

- **Treat bold anecdotes with caution**

  Goldner admits he wouldn't have believed some of the stories patients told him. Weigh uncontrolled reports and data from companies selling the products accordingly, and look for placebo-controlled trials before expecting a specific benefit.

- **Be extra careful with THC if you have a psychiatric illness or are a teenager**

  High-dose THC can worsen schizophrenia, and there's no case for using it recreationally on a developing brain. Medical use for teenagers is a decision to make with a clinician.

#71 – Katherine Eban: Widespread fraud in the generic drug industry

Guest: Katherine Eban
Date: 2020-01-14 · Duration: 2:41:33
URL: https://www.youtube.com/watch?v=46wAJYTap_A

KEYPOINTS

• Patient complaints started the investigation

Eban, an investigative journalist and author of Bottle of Lies, had seen generics as a public good: affordable, life-saving drugs that make programmes like Medicare and the VA workable. In 2008 Joe Graedon, host of NPR's The People's Pharmacy, told her he was deluged with complaints about generics not working. FDA officials dismissed them as psychosomatic, blaming switched pills that looked different. After about 20 years as a reporter, Eban says 'something tingles'.

• Generics are reverse-engineered, not copied

A patent discloses the molecule, but the manufacturing process is often 'the secret sauce'. Attia compares it to tasting a finished dish that took 12 hours, seven steps and 13 ingredients, then trying to recreate it. Generic makers only have to show bioequivalence, meaning the drug behaves the same way in the body. They skip the phase 1–3 trials that test safety and efficacy, so the integrity of their data is everything.

• Hatch-Waxman created the modern generic industry

The 1984 Hatch-Waxman Act, signed by Reagan, let generics be approved without new clinical trials. It gave the first generic filer six months of exclusivity, a valuable prize because prices collapse once about ten generics enter (to roughly 30 cents on the dollar). Attia wonders whether the trade-offs, including patent life, were set well. A bribery scandal at the FDA in the late 1980s showed that both industry and regulator could be compromised.

• Globalisation outran the FDA

By 2005 the FDA had more plants to inspect overseas than in the US. Today about 80% of active ingredients in all US drugs, brand or generic, come from abroad. About 90% of prescriptions are generic, and about 40% of generics come from India. The US makes almost none of its own antibiotics. PEPFAR, the Bush administration's HIV programme in Africa, helped normalise cheap Indian generics, and Scott Gottlieb, then in the Bush White House, pushed questions about how to guarantee their quality.

• Ranbaxy fabricated data for more than 200 products in about 40 countries

In 2003 engineer Dinesh Thakur left Bristol-Myers Squibb's spotless New Jersey campus for Ranbaxy in Gurgaon, India's would-be 'Pfizer of the 21st century'. Ranbaxy was nearing $1 billion in sales and held first-to-file rights on drugs including generic Lipitor. His new boss, R&D head Rajinder Kumar, who had come from GlaxoSmithKline, had Thakur's team audit its filings. They found the company had tested brand-name drugs and passed them off as its own to fake bioequivalence, then sold untested or substandard products. Eban says the 200 products were essentially the whole portfolio.

• The 'self-assessment report' went straight to the board

Kumar presented the findings to Ranbaxy's board in a blandly titled 24-slide 'self-assessment report' (SAR), 'smoke and fire' on every slide. Attia compares it to finding bodies in every room of a house and showing the killer a PowerPoint. Rather than fixing the problem, the company moved to contain it. Thakur, anonymously through a Yahoo email account, went to the FDA.

• The investigation took years

FDA agents raided Ranbaxy on February 14, 2007. A Ranbaxy enforcement team grew to about 30 people, unpicking each type of fraud, such as stability tests at 6, 9 and 18 months that were never actually done. The case settled in 2013. Eban's reporting drew on about 20,000 internal FDA documents and 16 Freedom of Information requests, and she even sued the FDA to obtain records.

• Ranbaxy was the tip of the iceberg

FDA chemist Peter Baker, a tattooed, motorcycle-riding 32-year-old 'new sheriff in town', refused the usual courtesies. Overseas inspections were pre-announced, and companies arranged inspectors' travel, gave souvenirs and offered massages. Over five years Baker inspected 86 plants in India and China and found some form of data fraud or manipulation in about four-fifths of them. Some plants even had staff whose actual job was data fabrication.

EXAMPLES

• Frances Kelsey and thalidomide

In the early 1960s, thalidomide was widely given in Europe to pregnant women for sleep and morning sickness. FDA reviewer Frances Kelsey refused to approve it in the US. That episode, after earlier tragedies, helped shape the modern FDA's demand for proof of safety and efficacy.

• Carcinogens in blood-pressure pills

Millions of Americans took valsartan, losartan or irbesartan whose active ingredient, made in Chinese and Indian plants, contained carcinogens, possibly for about six years. Dozens of versions were recalled. Eban says the FDA had found impurity problems earlier and done nothing.

• Attia's own patients

Attia has seen three cases in his practice where drugs with a predictable, measurable response simply didn't work. Before reading the book he had felt crazy arguing about it. Eban also describes Cleveland Clinic doctors who pieced together patterns of failure, and a boy whose infection didn't respond to a Ranbaxy antibiotic but cleared quickly on a GlaxoSmithKline one.

• Whistleblower and aftermath

Thakur received about $48 million as his share of the settlement, but his life 'really unraveled'. Daiichi Sankyo, which had bought Ranbaxy, paid around $500 million. It then won a $500 million arbitration award in Singapore against former CEO Malvinder Singh. Attia notes that 'it's easier to turn on one man than one culture'.

• Even branded companies aren't immune

One month after FDA approval of a $2.1 million gene therapy, the manufacturer told the FDA there had been data manipulation in its application.

OTHER RELEVANT

- **Investigate your own drugs**

  Eban's website has a step-by-step guide. Find out who actually manufactured your drug, since the pharmacy label may not say, and look up that manufacturer's FDA inspection history. She stresses that patients 'shouldn't have to be Sherlock Holmes' and that new laws are needed.

- **Price-shop and ask for a specific manufacturer**

  Attia shows how a price app lists cash prices for, say, thirty 10 mg atorvastatin tablets by pharmacy, from cheapest up, and they vary widely. Combined with manufacturer research, you can choose a source and know your maximum out-of-pocket cost.

- **Take 'it isn't working' seriously**

  If a drug with an objective, measurable effect (blood pressure, lipids, an infection) doesn't perform, consider the specific generic before assuming the patient is at fault. Attia now checks the drugs his practice prescribes, about 30.

- **Push for more and better inspections**

  Eban and Attia favour more Peter Bakers: unannounced inspections, a training programme for investigators and accountability for overseas plants. Attia calls it 'belt and suspenders', with regulators and patients both doing their part.

#72 – Dan Harris: 10% happier – meditation, kindness, and compassion

Guest: Dan Harris
Date: 2020-01-14 · Duration: 2:24:35
URL: https://www.youtube.com/watch?v=KRE_cbTJKrk

KEYPOINTS

• A panic attack on live national TV forced Dan's inner work into public view.
The on-air episode—fed by years of ambition, depression, and substance use—became the origin story of 10% Happier. He wrote the book as a skeptical newsman who backed into meditation because suffering, not spirituality, demanded a tool. Readers who met him through the book often say the same: if this guy can sit, maybe I can. ABC News colleagues who watched the spiral both worried and enabled the pace that fed it.

• Addiction sits on a spectrum that includes socially rewarded forms.
Dan owns cocaine-era choices and also the workaholism and status hunger that newsroom culture applauds. Peter and Dan map how 'acceptable' addictions still hijack the same reward circuitry and leave the same relational wreckage. Mapping the spectrum without ranking suffering helped him drop both denial and special-snowflake identity. Socially celebrated work addiction is harder to quit because the world pays you for relapse.

• Childhood self-protection scripts drove adult grandiosity and anger.
A defining early moment taught him to armor up. Mindfulness later let him watch anger and ego inflate without handing them the microphone—useful on deadline and at home. Self-protection had been adaptive in childhood and corrosive in marriage and newsroom politics. Understanding the childhood scene did not excuse adult cruelty; it explained where to aim the practice.

• Kindness has a selfish ROI he now advertises on purpose.
Compassion practices reduced his own misery and improved negotiations and marriages alike. Framing kindness as enlightened self-interest helped his skeptical audience try it without needing to become saints first. Selfish compassion is a door; once inside, many people discover less instrumental motives anyway. He pitches that ROI without apology because it converts holdouts who reject moralizing.

• He moved from scoffing at meditation to daily practice and a business around it.
Friends and reporting assignments nudged him; first sits were clumsy. Ten years on, the 10% Happier podcast and app package the same bridge he needed: secular language, short sessions, honest talk about how often the mind wanders. Secular packaging mattered: Buddha as pragmatic psychologist more than cosmic mascot for his audience. Co-founding the app forced him to productize the same on-ramp that saved him.

• New meditators should expect state changes before trait changes.
Early sits may bring calm (state); character shifts—less reactivity, more warmth—arrive slowly (trait). Misconception: emptying the mind. Reality: noticing thoughts and returning, thousands of times, without self-violence. Conflating a pleasant sit with permanent transformation is how beginners quit when life gets loud again. Teachers who promise instant bliss set students up to abandon the cushion after week two.

• A 10-day silent retreat taught 'you're trying too hard.'
Straining for special states backfired. Teachers redirected him toward relaxed diligence. That lesson still governs how he coaches beginners away from achievement-oriented meditation that recreates the striving that hurt them. Trying too hard is the achiever's favorite way to fail at a non-achievement practice. Retreat silence also revealed how much of his identity was verbal performance.

• A brutal 360 review exposed selfishness and redirected him toward compassion training.
Colleagues' feedback hurt because it was accurate. Instead of defensiveness-only, he used it as curriculum: more metta/compassion reps, more listening, less starring in every story. The review's gift was specificity—names, moments, patterns—not vague 'be nicer' advice. Compassion reps after the 360 were scheduled like gym sessions, not vibes.

• Meditation helps hard seasons without magically erasing them.
He is frank about what practice did and did not do in grief and career stress. It shortened the half-life of spirals and made him a better husband; it did not grant immunity. He still uses short emergency sits when cortisol spikes, without pretending they replace therapy or sleep. Hardest moments still hurt; the win was fewer secondary wounds from rumination.

• Parents must interrupt shame transfer.
Dan and Peter discuss letting kids see flawed humans who repair, rather than perfect performers who hide. Insecurity can fuel professional success and still be a rotten gift to pass down; emotional-health pillars matter alongside ambition. Peter connects this to his own fear of exporting unfinished trauma into his kids' nervous systems. Emotional health pillars he names include sleep, therapy when needed, and friends who tell the truth.

EXAMPLES

• On-air panic attack
The career crisis that made inner chaos non-optional and launched the book that reached other skeptics. Without that humiliation in public, he doubts he would have prioritized inner work over the next assignment. It remains the most expensive free lesson of his career.

• 10-day silent retreat note
'You're trying too hard' as the teaching that unlocked progress after forceful striving failed. It reframed progress as relaxation-with-discipline rather than more force.

• 360 review shock
Documented selfish patterns from people who worked with him—painful enough to change his practice priorities toward kindness. He treats revisiting that feedback as ongoing practice, not a one-time purge.

• Peter Jennings as flawed mentor
Learning excellence and humanity from a legendary, imperfect boss—permission to be excellent without pretending to be

unblemished. Excellence without emotional honesty was the inheritance he did not want to pass on untouched.

- **App/podcast bridge for skeptics**
  Secular framing, short sits, and humor as the on-ramp Dan wished he had found sooner. Humor lowers the dignity threat that keeps Type-A skeptics away from cushions.

OTHER RELEVANT

- **Start tiny and drop the empty-mind myth.**
  Five to ten minutes of noticing and returning beats an hour of self-attack about doing it wrong. If you miss a day, the next sit is the practice—no makeup punishment sessions.
- **Train kindness for selfish reasons if that is what gets you started.**
  Reduced personal suffering is a valid hook; motives can purify later. Track whether you interrupt less or apologize faster; those are kinder metrics than 'bliss minutes.'
- **Use feedback as meditation homework.**
  When a 360 stings, pick one interpersonal habit and practice it as deliberately as the breath. Pair each critical theme with a weekly behavioral experiment you can measure.
- **Let your kids watch repair, not perfection.**
  Model apology and regulation so your ambition does not ship as their shame. Narrate your own mistakes at dinner in age-appropriate ways so perfection is not the family religion.

#74 – Jason Fried: Optimizing efficiency and work-life balance

Guest: Jason Fried
Date: 2020-01-14 · Duration: 2:24:35
URL: https://www.youtube.com/watch?v=TvFOUCeEsLI

KEYPOINTS

• Luck and timing explain more success than founders admit

Fried, co-founder and CEO of Basecamp, says he used to believe everything he did was intentional. Now he thinks that if he started the business today, there's a good chance he couldn't do it at all. Timing has many dimensions: personal, market, competitors and public appetite. He also says business only gets harder over time, with more customers, staff, expectations and competitors, and the risk of becoming blind to new ideas.

• Profit is a skill you have to practise

Fried compares companies that claim they can 'pull the lever' on profitability whenever they want to someone claiming they could walk on stage and play guitar without practising. Profit is the business making 'its own fuel'. Relying on outside money puts undue pressure on founders.

• Uber, Lyft and WeWork are 'terrible businesses'

Fried says Uber lost about $1.8 billion on roughly $11 billion in revenue, though he isn't sure whether that was a year or a quarter. He points out it had raised over a billion dollars and been in business about a decade. He says WeWork's IPO filing admits it may never be profitable, and calls Uber's ethics a 'dumpster fire' driven by growth pressure. The corner dry cleaner, he argues, is a better business.

• Amazon is the exception, not the model

Attia recalls a hedge-fund friend in 2013 arguing that Amazon's share price was entirely explained by AWS, its cloud business, so the retail business came free. Fried's answer is that outliers don't matter for real businesses. A pizza shop that loses money on every slice to sell more would obviously fail.

• Fried doesn't set goals

In high school, Attia rewrote a long list of fitness goals every day. He changed one, five miles in 25 minutes, to five 6-minute miles when he saw his long, slow training would plateau. Fried says goals end in disappointment or an endless treadmill of new 'fake numbers': running a 6:06 instead of 6:00 says nothing about whether the run was enjoyable, got him outside and moved his body. He just wants to do his best work. Attia pushes back that 'objectives', like what the 85-year-old Jason should be able to do, are still goals.

• A calm workday means eight uninterrupted hours

Fried argues long hours aren't caused by more work but by days chopped into smaller and smaller pieces. You need contiguous blocks for creative work. At Basecamp, the theme of his book It Doesn't Have to Be Crazy at Work, people get eight hours to themselves and nobody can see others' calendars or take their time. He compares eight hours to a flight to Amsterdam: a long time when it isn't interrupted.

• Small teams, six-week projects and few dependencies

Every feature at Basecamp must fit in six weeks or less, many in two or three, with at most three people, typically two programmers and a designer. Three can self-manage without ties; a fourth creates sides. Teams work like 'glide wheels, not gears' so they rarely wait on each other. Progress is shared through automatic daily check-ins and a six-week summary instead of presentations.

• Find the 'epicenter' and accept trade-offs

A hot dog stand without ketchup or a bun is still a hot dog stand; without the hot dog, it isn't. Fried's team asked what customers really wanted from a calendar: to see which days have something on them. That took far less work than a Google Calendar clone, which he says can't be built in six weeks, but a version solving 80–90% of needs can. Rougher screen transitions or cutting his book from 40,000 to 20,000 words are accepted trade-offs.

• Saying no is precise; saying yes is a shotgun

Fried says agreeing to one thing rules out a thousand others, while declining removes one and keeps options open. Attia notes a one-hour talk can cost 48 hours. Fried cites a story, which he isn't sure is true, that Warren Buffett books meetings only a day ahead. His point: 'we block our future with present obligations'. He values flexibility, which is also why Basecamp will stay independent.

EXAMPLES

• Basecamp started as an internal tool

Fried's web design firm ran projects through email, calls and paper until things slipped through the cracks. He and partner David, a Copenhagen Business School student from Denmark, built a tool for themselves. Clients asked to use it. It launched as Basecamp on February 5, 2004, the same day as Facebook, and within about a year and a half it out-earned design work.

• A two-page proposal won as many jobs

Early on, Fried replaced glossy, personalised proposals with one or two pages giving what, cost and timeline. He won no fewer jobs and slept more. That convinced him that much effort is wasted, and he says he learned to put a little time into the core of each task.

• Published, non-negotiable salaries

Basecamp pays everyone in the top 10% of industry rates using San Francisco benchmarks, though no one lives there. People with the same skills and experience get the same pay, and the number is published. A candidate who wants more is told to find another job. Fried says your livelihood shouldn't depend on being a good negotiator.

• Writing is the first hiring filter

Because the company communicates mostly in writing, a bad cover letter disqualifies anyone, 'even the best scientist in the world'.

- **Deleting Instagram mid-interview**

  Fried admitted he used Instagram mainly to browse watch photos and show off new watches, which he called unhealthy. He deleted it from his home screen during the recording, noted the moment it 'made me feel weird', and decided the app shouldn't have that control. He keeps Twitter, mostly to broadcast.

OTHER RELEVANT

- **Treat phones like modern cigarettes**

  Attia removed nearly all notifications, including a Hodinkee watch-news alert, and suspects phones may cause more total suffering than cigarettes because people don't see the harm.

- **Prefer async, long-form communication**

  Fried calls chat rooms 'all-day meetings with an unknown set of participants', a virtual open office. He expects a swing back to deliberate, complete writing; Attia calls email toxic overall.

- **Seek advice from recent founders**

  Fried says expert advice has a shelf life. Someone who started a business six months ago knows today's ground game better than he does.

#79 – Ric Elias: Earning the gift of life

Guest: Ric Elias
Date: 2020-01-14 · Duration: 1:41:53
URL: https://www.youtube.com/watch?v=XKhh3hzyd5M

KEYPOINTS

• Ric was a passenger on US Airways Flight 1549—the Hudson River landing.
Thursday, January 15, 2009: after basketball at a Upper East Side club in falling snow, he boarded the flight that lost engines to birds shortly after takeoff. In the minutes before impact he was certain he would die, and the inventory of regret that flooded him permanently reordered what he valued. Red Ventures at that moment was finally working after years when failure felt likelier than a TED-worthy recovery story.

• The landing required stacked improbabilities within tiny margins.
Ric recounts airspeed near ~151 mph where a few miles per hour either way meant cartwheel or survival, wind around 12–13 mph, and clearance over the George Washington Bridge he could see as they passed. Captain Sully's speed of decision—not just the decision itself—is what Ric thinks mattered most; fifteen extra seconds of dithering would have erased the window. He is careful to say he is not a pilot; the margins are how the event feels from seat 15F, not an NTSB brief.

• Afterward he refused the airline's $10,000 check as disingenuous.
The gesture felt like hush money next to the existential reset. He has told Peter's audience a post-landing story he had kept private, and he holds a separate reverence for Sully's composure under a clock measured in seconds. Friends still tease him about the uncashed check sitting as a relic of a refusal to close the emotional books.

• He adopted an 'earn this' second-life ethic.
Borrowing the Tom Hanks line from Saving Private Ryan, Ric treats remaining years—whether six months or sixty—as something to justify through how he loves family and serves strangers, not through another growth spurt at work alone. The vow is checked against ordinary Tuesdays—school pickups and hard conversations—not only against keynote stages.

• Time became the ultimate currency; saying no became a skill.
Pre-crash he was scaling Red Ventures through a growth spurt after four brutal early years (~700 employees then). Post-crash he plays what he calls an infinite game: protect attention, decline status meetings, and measure days by presence with kids more than by enterprise value. Infinite-game language also changed how he negotiates: leave room for the relationship after the deal.

• Parenting in achievement culture means finding each child's gift.
Hard-driving parents, he warns, project their own scoreboard. His job is to notice what each kid is built for and to tug-of-war through teenage phone culture without confusing GPA with a life successfully lived. He dreads aspects of modern adolescence frankly, even while refusing to outsource values to the phone.

• What is actually worth getting upset about shrank.
Traffic, slights, and deal friction lost altitude next to the memory of the river. That selectivity frees energy for problems with human stakes—immigration, education access, community safety—rather than inbox theater. Colleagues notice the difference as shorter fuses replaced by selective intensity on issues with human stakes.

• Red Ventures' principles show up as hiring undocumented talent and funding college.
Ric describes dozens of DACA/work-permit colleagues on staff and hundreds supported through college pathways, including a Golden LEAF–linked college effort that started with a tiny first class and now reviews larger applicant pools. Business acumen and moral imagination are not separate ledgers for him. Supporting undocumented young adults through work and tuition is, for him, earning the river rather than branding it.

• He hires for judgment and character under pressure, not pedigree alone.
Negotiation tips he offers juniors emphasize listening for the other side's real constraint. The next 'big problem' he wants to solve keeps returning to opportunity gaps for young adults who get locked out before they get a first fair shot. He listens for whether candidates take responsibility when stories go badly, because Sully-seconds show up in business too.

• If he could speak to himself that snowy morning, he would not warn about the plane.
The imagined message is about how to live after surviving—not how to avoid the flight. The crash is already the teacher; the homework is earning the gift daily. The thought experiment ends in gratitude practice, not survivor guilt cosplay.

EXAMPLES

• Snow walk to the Reebok club
Beautiful flakes, chosen walk, ordinary morning—the banality before the bird strike that makes the later clarity sharper. The contrast between beauty and catastrophe is why he still tells the walk-to-the-club detail.

• Bridge and airspeed margins
Seeing the George Washington Bridge on the way down; ~151 mph and light wind inside a narrow survival band. Compounding small tolerances is the metaphor he now uses for organizational near-misses too.

• Saving Private Ryan 'earn this'
Ric's internal vow after impact mirrored the film's charge to justify a life others paid to save. He has told the story to his son to translate abstract mortality into a usable ethic.

• DACA colleagues and college pipeline
~50 undocumented/work-permit employees at Red Ventures in his telling, plus hundreds sponsored through college—philanthropy wired into ops. Classes grew from 12 to larger cohorts as the model proved it could survive contact with reality.

• $10,000 check refused
Symbolic rejection of a transactional close-out on an experience that rewrote his identity. Keeping the check uncashed is a physical reminder more durable than a journal entry.

OTHER RELEVANT

- **Inventory your regrets before the emergency.**
  Ric's river minutes were about unfinished love and misplaced priorities. Do the audit on a calm Tuesday. Write the three relationships you would regret most neglecting, then schedule them like board meetings.
- **Practice saying no to protect the infinite game.**
  Growth-company muscle defaults to yes; second-life math defaults to presence. Default decline on status invites; accept only what serves people you love or problems you named.
- **Raise kids for gifts, not résumés.**
  Achievement culture is the water; parents have to name a different scoreboard out loud. Ask each child what feels like play when no adult is grading it—and protect that hour.
- **Put opportunity work on the operating budget.**
  Hiring and tuition support beat press-release philanthropy when the goal is changing trajectories. Measure philanthropy by named humans moved through school or jobs, not by press hits.

#78 – Sasha Cohen: The price of achievement, and redefining success

Guest: Sasha Cohen
Date: 2020-01-14 · Duration: 2:13:48
URL: https://www.youtube.com/watch?v=ozDGp7XG4Xo

KEYPOINTS

• Cohen went into Turin 2006 as a favorite but physically underprepared.
It was her second Olympics, after finishing fourth in 2002 at 17. Six months before Turin she had felt in the best physical and mental shape of her life. Over that winter, injuries and equipment problems piled up, and she arrived feeling like she was 'walking a pirate's plank'. Women's figure skating comes at the very end of the Games, so skaters often stay away from the Olympic Village and skip opening ceremonies to protect their focus.

• She led after the short program despite not having skated it cleanly in weeks.
Because of her injuries she had struggled even to get through full run-throughs. Landing all three jumping passes and seeing her name in first place felt like a triumph, but a 'temporary victory'. She strained her leg during that skate and, with her coach and physical therapist, chose to skip her 40-minute practice slot the next day, which confused observers because no one skips practice.

• Small doubts in the warm-up shook her confidence in a sport decided by milliseconds.
In the five-to-six-minute warm-up before the long program she fell on a triple flip and a triple lutz, jumps she rarely missed. She explains that in figure skating, hesitating for a millisecond throws off a jump's timing. She buried the doubt and broke the moments before the skate into tiny tasks: put on makeup, put on your pants, get on the bus, jog around the arena.

• Her coach taught her 'you don't fall, you bounce'.
She fell on the opening triple lutz combination and missed her second jump. Attia marvels that after a fall a skater lands in an unpredictable position yet has to rejoin the choreography and the music right away. He notes that a mistake in tennis does limited damage, while in skating one error can cost everything. Cohen got through the rest with word-by-word self-coaching ('set the shoulders, pull back, snap') and let herself feel the emotion of Romeo and Juliet.

• In skating, a medal contender who finishes second has 'lost the gold'.
Cohen won silver because the top three all made mistakes on a messy night. She says that at another Games she might have placed eighth or tenth. Instead of hearing congratulations, she faced questions about her dreams being dashed. She could get through only 30–40 seconds of each of eight interviews before crying, then went through drug testing, an exhibition skate and the closing ceremony, feeling like 'a porcelain doll that's shattered and glued' back together.

• Winning doesn't settle the question of identity.
Cohen once assumed that a perfect skate and a gold medal would have left nothing to resolve. Yet she notes that multiple gold medalists like Apolo Ohno and Michael Phelps still struggle, because the moment passes and a new way to prove yourself is needed. Attia is struck at how quickly the public discounted Phelps when two of his butterfly world records fell in 2019.

• Athletes in her sport get a tiny window, and the public often treats them as resources.
Most Olympians attend only one Games and very few win medals. In women's skating and gymnastics there is a minimum age of 15, while some Russian skaters peaked at 12 to 14 and were past their best by the time they were eligible. Attia cites Missy Franklin, who was criticized in 2016 after her dominant 2012, as an example of toxic fan expectations.

• Cohen channeled a diagnosis of ADHD into figure skating.
She went through three elementary schools in Pasadena. One teacher thought she was deaf, and another gave her mother a book on juvenile delinquents. Her mother chose not to medicate her and put her in gymnastics at five, four hours a day, with 100 V-ups and 300 jumping jacks. A skating birthday party introduced her to gliding, which never felt like a sacrifice to her.

• Retiring takes away both the highs and lows that defined an athlete's life.
After stepping away from competition she toured, took acting classes and guest-starred on CSI. She came back for the 2009–10 season and then left. Life felt pleasant for about a year and then 'slack'. She thinks the commonly cited figure that 80% of former Olympians experience some form of depression may be an undercount, because athletes are trained not to admit weakness, even to themselves.

• She chose to be 'the tadpole in the ocean'.
Rather than staying a big fish by coaching or judging, she enrolled at Columbia alongside classmates a decade younger, went by her legal name Alexandra, and moved into finance as 'the next competitive thing'. She eventually found that climbing the same kind of mountain felt hollow. She came to see that success is self-defined, fleeting and not the same as happiness.

EXAMPLES

• Scoring and program structure at the time
The short program ran 2 minutes 50 seconds, with three jumping passes, footwork, a spiral sequence and three spins. The long program lasted just over four minutes, with up to eight jumping passes. Under the post-6.0 system scores had no cap, so skaters only knew how good a score was by comparing it with others.

• Booed in Moscow
Although her family has roots in Odessa, Russian crowds booed her whenever she competed against their favorite, Irina Slutskaya. Without a Russian rival in the event, the same fans supported her.

• The Weight of Gold and Steven Holcomb
A documentary on athletes' mental health that Cohen took part in began as a comeback story about bobsledder Steven Holcomb. He was interviewed 12 days before he died by suicide. He had been isolated at the Lake Placid training center, losing his vision, and expected to end up in his mom's basement even if he won.

• Two weeks as the peak of a career
Attia points out that for a typical one-time Olympian, the peak of years of work lasts two weeks. He finds it hard to believe that this is unrelated to high rates of depression afterward.

OTHER RELEVANT

- **Widen what counts as success.**

  If second best in the world counts as failure, success becomes so narrow that even reaching it gives only a short high, like eating a piece of chocolate cake. Cohen suggests building life around relationships, meaningful work and well-being rather than fleeting peaks.

- **Enjoy the rare season while you're in it.**

  Her advice to her 15-year-old self is to enjoy a body trained to an extraordinary level and the Olympic experience, because later you'll be winded on a jog. She thinks that would matter more than squeezing out extra results.

- **Let go of trophies that keep you tied to an old identity.**

  Her silver medal sits on her mother's dresser, and she left both Olympic rings with her mother, who gave more than 15 years to driving her to rinks and therapists. Expecting a son, she hopes he'll play sports at a healthy level and try debate, guitar and wilderness classes.

#82 – Mark Messier: Leadership, personal growth, and performing under pressure

Guest: Mark Messier
Date: 2020-01-14 · Duration: 2:10:00
URL: https://www.youtube.com/watch?v=wFOVq6uEJHk

KEYPOINTS

• Twenty-six professional seasons and six Stanley Cups

Messier turned pro at 17 in the World Hockey Association, with Indianapolis and then 52 games for Cincinnati after Indianapolis folded. He then played 25 NHL seasons and retired in his mid-40s. He won five Cups with Edmonton and one with the New York Rangers, and is the only player to captain two different teams to the Cup. Attia, who grew up in Toronto idolising him, says the episode is less about stats than about how a leader matures.

• Late development and natural talent both matter

Messier cites NHL players who didn't start until 14 or 15 as proof that you don't have to play 365 days a year from age two. You need 'god-given talent', then the desire to hone it at the right time, and many kids who do everything right still never make it. He grew from about 5'9" and 150 pounds at 15, when he made junior, to 6'1" and around 200 pounds by the end of junior.

• His father and older brothers taught him what a teammate is

His father was a tough defenceman, with the Portland Buckaroos among other teams, who protected his teammates and later became a teacher. Young Mark tagged along to his practices from age three or four. From 12 to 14 he was stick boy for his brother's junior team, which gave him a close view of team culture. He traces his later leadership to that apprenticeship.

• Losing in 1983 taught the price of winning

The young Oilers, average age about 20 to 23, were swept by the Islanders, who had won three straight Cups. Walking past the Islanders' dressing room, they expected champagne. Instead the champions sat quietly at their stalls covered in ice packs. 'That told us that we weren't paying the price that we needed to.' Messier says they had been playing checkers while the Islanders played chess. Edmonton beat them in the 1984 final and won again in 1985.

• Gretzky was a different kind of player

Gretzky was chasing record books, scoring over 200 points in a season several times (215, 212, 205), and 50 goals in 39 games. Messier says the Oilers' approach was to 'grab an oar', fill a need and follow Wayne. They were all superb skaters, and coach Glen Sather let them abandon the 'tabletop hockey' of the era for the weaving, free-flowing style that resembles today's game.

• The 1988 trade and the 1990 Cup without Wayne

Gretzky's trade in July 1988, after four Cups in five years, stunned the team. They regrouped, and in 1990 Messier led Edmonton to another Cup. Messier says winning without Wayne 'never even crossed our minds'. They were disappointed he wasn't there to share it. He calls those Oilers perhaps 'the best team that probably ever laced up skates'.

• New York at 30: a pressure cooker he wanted

Coming off five Cups in seven seasons and at the peak of his career, Messier wanted a new challenge. The Rangers hadn't won since 1940. He deliberately immersed himself in the city and its culture, while keeping his focus on 7 to 10 p.m. on game nights. Missing the playoffs in 1992–93 was a painful low before 1994.

• Leadership grows with age and introspection

At 18, he says, hockey needs all your attention, but it wasn't who he was as a person. At 30 in New York he had time to think about what success required: how to be a good citizen and contribute to the community. That 'doesn't happen when you're 18 or 20', he says, but over time as you evolve.

• He left the game fulfilled

Messier contrasts athletes who can't get over no longer being 28 with those who move on. Retiring in his 40s after 26 pro seasons, he felt he had done everything. He says a forced retirement at 25 through injury would have been far harder.

EXAMPLES

• The 1994 Game 6 guarantee

Down 3–2 to the Devils in the conference final, Messier told reporters the Rangers would win Game 6. He says it was meant for 'our 20 guys on the bus', to restore the confidence they had shown all year, not 'for 12 million New Yorkers'. He then scored a hat-trick, the Rangers won Game 7 on Stéphane Matteau's overtime goal, and they went on to end their 54-year drought.

• Steve Smith's own goal, 1986

In a tied third period against Calgary, defenceman Steve Smith's pass from behind his net went in off his own goalie, and Edmonton was eliminated. Messier has never rewatched the game. When the Oilers won the next Cup, Gretzky handed it first to Smith. Attia contrasts this with Andrés Escobar, the Colombian defender who was murdered after scoring an own goal at the 1994 World Cup.

• Terrified of losing

Before clinching games, Messier says, thinking about winning the Cup was 'overwrought with fear' of giving a dangerous opponent like the Islanders a way back into the series.

• Bobby Orr and Guy Lafleur

Attia tells the story of the Bobby Orr–signed stick on his childhood wall. Messier recounts the story that Guy Lafleur sat in full gear in the Boston Garden at 2 p.m. smoking cigarettes, then scored a hat-trick, and says he knew how much pressure performing in that building meant.

• Life after hockey

Messier now commutes into New York most days by train and subway, and still poses for selfies. He leads the Kingsbridge National Ice Center project in the Bronx to expand kids' access to hockey. He ran the New York City Marathon in 2011 for the

10th anniversary of 9/11. He weighs about 215 pounds, close to his playing weight, though with less muscle.

OTHER RELEVANT

- **Avoid early burnout in young athletes**
  Find a balance that is healthy for the family and gives the child the best chance at their own dream. Passion and late development can still lead to the top.
- **Learn from what champions are willing to endure**
  The ice packs in the Islanders' room were a lesson in what it really takes. Ask what price the best in your field pay, not just what they achieve.
- **Speak to the room, not the crowd**
  Messier's guarantee was aimed at restoring his own team's belief. Leaders' words should serve the people who have to deliver.
- **Keep training for how it makes you feel**
  As a player, he needed 10–15 minutes just to reach the concentration to train. In retirement the three-hour windows disappeared with kids, so he trains loosely two to four days a week. He keeps doing it because he feels more awake, alive and energised.

#66 – Vamsi Mootha, MD: Aging, T2D, cancer, dementia, Parkinson’s—do all roads lead to mitochondria?

Guest: Vamsi Mootha
Date: 2020-01-13 · Duration: 2:27:53
URL: https://www.youtube.com/watch?v=k3ZPCyfKvYo

KEYPOINTS

• Mitochondria are domesticated bacteria with a stripped-down genome

Over evolution, about a thousand genes from the original bacterium were lost or moved to the nucleus. The human mitochondrial genome is now about 16,000 base pairs and encodes 13 proteins, two ribosomal RNAs and 22 tRNAs. Mootha notes the malaria parasite's mitochondria encode only three proteins, while Giardia ('beaver fever') has lost its mitochondrial DNA altogether.

• Mitochondrial disease isn't just 'maternal'

There are about 250 distinct syndromes caused by mutations in mitochondrial DNA. But most of the roughly 1,000 proteins that mitochondria need are encoded in the nucleus, so many disorders are recessive nuclear mutations rather than maternally inherited. Mootha says clinical training overemphasised maternal inheritance because those cases were easiest to recognise.

• Why mitochondrial DNA comes from your mother

An unfertilized egg holds about half a million copies of mitochondrial DNA, more than any other cell, while a sperm has a few hundred at best. Beyond being outnumbered, sperm mitochondria are tagged with ubiquitin and actively destroyed after fertilization.

• Mitochondria turn over within days

In non-dividing tissues such as muscle and neurons, Mootha estimates the half-life of mitochondrial components at a few days, so the body is constantly building and recycling them. Counting individual mitochondria is ambiguous because they continually fuse and divide, so copies of mitochondrial DNA are the better unit.

• NAD is both an electron carrier and a consumable

NAD shuttles electrons in the electron transport chain to power ATP production, but sirtuins and DNA-damage enzymes also use it up. That's why NAD can fall quickly in cells with damaged DNA. Muscle biopsies show NAD, mitochondrial content and VO2 max all declining with age, but Mootha says the open question is whether sick mitochondria cause tissue aging or simply accompany it.

• Too much oxygen, not just too little ATP, may drive some mitochondrial disease

The textbook view is an energy shortage, but Mootha's lab finds that glycolysis largely defends ATP at rest. Because mitochondria consume most of the oxygen we breathe, broken ones leave unused oxygen in tissues, which can be toxic. Patients often show unusually high oxygen in venous blood.

• Reduced mitochondrial function shows up before type 2 diabetes

Papers in 2003–04 from Mootha, Leif Groop, David Altshuler, Ron Kahn, Gerald Shulman and others found that healthy people with a family history of diabetes had slightly lower expression across the whole set of mitochondrial genes, fewer mitochondria and lower VO2 max. Fifteen years later, whether this causes diabetes or reflects some upstream factor remains unresolved. Mootha's team was attempting to answer it with Mendelian randomization.

• Partly blocking the electron transport chain can extend life in worms

RNAi screens by Gary Ruvkun and Cynthia Kenyon found electron-transport genes among those whose disruption lengthened worm lifespan, and also among those that shortened it. One explanation is dose: gentle inhibition triggers protective responses, while severe loss kills. Mootha suggests metformin, a complex I inhibitor, may work through such a mild hit.

• Exercise is the best known way to renew mitochondria

Mootha says no drug yet rejuvenates mitochondria directly. Exercise both clears damaged ones and builds new ones. Both he and Attia are skeptical of 'exercise in a pill' headlines; Attia points to crude news coverage of irisin.

EXAMPLES

• Hypoxia rescued mice with Leigh syndrome

Mice lacking a complex I subunit look normal at birth, sicken around days 30–35 and meet euthanasia criteria by day 55–60. Raised at 11% oxygen (similar to 18,000 feet, about Everest base camp) instead of 21%, they lived to a median of about one year and looked so healthy that the team suspected a genotyping error. Mootha stresses this is in mice only and works in some models of mitochondrial disease, not all.

• Attia's metformin and lactate experiment

Testing himself on a bike in 5–10-watt steps, Attia found his resting lactate rose from below 1 mmol/L to between 1 and 2 on metformin, about double, with higher lactate during exercise too, confirmed using two meters. He calls it an N-of-1 observation consistent with complex I inhibition diverting pyruvate to lactate. Mootha offered to run fuller metabolite profiles on and off the drug.

• A textbook on a cousin's bookshelf

Stranded at his dad's cousin's home in Somerville on a Friday night when the subway shut down during his miserable first year of medical school, Mootha found a mitochondrial biology textbook, read about 100 pages that night and decided on his life's work.

• Hyperbaric oxygen for selected cancers

Flooding tumours that have weak mitochondria with oxygen might harm them, and Mootha has an oncologist in his lab exploring this. Past results with hyperbaric oxygen in cancer have been mixed. He expects any benefit to be limited to a rare subset of tumours with mitochondrial defects, identified by sequencing rather than by tissue type.

OTHER RELEVANT

- **Don't read too much into supplement hype**
  Mootha's distinction between correlation and causation applies to NAD boosters: falling NAD tracks aging, but replacing it hasn't been shown to reverse tissue decline in humans.
- **Metformin may blunt exercise adaptations**
  Attia's lactate data and the complex I mechanism raise the question of whether metformin interferes with exercise benefits in non-diabetics. Its benefits in diabetes and insulin resistance are well supported, while longevity benefits in healthy people are the open question Nir Barzilai's TAME trial aims to answer.
- **Low-oxygen therapy is still experimental**
  Mootha and Attia picture a future where families of children with Leigh syndrome might move to high altitude. For now it's an animal finding, as both of them emphasise, not a treatment to attempt.

#68–Marty Makary, MD: US healthcare system—why it’s broken, how to fix it, & how to protect yourself

Guest: Marty Makary
Date: 2020-01-13 · Duration: 2:49:56
URL: https://www.youtube.com/watch?v=Gjjrs8lE3pQ

KEYPOINTS

• Healthcare delivery is a science, and the system is the problem

Makary, a Johns Hopkins pancreatic surgeon and Attia's friend from their surgical training there, was drawn to patient safety by pioneers such as Lucian Leape and David Bates, then seen as radicals. They argued that you can study medical mistakes as rigorously as diseases. He insists that no single party is to blame. Hospitals, insurers, middlemen and doctors are all responding to misaligned incentives.

• Unaccountable and the surgical checklist

His first book, a New York Times bestseller that inspired the TV show The Resident, grew out of stories his father urged him to write down during training. Makary is a co-creator of the surgical checklist adopted by the WHO's Safe Surgery Saves Lives effort. The checklist prevents errors like wrong-side surgery, which Attia saw happen in medical school.

• A small share of surgeons shouldn't be operating

Makary estimates that fewer than 1% of the residents he saw at Hopkins were truly horrible. Nationally, he sees 5–15% of surgeons who should not be practising. Of the roughly 10% of doctors who contacted him about his provocative book title, most thanked him for speaking up.

• Honesty reduces lawsuits

Makary and Attia's takeaway from the research is that the severity of litigation tracks what happens after an error, meaning whether patients are told the truth, more than the error itself. Patients crave honesty and transparency.

• Healthcare is now America's largest industry

As of January 2018, healthcare was the number one US industry. Pittsburgh's skyline, once steel, is now dominated by health care, insurance and administration. Healthcare is about 18% of GDP. Makary says it takes about 43% of Massachusetts state spending, and US spending per person (about $12,000 a year) is more than double some countries'.

• Negotiated prices can be absurd, and insurers may not fight them

An insurance actuary was billed $70,000 for a hip replacement that Medicare pays about $20,000 for, with a fair benchmark of $28,000–29,000. That was the negotiated price, not the sticker price. Part of the reason, Makary argues, is the Affordable Care Act's medical loss ratio rule. Insurers must pay out 80% of premiums in claims, so higher claims can mean more revenue.

• Middlemen and fake discounts add cost

Makary uses a Girl Scout cookie analogy to explain pharmacy benefit managers. Attia says it took him two years to understand what a PBM did. Hospitals and insurers negotiate theatrical deals: prices up 15%, a 12% discount, and both claim victory. A 1987 law gave PBMs and group purchasing organisations protections that enabled the system. Makary estimates bogus discounts and middlemen at around 15% of spending.

• About 21% of care is unnecessary

In a Hopkins survey of about 2,000 doctors, respondents said roughly 21% of healthcare services are unnecessary. Makary describes watching relentless testing on patients who don't want it. He also points to the US writing about 2.4 billion prescriptions a decade earlier, and to high-volume, under-resourced primary care that burns doctors out.

• Predatory billing ruins working families

At a New Mexico hospital profiled in The Price We Pay, the hospital had sued about half of a 28,000-person town, mostly oil workers with insurance. The court clerk said around 95% of civil cases were hospital suits to garnish wages. Attia cites an estimate that one in four or five women treated for breast cancer is pursued by collections within about a year. Half of Americans have less than $300 in savings.

EXAMPLES

• Attia's prescription

Attia's insurer was charged almost $1,000 for a 30-day supply of a drug. He paid a $30 copay, while the cash price on GoodRx was $227. He also mentions a roughly $15,000 ambulance bill.

• Out-of-network anesthesia

A friend's son had an endoscopy and received a $10,000 anesthesia bill for an IV and propofol, from an out-of-network group that had set a ridiculous price. Makary compares pricing that depends on who your employer is to ordering tikka masala and being charged $1,000, $100 or $49 depending on where you work.

• Keith Smith's bundled prices

Keith Smith's surgery centre in Oklahoma City posts one honest bundled price for each service, with no separate bills for the anaesthetic. Patients fly in from as far as Japan. Makary's Hopkins team has studied medical centres before and after they went fully price-transparent.

• Jonas Salk's gift

When 20,000 people lived in iron lungs, Salk declined to patent the polio vaccine, forfeiting what Forbes estimated at $8 billion. Makary calls it the heritage of medicine and contrasts it with suing patients.

• Trauma without time to process

In residency they saw many gunshot victims, and about 95% of the trauma was drug-related. Exhausted after 36 hours awake and with the next case waiting, they coped by default by not processing it, and never discussed it even with peers.

• Billing as an industry

Makary describes a revenue-cycle conference of 4,000 people and a 900-bed hospital with about as many billing and coding

staff as beds.

OTHER RELEVANT

- **You may not owe an undisclosed price**
  Makary's pro bono lawyers argue that without an agreed price there is no legal contract: you can't mow someone's lawn and then bill $5,000. One in five Americans has medical debt in collections. Ask for prices in advance, and don't sign agreements you think are unfair.
- **Check cash prices**
  Tools like GoodRx can beat your insurance copay. Compare both before paying. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Get help with bad bills**
  Makary's Restoring Medicine movement and outlets like Kaiser Health News collect bills and connect patients with help.
- **Push hospital boards**
  Hospitals suing patients is a choice. Ask your local hospital's board members how often they sue patients and what their average markup is.

#61–Rajpaul Attariwala, M.D., Ph.D: Cancer screening with full-body MRI & a masterclass in radiology

Guest: Rajpaul Attariwala
Date: 2020-01-12 · Duration: 2:13:15
URL: https://www.youtube.com/watch?v=ZYviNY8xpes

KEYPOINTS

• Radiation dose varies by orders of magnitude across imaging tests

Attariwala puts a mammogram at roughly 0.05 millisieverts, which he calls negligible, while a whole-body PET-CT stacks the CT's x-ray dose on top of radioactive fluorine-18 glucose and can easily total 30–40 millisieverts. Attia notes the US regulatory ceiling is 50 millisieverts a year and that simply living at sea level contributes about 2–3, more at altitude or with radon. His rule: if you are going to irradiate someone, extract as much information as possible from that exposure.

• A CT is an x-ray done in three dimensions, calibrated so tissues are comparable anywhere

CT uses Hounsfield units, with water fixed at zero and air and bone at the extremes. Because the eye cannot see the whole range at once, radiologists 'window' the image, centring it on lung, bone or soft tissue. Attariwala says that for non-moving organs such as the pancreas, slice count matters less than people think; 256-slice machines mainly help with fast-moving structures like the heart.

• Ultrasound is fast and radiation-free but depends heavily on the operator

High-frequency sound waves bounce back from tissue boundaries, which makes ultrasound ideal for quick bedside answers and, through a window that avoids lung air, for watching heart valves move. Attariwala stresses that the skill of the person holding the probe can't be replaced, which is the main reason results vary so much.

• Mammography accuracy depends on breast density

Attia recalled all-comer figures of about 84–85% sensitivity and 90–91% specificity, while acknowledging the numbers may be dated. Attariwala said averages hide the real story: in fatty breasts sensitivity can exceed 95%, but a single mammogram in dense glandular tissue may be only about 55% sensitive, because low-energy x-rays don't penetrate that tissue well. That is why some women are told they also need an ultrasound.

• Sensitivity and specificity measure two different failure modes

Using 100 women with cancer, 80% sensitivity means 20 are missed (false negatives). Using 100 women without cancer, 90% specificity means 10 are wrongly flagged (false positives). Attia pushes listeners to ask which error a test makes, and in whom, rather than accepting a single accuracy number.

• MRI uses strong magnets to align hydrogen in water and fat

Field strength is measured in tesla (one tesla is 10,000 gauss), and scanners commonly run at 1.5, 3 or 7 tesla. Higher fields align more hydrogen nuclei, which gives more signal. Contrast-free 'dry' MRI is usually described as harmless, but Attariwala described a patient with severe migraines whose headache was triggered by the scanner.

• Diffusion-weighted imaging finds cancer by how freely water moves

DWI, or DWIBS with background suppression, compares water motion at two points within microseconds. Tumours are densely packed with cells, so water diffusion is restricted. Attariwala compares this to how a surgeon feels a hard lump. Pairing this functional signal with anatomical detail approaching 1×1×1 mm is his version of PET-CT's 'one plus one equals three', without ionising radiation.

• The main harm of screening is the false positive, not the scan itself

Attia calls whole-body cancer screening a very personal decision that isn't for everyone. Outside of rare issues like a magnet-triggered migraine, the harm is what a false alarm sets off: anxiety, extra imaging, biopsies and the small but real risks of each procedure.

• MRI quality isn't standardised, so 'a DWI MRI' isn't one product

Unlike Hounsfield-calibrated CT, MRI signal varies with vendor, coils and protocol. Attariwala calls it buyer beware. The Quantitative Imaging Biomarkers Alliance (QIBA) at the Radiological Society of North America is pushing standards organ by organ, starting with prostate and liver, with breast following. Attia admits that even he couldn't judge differences between scanners in another city.

• Machine learning helps most where the problem is narrow

Algorithms are already being tested as a second reader for mammograms, especially for comparing a woman's current images with her previous ones. Attia floats 97–98% sensitivity and specificity as the level needed for confidence. Attariwala thinks that will be hard to reach because breast compression and positioning differ each time. In whole-body images, even telling which organ is the liver or the kidney is still unsolved for machines.

EXAMPLES

• Two false positives in roughly 1,000 scanned people

One was a man with breast tissue on one side only. Because gynecomastia is usually on both sides, he was sent for an ultrasound, which also couldn't rule out cancer, and the biopsy came back as normal tissue. The other was a woman in her late 50s, who had never had a mammogram, with a fluid-trapping scar from a seatbelt injury.

• Prostate: MRI plus a 4K blood test avoided biopsies

FDG-PET is close to useless for the prostate: the gland gets little blood flow, and tracer pools in the bladder next to it. Attia described two of his patients with high PSA and high 4K scores who, instead of the biopsy they would once have had, got a DWI MRI that came back clean. Attariwala said MRI is becoming the de facto prostate screening tool in places like the UK, Scandinavia and Australia.

• A cycling friend's fatal aneurysm

Attia recalled a riding partner, six or seven years older than him, who got a sudden headache at Disneyland and died of a congenital aneurysm. Attariwala put mortality after rupture at roughly 93–95%. Aneurysms found early can be electively coiled or

clipped, and his non-contrast MRI shows brain vessels with angiogram-like detail.

• From robot eye surgery to building his own MRI

Attariwala trained in chemical and then biomedical engineering (PhD, Northwestern), helped build a robot for keyhole eye surgery, then went to medical school, radiology and nuclear medicine, training at Memorial Sloan Kettering, UCLA and USC. In Vancouver he bought an MRI 'so I could play with it', which led to the AIM clinic and later Prenuvo. A brain scan there is fully isotropic and a whole-body scan takes about 55 minutes.

OTHER RELEVANT

• Ask about your breast density

If you have dense breasts, a normal mammogram is far less reassuring, because sensitivity may be near 55%. Ask whether supplemental imaging such as ultrasound or MRI makes sense, and keep earlier images so they can be compared over time.

• Weigh radiation against the information you get back

A mammogram or chest x-ray adds little to your yearly exposure. Repeated PET-CTs at 30–40 millisieverts each add up quickly against a 50-millisievert annual limit. Ask whether a non-ionising option like MRI or ultrasound would answer the same question.

• Before screening, plan how you'll handle a false positive

Decide in advance how you would respond to an ambiguous finding, including follow-up imaging, a possible biopsy and the wait in between. Attia treats this as the real cost of screening and the reason it should be an individual choice.

• Ask exactly how an MRI will be done

Because protocols aren't standardised, ask whether diffusion-weighted sequences are included, what the resolution is and who reads the scan. Two 'full-body MRIs' can differ enormously in quality.

#64 – Zol Kryger, M.D.: Plastic surgery—common procedures, reducing risk, & picking the right doctor

Guest: Zol Kryger
Date: 2020-01-12 · Duration: 2:13:17
URL: https://www.youtube.com/watch?v=OvY3WUzd24Q

KEYPOINTS

• Most US plastic surgery isn't done by plastic surgeons

Kryger, a board-certified plastic surgeon who was Attia's medical-school classmate, estimates that 90–95% of plastic surgery in the US is not done by board-certified plastic surgeons. Legally, any licensed physician can perform any procedure. A family doctor one month out of medical school could try heart surgery; what stops them is hospitals refusing privileges, so much cosmetic work happens in office suites and small surgery centres beyond that oversight.

• What real plastic surgery training looks like

Plastic surgery used to be a fellowship after general surgery. It is now usually its own six- to seven-year residency, with early years focused on general surgical basics and later years on reconstructive work across the whole body. Kryger contrasts that with doctors who learned liposuction or fat grafting at a weekend course.

• Hospital privileges are a key safety check

Kryger sits on a hospital credentialing committee that checks training, expertise and malpractice history, and grants privileges only for procedures a doctor is trained to do. A gynaecologist doing tummy tucks may be able to admit a bleeding patient but not treat the problem. Asking where a surgeon has privileges for this exact procedure tests what happens if something goes wrong.

• Ask how they handle complications, not just how often they happen

Attia recalls New York publishing heart surgeons' 30-day mortality rates, which led some to cherry-pick easy cases. Kryger splits complications into early ones, such as bleeding, infection and seromas (fluid collections), and late cosmetic ones, where the patient dislikes the result. Patients rarely sue over a bad result itself, he says, but over how they were treated; sometimes a surgeon should 'eat some money' to put things right.

• Capsular contracture is the main long-term risk of breast augmentation

The body walls off any implant with scar tissue. When that capsule hardens and tightens, the implant can ride high and feel firm. Kryger cites rates of 2–8%, lower with saline implants (closer to 2%) and with placement under the muscle. He also says many implant studies are run by surgeons paid by implant companies.

• Textured implants carry a rare lymphoma risk

Textured implants, including all teardrop-shaped ones, which need texture to stay in place, are linked to a lymphoma that forms in the capsule. The estimate has risen from about one in 300,000 to about one in 3,000 for certain implants. Kryger says there are no cases with smooth implants, and Europe pulled many textured implants. In his view texturing offers no clear advantage.

• Kryger's breast augmentation defaults

He favours an incision under the breast fold over the armpit or nipple, where pain, numbness and other problems are more common. Most implants go under the muscle, which looks and feels more natural, interferes less with mammograms, lowers contracture rates and supports the implant's weight. He makes a strong case, but the patient decides.

• Tummy tucks fix skin, muscle separation and hernias

About 95% of tummy tucks are on women after pregnancy; 5–10% are men, mostly after massive weight loss. The operation removes skin below the navel and tightens stretched rectus muscles (diastasis). It also repairs belly-button hernias, which can trap intestine. Seromas are usually drained in clinic, about 95% of the time without help. Scars are worst at the high-tension centre.

• Liposuction is a 'wild west'

Kryger guesses that 80–90% of liposuction is done by non–plastic surgeons, often in offices using one of 20–30 marketed devices. He isn't a believer in CoolSculpting. Prices run from about $1,000 for one small area to $7,000–8,000 for several. Less-trained providers often charge a third as much, partly because they operate without an anaesthesiologist or operating room. Adding liposuction to a tummy tuck raises the complication rate.

EXAMPLES

• The Brazilian butt lift may carry a 1-in-1,000 death risk

A BBL involves no actual lifting: fat removed by liposuction is injected into the buttocks. If fat enters the large veins there, it travels to the lungs, and autopsies find lungs full of fat. Kryger estimates fatal fat embolism at about one in 1,000 or higher, and says it is nearly impossible to treat. His societies have discussed a moratorium; he cites Florida deaths and one surgeon doing seven or eight a day.

• Miami's 'happy meal' clinics and the subprime comparison

Kryger cites a USA Today exposé on Miami clinics with many deaths and complications. Patients keep returning because of price. Advertising targets Hispanic radio and inner-city billboards, which Attia likens to the subprime mortgage crisis. Florida was amending its laws.

• A friend's implant contracture happened twice

Attia's friend developed capsular contracture that was never mentioned in her consent. The surgeon redid the procedure, and it recurred. Attia then urged a second opinion before any further fix.

• Surgeons couldn't tell teardrop implants from round ones

Shown 100 post-augmentation photos, half with each implant shape, plastic surgeons guessed correctly only 50% of the time.

• Filler can cause blindness

Kryger counts about 25 reported cases. Filler injected near the inner corner of the eye or above the eyebrow can travel

backwards in an artery into the retinal artery. He also mentions permanent pigment damage from lasers and peels, and HIV infections from poorly cleaned 'vampire facial' equipment at one clinic.

OTHER RELEVANT

- **Questions to ask a cosmetic surgeon**
  Are you board-certified in plastic surgery? How long have you done this procedure and how did you learn it? Do you have hospital privileges for it? What complications have you seen and how do you manage them? Ask about lawsuits and to see photos.
- **No risk, no downtime usually means no result**
  Kryger's rule is that a cheap, risk-free, 30-minute 'lunchtime' procedure with no recovery won't do much. Minimally invasive treatments still carry real risks.
- **Efficiency and a second surgeon reduce risk**
  Longer anaesthesia raises complication rates. Kryger operates with his brother, also a plastic surgeon, so every step is double-checked.
- **Consider asymmetric risk**
  Attia's frame is to weigh a small chance of a catastrophic, untreatable outcome, like a fat embolism, far more heavily than its probability alone suggests.

#60 – Annie Duke: How to improve decision making, learning, & apply ‘backcasting’ for future success

Guest: Annie Duke
Date: 2020-01-12 · Duration: 2:35:34
URL: https://www.youtube.com/watch?v=ca7TptT9VTI

KEYPOINTS

• Poker models real decisions better than chess

In chess both players see the whole board, so in principle a loss traces back to a mistake. Poker adds hidden information and luck, which is why Attia, who has often had to explain this to his wife, thinks it matches medicine, where you almost never have complete facts. Duke, author of Thinking in Bets, agrees that the gap between what you know and what's true is the essence of most life decisions.

• 'Resulting' means judging a decision by its outcome

Duke's term describes working backwards from the quality of the outcome to the quality of the decision. Judging a decision properly requires knowing the possible outcomes, how likely each was and how much you'd prefer each, compared across the alternatives you didn't choose. Most people take the shortcut instead.

• Learning has to cover all four quadrants

Picture a two-by-two of good or bad decisions against good or bad outcomes. Attia argued the most painful square is a good decision with a bad outcome. Duke pushed back that people naturally dig into bad outcomes; what nobody examines is good outcomes. 'We're never having the my-life-is-great conference' to ask whether a win came from skill or luck.

• Fear of the 'idiot quadrant' pushes people to the status quo

A consensus decision that turns out badly earns 'tough luck'. A non-consensus decision that turns out badly earns 'idiot'. As a result, people default to doing nothing over doing something, demand more certainty than needed, seek sign-off and avoid innovating. Duke argues that leaders who only review failures, as in medicine's weekly morbidity and mortality conference, reinforce this cover-yourself behaviour.

• Bill Belichick earned the right to be unconventional

Attia, an admitted Belichick obsessive, and Duke discuss how the Patriots coach increasingly made calls like going for it on fourth-and-5. Duke notes that came only after two Super Bowl wins, once fans would tolerate decisions they didn't understand. Credibility buys room to leave the status quo.

• Look for luck in your wins too

Nothing happening after Y2K could mean the preparation worked, the threat was never real, or the effort was wasted. There's also a fourth possibility: the downside was severe enough that hedging was correct either way. Attia raised D-Day: was Eisenhower simply lucky with the weather? Without examining the 'win', you can't tell.

• Four levels of skill, and a fourth level of thinking

Duke learned to swim at 31, swam twice a day and filled journals with free-body diagrams. She describes moving from unconsciously incompetent to consciously incompetent (knowing why you fail, through ideas like Archimedes' principle and Bernoulli), then consciously competent, then unconsciously competent. The matching thinking skill at the top is refusing to accept a well-played win without asking whether there was a better line. Attia admitted he had 'never once had a level-four thought'.

• Wide skill gaps hide mistakes

When you're far better than your competition, sloppy thinking still wins, which Duke calls a soft landing. Swimming is similar: you can swim badly for years, while a bike punishes imbalance immediately. Where feedback is gentle and delayed, deliberate self-examination matters even more.

• Quit fast, and try many things that cost little

Duke argues we over-praise sticking with things and ignore opportunity cost. Her approach is to try lots of things with little downside ('go try out piano'), drop the ones that are negative expected value for happiness, health or money, and commit only to what you love. Poker players are naturally comfortable folding.

EXAMPLES

• Pete Carroll's Super Bowl pass

Down four to the Patriots at the end of the 2015 Super Bowl, Seattle passed instead of handing off to Marshawn Lynch. Malcolm Butler intercepted and the play was called the worst in history. Duke and analyses such as FiveThirtyEight's argue it was a sound call with a bad outcome. Attia, a Patriots fan, recalls screaming at his TV, but agrees that Carroll was thinking only about winning, not about defending the call at a press conference.

• Attia loses about one arrow a day

Shooting at softball-sized targets from 60–70 yards, Attia can list a hundred reasons for every miss but has never examined a perfect shot. Duke said that's typical: roughly 90% of his reflection goes to the 10% of shots that went wrong.

• Erik Seidel's post-game talk

Duke says the biggest difference between fast and slow improvers is how they explore what might have happened. Listening to Seidel review a tournament, you couldn't tell whether he won, because he explores every alternative line and bet size. Players who improve slowly dwell on someone 'sucking out' on them.

• How Duke got to poker

Her brother deferred Columbia to study chess with a grandmaster in New York, started playing poker and lost his college savings before eventually doing well. Duke, on a National Science Foundation fellowship in cognitive science at Penn, later followed him into the game. She says she'd be crushed by today's analytics-driven professionals.

OTHER RELEVANT

- **Hold a 'what went right' review**
  After a good result, ask whether it came from your decision or from luck, and whether a better option existed. Give it the same scrutiny as a failure, and reward people for good process on bold calls, not just outcomes.
- **Backcast your physical future**
  Duke said she didn't coin 'backcasting'. Attia applies it to exercise: most people exercise for looks, mood or eating freedom, but the better reason comes from imagining how you want your body to work the day before you die, his 'Centenarian Olympics'. Train backward from that.
- **Run a pre-mortem**
  Before committing, imagine the plan has failed and list the reasons. Pairing that with backcasting makes the hidden assumptions behind a forecast visible.
- **Read The Success Equation**
  Duke strongly recommends Michael Mauboussin's book on separating luck from skill across sports, investing and life as a companion to the four-quadrant thinking discussed here.

#57–Rick Rubin: collaborating with the greatest living musicians, & his personal weight loss story

Guest: Rick Rubin
Date: 2020-01-12 · Duration: 3:03:52
URL: https://www.youtube.com/watch?v=stulZl8eqM8

KEYPOINTS

• Rick built Def Jam as a dorm-room/hobby operation that rewired popular music.
As a teenager obsessed with New York hip-hop's birth, he treated production as play before it was a career. Early Def Jam work with LL Cool J, the Beastie Boys, and Run-DMC helped move hip-hop from a local scene to a global commercial force, eventually partnering with Columbia when the majors could no longer ignore the sound. The through-line from hobbyist to Time-100 influencer was obsessive listening more than industry schooling.

• Deal math taught him to protect artists' economics early.
He walks through gold/platinum/diamond thresholds and how royalty percentages of retail vs wholesale diverge. Unusual artist-friendly splits mattered because he was still close enough to the culture to care what happened to the music after the advance cleared—late-80s lessons he carried into later American Recordings work. Diamond-scale success made those early contract lessons look prophetic rather than naive.

• Geography shaped which rap lineages he understood firsthand.
New York's scene differed from LA's gang-rooted gangsta rap emergence; Rick says he rarely bumped into that world during his New York years. Public Enemy was his north star in that era, and he is careful about timelines when people casually lump N.W.A and Public Enemy into one undifferentiated '80s moment. That geographic humility keeps him from cosplaying expertise about scenes he did not live.

• Longevity in bands often hinges on not dying—literally or relationally.
He notes how many peers who could have been Motley Crue-level acts burned out through overdose or interpersonal detonation. Survival itself becomes an underrated artistic skill; the catalog only compounds if the humans remain intact enough to keep making it. He has watched genius paired with chaos enough times to treat sobriety logistics as creative direction.

• His producer role is creating space for artists' genius amid pain and addiction cycles.
Working with everyone from Johnny Cash to Chili Peppers to Adele, he describes listening for the true song underneath chaos. Helping artists through depression and substance storms is not separate from the job—it is often the job that makes the recording possible. Cash's late voice is the exhibit A he returns to when people equate production with stacking more tracks.

• Rick's own health story includes obesity, depression, and a radical recomposition.
He recounts a shake-heavy phase (~120 calories each) plus a savored daily apple that let him stay near ~1,400 calories while still eating dinner. Across about 14 months he lost roughly 135 pounds, crossing below 200 and meeting surf/fitness peers like Laird Hamilton along the way. Savoring the apple was mindfulness training disguised as a diet hack—attention as satiety.

• Fitness role models in their 70s and 80s recalibrated what aging permitted.
A friend, Don Wildman, still knocking out large sets of pull-ups on the beach into old age (Rick recalls a striking number around age 80) made 'too late' feel like a story, not a law. Body composition became part of creative stamina, not vanity adjacent to the studio. Seeing older athletes jacked and capable rewrote Rick's prior that decline was strictly chronological.

• An emergency heart surgery became another before/after line.
The scare forced the same seriousness he once reserved for artists' crises onto his own mortality. Recovery reframed scheduling, stress, and what 'urgent' means when the body has already called once. Post-surgery, calendar defaults flipped from 'can I fit this?' to 'what does this cost my heart?'

• Shangri-La studio carries living music history.
The Malibu space where Bob Dylan helped establish a studio culture in the 1970s—complete with Dylan's old trailer lore—hosts rehearsals and interviews in a lineage Rick is consciously stewarding, not merely renting. Stewarding Shangri-La means protecting a feeling in the room, not only the gear list.

• Taste across decades is a humility exercise.
He wonders aloud whether tomorrow's listeners will hold Taylor Swift the way his generation holds the Beastie Boys, and how Bonham-already-dead Zeppelin fandom differs from watching careers in real time. The point is less ranking than recognizing how incomplete contemporary judgment is. Holding canon loosely lets him keep working with new artists without nostalgia as a prison.

EXAMPLES

• LL Cool J 'Radio' via Columbia partnership
Still roughly 20–21 years old while negotiating with the world's biggest label—an apprenticeship conducted at full commercial scale. Age and leverage rarely line up that cleanly in modern label deals.

• ~135 lb loss in ~14 months
Shake protocol plus one apple; met Laird after ~90 pounds down—proof-of-change that paralleled his artistic reinventions. The same discipline he asked of artists finally applied at home.

• Don Wildman pull-ups in old age
An embodied argument that strength training and VO2 culture need not expire at midlife. Those pull-ups did more persuasive work than any abstract longevity lecture.

• Johnny Cash American Recordings arc
Late-career stripped recordings as the canonical example of Rick's space-making producing more truth than maximal production. Stripped arrangements made space for mortality and faith without sermonizing.

• Beastie Boys / Run-DMC bridge era

Cross-genre collisions that made hip-hop unavoidable for rock audiences and vice versa. Those crossovers were cultural infrastructure, not just chart tricks.

OTHER RELEVANT

- **Protect the humans if you want a long catalog.**
  Addiction and relational explosions erase future albums; producer-as-caretaker is not soft, it is strategic. Build recovery plans into tour and studio calendars before the crash.
- **Treat body recomposition as creative infrastructure.**
  Rick's weight loss and heart scare argue that studio stamina has a physiologic substrate. Lift, sleep, and eat for multi-decade output, not next quarter's pants size.
- **Negotiate like someone who still loves the music.**
  Royalty structure literacy protects artists when enthusiasm would otherwise sign anything. Learn how money actually moves before you sign enthusiasm into a bad deal.
- **Hold contemporary taste loosely.**
  Decades re-rank canons; make what is true now without demanding immediate consensus. Make the record true now; let history argue later.

#59–Jason Fung, M.D: Fasting as an antidote to obesity, insulin resistance, T2D, & metabolic illness

Guest: Jason Fung
Date: 2020-01-11 · Duration: 2:42:05
URL: https://www.youtube.com/watch?v=nqBkG0ZECn8

KEYPOINTS

• Fung reframes insulin resistance as an overflow problem, not a locked door.
The standard 'lock and key' model says glucose can't get into a cell because the cell has stopped responding to insulin. Fung argues it may instead be unable to enter because the cell, especially the liver cell, is already overfilled with glucose and fat. He says this explains the paradox of an 'insulin-resistant' liver that is still busily turning glucose into new fat. In his view the underlying problem is hyperinsulinemia, too much insulin over time, rather than insulin resistance itself.

• Pushing in more insulin covers up type 2 diabetes rather than treating it.
Fung's view is that sulfonylureas, insulin and DPP-4 inhibitors all raise insulin and push more glucose into tissues that are already full. Blood sugar improves while total-body glucose gets worse. He says this is why the disease looks 'chronic and progressive': patients go from one drug to large insulin doses over ten years and the disease never gets better.

• Lowering blood glucose with more insulin protected small blood vessels but not the heart or brain.
Attia notes that intensive glucose-control trials improved some small-vessel (microvascular) outcomes, such as in the kidneys, but not large-vessel (macrovascular) outcomes in the heart and brain. If insulin doses have to double to get glucose from 200 to 150, those outcomes may even get worse. Fung connects this to the failures of ACCORD, ADVANCE and VADT. Attia says seeing this pattern about three years earlier was the 'aha moment' that made him see hyperinsulinemia itself as harmful.

• SGLT2 inhibitors fit Fung's model because they remove glucose from the body.
These drugs make the kidneys excrete glucose, which lowers total-body glucose and insulin rather than moving sugar into the liver. Fung credits them with organ protection not seen with older drugs, and notes that people lose weight on them. As a nephrologist, he points out that they were the first new drugs to slow diabetic kidney disease since ACE inhibitors in the 1980s.

• Fung sees insulin resistance and fatty organs as the body protecting itself.
In his analogy, insulin delivers glucose to houses on a street. Once a house is full it stops answering the door, which is insulin resistance, so insulin bangs harder. He cites lipodystrophy, where people with almost no body fat have some of the worst insulin resistance ever measured, as evidence that storing fat protects against excess glucose. Without places to store it, fat ends up in the liver.

• Fung thinks causation runs mostly from insulin to obesity.
Whenever insulin rises, with insulin injections or sulfonylureas, people gain weight. When it falls, with SGLT2 inhibitors or untreated type 1 diabetes, they lose weight. Attia adds a counterpoint: in Samuel Klein's New England Journal of Medicine study, liposuction removed about 20 pounds of fat with no metabolic benefit, although critics note liposuction only removes fat under the skin, not visceral fat. Attia says the direction of causation may not change what you do clinically.

• Many chronic diseases may be 'diseases of too much growth'.
Fung links hyperinsulinemia to breast cancer and to proliferative disease through shared nutrient-sensing pathways: insulin, mTOR and AMPK. Attia describes meeting a researcher whose 2006 theoretical paper, rejected by nearly every journal, predicted rapamycin would be the top longevity drug. The first study showing rapamycin extends lifespan came in 2009. Attia calls it the most promising longevity agent as of 2019.

• Hormones send growth signals to muscle and fat in different directions.
Attia explains that insulin builds both muscle and fat, which is why some bodybuilders use it. Testosterone builds muscle but breaks down fat. Cortisol is the worst of both, breaking down muscle while building fat. He sketches this on a whiteboard for patients to show that nutrition, exercise and hormone therapy are all ways of steering these signals.

• Fung believes the effect of bariatric surgery on diabetes is mostly due to fasting.
Attia notes that after a Roux-en-Y gastric bypass, patients often stop needing insulin within about 10 days, before they've lost much weight, and that insurers have treated surgery as the only recognized way to reverse type 2 diabetes. Attia once worked on designing a trial to separate the surgical, dietary and calorie-restriction effects. Fung's view is that 'the fasting does everything', and that 7- to 14-day fasts can produce the same resolution.

EXAMPLES

• The suitcase analogy
If the last two shirts won't go into a suitcase, it may be because it won't open or because it's already full. Standard treatment assumes it won't open and keeps forcing more in, like a spouse asking, then yelling, then throwing a football. Fung's answer is to take shirts out by lowering insulin.

• A 1990s insulin study as Fung recalls it
People with type 2 diabetes went from no insulin to about 100 units over six months. Their blood sugar improved, but they gained about 20 pounds while eating roughly 300 fewer calories a day, which Fung takes as evidence that insulin itself drives weight gain.

• A foot ulcer that had not healed for a year
A man in his 40s had a diabetic foot ulcer for a year and was at risk of amputation. With his father's support, he did a 7-day fast and then 36-hour fasts three times a week. Fung says the ulcer healed within about three weeks. Attia notes he himself is less aggressive and never starts patients with water-only fasting.

• Skipping breakfast and heart deaths
Both dismiss a recent study linking skipping breakfast to higher cardiac mortality as confounded. If everyone is told to eat breakfast, the people who skip it differ in ways that can't be measured.

• Kidney function as an early warning

Attia tracks cystatin C and microalbumin. A person in their 40s whose kidney filtration (GFR) is already 80% of predicted raises the question of what it will be at 80, so he now treats even stage 1 blood pressure. Fung sees IgA nephropathy patients who had lost about 95% of kidney function without knowing.

OTHER RELEVANT

• Narrow your eating window before counting macros.

Fung says Satchin Panda's work found people eat across about 15 hours a day, compared with a 14-hour overnight fast in the 1970s. He finds telling someone to eat only between noon and 8 p.m., with nothing that came in a box, easier to follow than carb targets. Attia sees the main benefit of time-restricted eating as psychological.

• Expect hunger during a fast and plan for it.

Attia stays hungry at some point on every day of a seven-day fast, but says it's no worse than an ordinary hungry day, and that anticipating it is harder. Fung tells patients that being hungry is fine, but feeling lethargic or unwell means they should stop right away and try again another day.

• Watch magnesium, and do longer fasts only under medical supervision.

Fung's clinic monitors patients closely. Many people with type 2 diabetes start out low in magnesium, so they supplement it, and they use salted bone broth for dizziness. He says he has almost never had to stop a fast because of electrolytes. Attia uses phosphatidylserine and GABA at night to calm the surge in sympathetic activity during a fast.

• Healthy people probably need only occasional, modest fasts.

Fung suggests periodically lowering insulin, similar to the traditional balance of feasts and fasts such as Lent, Ramadan or Yom Kippur. He says the data for healthy people are not there yet for longer protocols like Valter Longo's quarterly five-day fasting-mimicking diet.

#56–Jocko Willink Part 2 of 2: Sleep, fasting, kids, discipline, ownership, & the impact of war

Guest: Jocko Willink
Date: 2020-01-11 · Duration: 1:31:44
URL: https://www.youtube.com/watch?v=p3hZgedgiDw

KEYPOINTS

• 9/11 sent Jocko back to the teams

Jocko spent 20 years as a Navy SEAL and commanded SEAL Team Three's Task Unit Bruiser in the Battle of Ramadi. On 9/11 he was in college at the University of San Diego, working toward his commission. When the second plane hit, he knew 'we're under attack'. Within a day or two he was begging a senior officer to send him back to a SEAL team. He returned in spring 2003, about six months after the Iraq invasion, and took over a platoon preparing to deploy.

• Insurgents exploited a weakness: we care about casualties

Drawing on accounts of the Soviet war in Afghanistan, Jocko says you cannot beat an enemy who doesn't care about losses in a war of attrition. They learn that 'you can kill 200 of us and we'll kill one of you', and eventually the side that values life grows tired.

• The principles of combat don't change with terrain

Jocko visited Afghanistan but didn't fight there. Bruiser veterans who later went told him the geometry was the same. In Ramadi, streets were the low ground and buildings the high ground. In Afghanistan, valleys and peaks. Either way you dominate the high ground and get good angles, only over greater distances.

• ISIS made a strategic error by becoming a conventional army

With vehicles, flags and uniforms, ISIS fought like an inferior nation-state rather than an insurgency. Jocko estimates around 50,000 of its fighters were killed as Ramadi and Mosul were retaken. Asked where he would take his family in Iraq, he says Ramadi, then Baghdad.

• Civilians are disconnected from 20 years of war

Jocko recalls Roger Hayden, a SEAL he looked up to, who came home from Vietnam to no protests and no attention. He argues that today's civilians are similarly separated from the wars. Predicting who the US will fight in 25 years is nearly impossible, but machines will play a growing role.

• Why people distrust machines more than teenage drivers

Huge numbers of people die in car accidents, yet one Tesla crash makes the front page. We trust a 16-year-old driver but not an autonomous system. Jocko expects the same tension over machines in warfare.

• Sleep is short, steady and probably partly genetic

At home in San Diego Jocko goes to bed around 11 after jiu-jitsu (home by 7:30–8), his biggest meal, time with his kids and some work. His alarm is set for 4:30, and about half the time he wakes on his own between 4 and 4:30 feeling fine. If he goes to bed at 9:30, he wakes at 3:30. His oldest daughter barely slept in high school, while his wife sleeps a lot. He suspects genetics and hasn't tried a long sleep-extension experiment. Attia suggests they discuss it with Matt Walker.

• Ownership and free will

Jocko used to believe absolutely in free will. Now he calls himself 'a free-will agnostic', maybe heading for atheist. Sam Harris has told him free will and extreme ownership align. For Jocko, it is simple: if you want to do something, do it, and if you're making excuses, own them, up and down the chain of command.

• Lessons for kids belong at the kitchen table

Jocko wrote children's books to put the 'very clear, very simple', timeless lessons kids need to become good humans in one place. His children saw how crushed he was when his best friend died, which he thinks showed them he is human. He hides no mistakes. When he messes up he laughs and says 'I'm an idiot'. He only lets himself get angry at printers, because they have no feelings.

EXAMPLES

• Attia's Chesapeake Bay Bridge swim

Attia trained specifically for the 4.5-mile swim between the two bridge spans, aiming for the top ten. Swimmers who drift outside the spans are pulled out. Struggling in the current, he told himself to 'put your head down and swim'. His wife still tells the story of how furious he was on the beach. He uses it to separate quitting a failing plan from quitting in a moment of weakness.

• The day Jocko didn't make it out

Paddling out with his best friend on a huge day at Ocean Beach, San Diego, Jocko didn't make it through the surf. He concedes he 'could have paddled more' and sees it as no different from missing a deadlift rep.

• Attia's apology

Attia describes snapping at his kid ('how many times have I told you to turn off the light?') when he was really upset about something else. He went back to ask whether that tone was necessary. Apologising is new for him, while Jocko says it comes easily.

• The 4:30 a.m. 'routine'

Asked by a TV producer for detail about how he wakes at 4:30, Jocko joked through a fake yoga-and-meditation routine. The real answer: the alarm goes off and he gets out of bed.

• Fasting and dark chocolate

They compare multi-day fasts. Jocko, who considers himself a seasoned faster, found a recent one humbling until he turned the corner on day four. Attia says that if you can get to day three feeling good, five comes easily. Jocko reaches for 72% chocolate when indulging. Attia is satisfied by a few squares of 80–90%.

OTHER RELEVANT

- **Separate strategic quitting from weak quitting**
  Changing a plan that isn't working while keeping the goal is sound. Stopping because it hurts, when you still want the outcome, is the kind of quitting to resist.
- **Own the excuses**
  When you catch yourself making excuses, own them rather than debate whether you had a choice. Ownership applies whether you are leading or following.
- **Let your kids see you fail**
  Admitting mistakes, and apologising for a harsh tone, teaches kids that adults are human and models how to recover.
- **Find your own sleep pattern**
  Track whether you wake before the alarm feeling fine. Jocko's early schedule works for him but isn't a universal prescription.

#54–Kevin Sayer, CEO of Dexcom: Continuous glucose monitors–impact of food, sleep, & stress

Guest: Kevin Sayer
Date: 2020-01-10 · Duration: 1:44:35
URL: https://www.youtube.com/watch?v=W8JWAQq8i-Q

KEYPOINTS

• How a Dexcom sensor reads glucose

Sayer, Dexcom's CEO, explains that a wire about as thin as a human hair, made of special alloys and coated with membranes, sits roughly half an inch under the skin in interstitial fluid. It measures glucose there, not in blood. An enzymatic reaction produces an electrochemical signal, and an algorithm in the transmitter converts it to a glucose value. Attia notes that point-of-care tests suit analytes like glucose, ketones, lactate and electrolytes, whereas insulin or lipoprotein counts need lab methods such as ELISA or NMR.

• The G6 removed the scary part

Earlier models had users push the needle in themselves; Sayer says some patients emailed that they had stared at the device for six weeks without daring to insert it. The G6 inserts automatically, faster than a hummingbird beats its wings a couple of times. Attia saw the old applicator scare off some of his own patients after they had paid out of pocket.

• Most people with type 1 diabetes still weren't using one

At the time of recording (2019), Sayer estimated about 1.3–2 million Americans had type 1 diabetes, plus about 1.5 million with type 2 who use insulin intensively. Only about 20–30% of people with type 1 used a CGM, though he believes 80% of that intensive-insulin population should. Medicare began covering CGM for intensive insulin users with type 2 in January 2017.

• Insurance coverage is cyclical

Sayer describes one state that required a person with type 1 to document a number of readings below 50 mg/dL before getting coverage. He says payers often cover generously for a couple of years, then tighten criteria, and that price and access are traded off in constant negotiation.

• The biggest savings come from avoiding low-sugar hospitalizations

Sayer's economic models show the major acute saving is preventing hospital stays in 'hypoglycemia unaware' patients. Each such stay costs $10,000–30,000 by the numbers he has seen. Dexcom's share feature, which he says the company pioneered and got through the FDA, lets a spouse in another country see a low and phone the hotel to wake the wearer.

• Performance first, then experience, then cost

Sayer's framework for the Verily (Alphabet) partnership is performance, then patient convenience, then cost. Dexcom supplies the membranes and algorithms; Verily supplies miniaturised electronics and Bluetooth. Attia suggests average accuracy has reached diminishing returns. Sayer agrees, saying the remaining gain is 'eliminating the outliers' so every sensor behaves the same.

• Type 1 and type 2 deserve different names

Attia argues that lowering glucose in type 2 by adding insulin, or drugs that raise the body's own insulin, reduces small-vessel complications but doesn't save lives. Patients still get heart disease, cancer and Alzheimer's at higher rates, because the problem is high glucose combined with high insulin. He points to drugs that remove glucose without adding insulin, such as metformin and SGLT2 inhibitors. Sayer says Dexcom's type 2 software focuses on daily feedback rather than nighttime alarms.

• Real-time feedback changes behaviour

Attia believes CGM improves outcomes even without a formal intervention, simply because it's hard to ignore how food, stress and sleep move the number. He finds the 7-day average and standard deviation, and the 90-day trailing average, more useful than single readings.

EXAMPLES

• Nighttime cortisol and morning glucose

Attia would go to bed at 93 mg/dL hours after dinner and wake at 105. Overnight urine cortisol tracked the rise. He now tells patients a fasting glucose of 100 versus 90 often reflects cortisol or liver glucose output rather than insulin resistance, though 130 is a different story.

• A1c can mislead

Attia has beta thalassemia minor, so his small red blood cells live longer. His lab A1c reads 5.6–6.0, in the prediabetic range, while his CGM-derived figure is 4.5–5.1. He says this has complicated his life-insurance applications.

• The airport trail mix he didn't eat

Stuck on a delayed flight, Attia bought a big bag of trail mix as a treat, looked at his glucose and put it away, certain he would have eaten it without the sensor. Sayer's worst spike, his only reading over 200, came 30 minutes after a cup of yogurt-covered raisins in Boston airport. He then dipped to about 60 before settling in the low 70s.

• Sixty finger sticks in a day

When a meter used in an FDA submission turned out to read high, Sayer bought three meters and pricked himself 20 times with each. Attia, who still calibrates his G6 daily and sees it match a finger stick to within a point or two, likes the OneTouch Ultra. Sayer's tip: wash your hands first, because a crumb of food can falsely raise the reading.

• What it costs without diabetes

Sensors last 10 days and come in boxes of three. Attia's office buys nine at a time, a roughly 90-day supply. They agree about $9 a day is right for paying out of pocket. Sayer says a prescription is required and most insured patients pay a 20% copay; he wouldn't guess at a future wellness price.

OTHER RELEVANT

- **Context changes the curve**
  Attia says the same pasta produces very different responses 30 minutes after a hard workout than without exercise, and that poor sleep and high-carb dinners track with higher glucose.
- **Older-sensor caveat on acetaminophen**
  Acetaminophen pushed G5 readings high; Sayer says Dexcom studied large doses and the G6 no longer carries that warning.
- **Let kids fail**
  Sayer, a father of five, once told a coach to cut his son so he would learn something. He says people often learn more from failure than success, a lesson he applies to leading Dexcom.

#55–Jocko Willink Part 1 of 2: objective, strategy & tactics, leadership, protocols & lessons of war

Guest: Jocko Willink
Date: 2020-01-10 · Duration: 2:39:08
URL: https://www.youtube.com/watch?v=hIzCdqav9RM

KEYPOINTS

• Objective first, then strategy, then tactics
Attia borrows a framework from Dennis Calabrese: define the objective clearly (most people skip this step), build a strategy as the scaffolding, and only then hang tactics on it. People who even get the objective right tend to jump straight to tactics. Willink says he learned the same thing as a leader: unless frontline troops understand the strategic level, they can't make good decisions on their own.

• A tactical mistake can do strategic damage
Willink's example is Abu Ghraib. Soldiers aged 18 to 20 guarding detainees they believed were terrorists did things Americans shouldn't do, which he describes as closer to hazing than torture, though out of bounds either way. They also photographed it. Once the images reached al-Qaeda and Al Jazeera, they fuelled the insurgency. Small acts by junior people can undo the larger mission.

• Decentralized command only works if everyone understands the strategy
When a unit is cut off from headquarters and has to improvise, troops who don't know the 'why' are lost. Willink traces decentralized command to Prussian and German reforms after their defeats by Napoleon. Germany adopted it and maneuver warfare only at the end of World War I, too late, and 20 years later it had transformed how World War II was fought.

• Humility is the most important trait in a leader
Willink saw it in his first SEAL platoon. The enlisted men effectively mutinied against an arrogant, inexperienced officer, 'a horrible combination', and loved his experienced, humble successor. When subordinates despise a leader they start hoping the leader fails, which Willink calls the worst morale imaginable. Because people usually reach leadership through confidence, too little humility is the more common problem.

• You can also be too humble
Every trait has a dichotomy, the theme of Willink's book The Dichotomy of Leadership. Talking with bright, underprivileged kids aged 8 to 13 in LA, he had to coach them to sit up, stand and speak louder. A too-humble subordinate who defers to a boss they disagree with fails the team. Even poise taken too far makes a leader look like a detached robot; people need to see that the leader is devastated too.

• Following orders isn't absolute
Willink rejects 'just follow orders'. He wouldn't obey a plan he believed would get his platoon killed, but he acknowledges the dilemma: refuse and get replaced by a yes-man, or argue for an alternative and then carry out the plan as well as possible. He points to World War I generals who sent men into trenches day after day without any senior leader refusing, and to British soldiers with PTSD and brain injuries who were executed for refusing to fight.

• A protocol for when you don't know what's happening
Step back, assess everything, list your possible moves and their likely outcomes, then take a small step you can reverse rather than fully committing. Willink says no list of 20 planned scenarios covers everything, so this general protocol is the one that saves you. Attia sees parallels with Jordan Peterson's writing.

• Americans lack protocols for grief
Willink argues that by blending so many cultures, Americans have lost the clear rituals other traditions follow after a death. In combat there was no option to retreat for months; teams were back in their gear within 48 hours. He believes families and high-risk businesses such as construction firms should have protocols ready before something bad happens.

• Default to aggressive
Willink was wary of nervous operators because nervous people hesitate. Under fire, hiding gives the enemy time to maneuver on you; attacking keeps you alive. He applies the same attitude in civilian life: confront problems head-on, because the more defensive your mindset, the worse things turn out.

EXAMPLES

• The flat tire in Ramadi
Watching from a tactical operations center two miles away, Willink saw men pull something from a car trunk at a spot he suspected was set up for a mortar attack, while buildings kept blocking the overhead feed. It turned out to be a jack for a flat tire, and while he watched them, his men were attacked from another direction. With about 400,000 civilians and perhaps 1,000–5,000 insurgents in the city, he thinks they were quite possibly a decoy.

• A letter to a lost child
Willink's advice to a grieving father: expect a tidal wave of grief you can't control, and don't feel guilty when the waves weaken and grow further apart, because that means you're processing it. Eventually, write your child a letter about what they meant and how you'll live a good life to honour them, read it at the grave, then move forward. Staying stuck burdens their memory.

• The getting-dumped protocol
The key realisation, Willink says, is that the person who dumped you is not the person you thought they were, because that person wouldn't have left. Hard as that is, it's easier to live with than believing your 'forever person' doesn't want you.

• Attia's first bowhunt
After two years of shooting only targets, Attia hunted Coues deer in steep mountain terrain and found within 48 hours that everything happened far faster than his precision training had prepared him for. He uses it to illustrate how training differs from real conditions.

OTHER RELEVANT

- **Make sure your team knows the 'why'**
  Before delegating, explain the objective and strategy as well as the task, so people can adapt correctly when plans break.
- **Check yourself for both arrogance and excessive deference**
  Listen hard to people with more experience, as Willink's unit did with the reservists who had been fighting in Ramadi, but speak up when you disagree.
- **Ask whether it will matter later**
  Willink tells his teenagers that most crises will have 'no bearing' on their lives. He labels setbacks 'no factor' and saves his energy for what counts, including the things he can actually control.

#49–Matt Walker, Ph.D., on Sleep (Part 3 of 3): Effects of poor sleep on metabolism & performance...

Guest: Matthew Walker
Date: 2020-01-09 · Duration: 2:01:06
URL: https://www.youtube.com/watch?v=K5utMfG1rSg

KEYPOINTS

• Short sleep halves muscle glucose uptake in a clamp study

Attia recalls a small but tightly controlled University of Chicago study. As he remembers it, healthy subjects slept four hours a night for about two weeks and then repeated a euglycemic clamp, the gold-standard test of insulin sensitivity. Their ability to move glucose into muscle fell by about 50%. Walker notes the finding has been replicated with four, five or six hours a night for one week.

• Attia now credits residency sleep loss for his own metabolic decline

Looking back, Attia believes sleep deprivation, not just cafeteria food, drove his weight gain, insulin resistance and hypogonadism at the end of residency. He says his testosterone was about 200–220 ng/dL, against a cutoff of about 350 for two standard deviations below the mean, even though he kept exercising hard throughout.

• One week of six-hour nights changed the activity of 711 genes

Walker describes a PNAS study in which healthy adults were limited to six hours a night for a week and compared with themselves on eight hours. Blood samples showed 711 genes with altered activity, roughly 3% of the genome. About half went up, including genes linked to tumor promotion, chronic inflammation, stress and cardiovascular disease. The other half went down, including many immune genes. Walker argues six hours is an everyday amount of sleep, not an extreme lab condition.

• Lost sleep can't be banked back, but sleeping better still helps

Walker says sleep is not like a bank: damage done while under-slept doesn't seem reversible, so weekend catch-up doesn't erase it. But improving sleep from now on is still worthwhile. Attia compares it to quitting smoking, where risk falls steadily the longer someone stays off cigarettes.

• Sleep loss pushes appetite hormones in the wrong direction

After a week of four to six hours a night, leptin (the fullness signal) falls and ghrelin (the hunger signal) rises. Walker says people sleeping six hours on weeknights eat about 300 extra calories a day. He estimates that adds up to about 70,000 calories a year, while acknowledging the arithmetic is complicated by compensation.

• Six hours of sleep cuts time to physical exhaustion by about 30%

In healthy, active people restricted to six hours, Walker cites roughly a 30% drop in time to exhaustion. Force, aerobic output and motivation to train all fall too. His illustration: someone trained to hold out for a 10K could fail at about 7K. Attia raises the caveat that sleep may partly work indirectly, through better food choices and more activity.

• Caffeine has a quarter-life of about 12 hours

Caffeine's half-life is about six hours, so a midday coffee leaves about a quarter of the dose in the brain at midnight. A 200 mg dose in the evening reduced deep sleep by about 20% in Walker's studies, even in people who said they slept fine. He says matching that loss through aging would take 20 to 30 years. Genetic differences in caffeine metabolism exist, though Attia finds the link to how people feel imperfect.

• Alcohol sedates, fragments sleep and suppresses REM

Walker separates sedation from sleep: a nightcap knocks you unconscious faster but doesn't help you fall asleep naturally. Alcohol also causes many brief awakenings you don't remember and is a strong REM blocker, leaving people unrefreshed and reaching for caffeine. Attia adds that ethanol inhibits antidiuretic hormone, causing extra night-time urination. Its warming effect works against the 2–3°F drop in core temperature needed to start sleep.

• THC helps you fall asleep faster but costs REM and causes dependence

Walker says acute THC shortens the time it takes to fall asleep, but that is its only benefit. It robustly blocks REM sleep, tolerance builds, and stopping brings a harsh rebound insomnia that often drives people back to it. For the developing teenage brain, both men consider the answer clearly no.

• CBD looks more promising, but the evidence is thin

The early data suggest CBD may help people fall asleep faster. One small study even hinted at more deep sleep, which Walker refuses to rely on. He suspects a sweet-spot dose and two possible mechanisms: lowering core body temperature and reducing anxiety, where he thinks CBD's evidence is strongest. He says the research is hard to fund.

• Sleep and mental health run both ways

Walker sees the causes of insomnia shifting from biological to psychological, and says the rise in anxiety has moved in lockstep with the rise in insomnia. He says the two are probably significantly interrelated, but stops short of claiming more.

EXAMPLES

• CPAP users delayed Alzheimer's by about 10 years

In a group of middle-aged and older adults with sleep apnea, about half used CPAP consistently. Those who did staved off Alzheimer's disease by about 10 years. Walker calls it a causal demonstration, though Attia notes that people who stick with CPAP may also stick with other healthy habits.

• Five ways short-sleeping employees underperform

Walker cites work by his group and Christopher Barnes on employees sleeping six hours or less. They choose easier tasks such as email, produce fewer creative solutions, coast on teammates' work, and behave less ethically, for example falsifying data or expense claims. Employees also rated leaders as less charismatic after the leaders' short nights, without knowing how much they had slept.

• Attia's ring data on alcohol

Attia notes that he invests in and advises Oura. On his own data, one drink four to five hours before bed seems harmless. More than that, or one drink closer to bed, raises his resting heart rate by 6–8 beats, cuts heart-rate variability by about 20%, adds 1–2 breaths per minute and raises temperature by 0.3–0.6°F. He says patients who wear the ring report the same pattern.

- **An MDMA-assisted therapy case fixed a patient's insomnia**

  Attia describes a patient who had done everything: temperature, light, no alcohol or caffeine, an hour of daily meditation. Even 50 mg of Thorazine for rumination helped only intermittently. Clinical, therapist-guided MDMA therapy for underlying trauma resolved his sleep for months. Attia calls it an outlier, not a recommendation.

- **Using deep-sleep waves to support memory**

  Walker describes a head-worn device from one of his startups that reads deep-sleep brain waves and adds electrical stimulation in time with them, 'like a choir' backing a flagging lead singer. The aim is to boost deep sleep, learning and memory in older adults and people with dementia.

OTHER RELEVANT

- **Set a caffeine curfew**

  Given the 12-hour quarter-life, cut off caffeine well before afternoon. Walker also asks why you need caffeine before midday, if it's to cover poor sleep.

- **Treat snoring as a medical issue**

  Walker urges anyone who snores to get a sleep test and treat apnea, given its links to cognitive decline.

- **Use your own data to set an alcohol limit**

  Attia sees most people's limit somewhere between zero and two drinks, with timing mattering as much as quantity.

- **Keep the bedroom cool**

  Since sleep onset needs a drop in core temperature, a cold room helps. Alcohol, a hot room or a big late meal work against it; Attia says late binges of poor-quality carbohydrates hit his sleep much like two drinks.

#47–Matt Walker, Ph.D. on Sleep (Part 1 of 3): Dangers of poor sleep, dementia risk, mental health..

Guest: Matthew Walker
Date: 2020-01-09 · Duration: 1:43:19
URL: https://www.youtube.com/watch?v=VkX3nYpMr2g

KEYPOINTS

• Walker found his field by recording dementia patients asleep, not awake

As a PhD student in London, Walker spent two years failing to tell dementia types apart from waking brainwaves. Reading journals one Sunday, he noticed that some dementias attack the brain's sleep-generating centres while others spare them until late in the disease. He set up a sleep lab, got results, and began asking whether disrupted sleep is a symptom, a predictor or a cause of Alzheimer's. He now believes the evidence points to a causal role.

• Deep sleep powers the brain's 'sewage system'

The glymphatic system is a cleaning network run by glial cells. In deep sleep, Walker says, those cells shrink dramatically, giving cerebrospinal fluid room to flush out the day's metabolic waste. He compares it to Manhattan's buildings shrinking so a flood can wash the streets. That waste includes beta-amyloid, one of the two core proteins in Alzheimer's, so skimping on sleep lets it build up 'like compound interest on a loan'.

• The evidence chain runs from brain scans to spinal taps

In people in their 70s and 80s, PET scans show visibly more amyloid in those sleeping seven hours or less than in those sleeping more. That is associational, he notes. Rats deprived specifically of deep sleep, or with fragmented sleep, show immediate amyloid build-up. In humans, cerebrospinal fluid taken after one night of selectively disrupted deep sleep shows significant rises in amyloid and tau. That last finding is what led Walker to say publicly that sleep is a critical part of preventing Alzheimer's.

• Sleep has four pillars

Walker proposes regularity (avoiding 'social jet lag' from shifting bedtimes), continuity (unfragmented sleep), quantity (total hours and hours in each stage) and quality, meaning the electrical signature of sleep. He stresses that eight hours in bed doesn't guarantee eight hours of good-quality deep sleep, especially with caffeine or alcohol. He expects different sleep features to predict different subtypes of Alzheimer's.

• Non-REM and REM battle in 90-minute cycles

Non-REM sleep has four stages; stages 3 and 4 are the deep, restorative ones. REM is dream sleep, with rapid side-to-side eye movements. Awake, brainwaves are fast, at about 50–60 cycles per second, and small, like a stadium crowd chattering before the game. With eyes closed, the visual cortex at the back of the brain slows to an alpha rhythm of about 10 cycles per second. The two types of sleep alternate in cycles of about 90 minutes all night.

• Deep sleep dominates early in the night, REM late

Walker likens the night to a buffet. From about 9 p.m. to 3 a.m. the brain preferentially takes deep non-REM sleep; after about 3 a.m., REM and stage 2. So sleeping 9 p.m. to 3 a.m. preserves deep sleep but cuts most REM, while very late sleepers get the reverse. Attia sees this on his ring: more deep sleep after early nights back in California, more REM in New York.

• Memory needs sleep both after and before learning

Deep non-REM sleep after learning 'hits the save button' on new memories, so getting the first half of the night protects them. Stage 2 sleep, rich in brief bursts of activity called sleep spindles, peaks in the last two hours of the night and prepares the brain to take in new memories the next day. Cutting the morning short reduces that capacity.

• Lack of REM sleep hits mental health hardest

Walker calls sleep 'emotional first aid'. He links REM loss most strongly to depression, anxiety and suicidality. In young teenagers, he says, insufficient sleep is one of the strongest predictors of suicidal thoughts, attempts and deaths. Sleep problems and anxiety feed each other, but a four-year-old's meltdown after one bad night suggests sleep can drive the problem.

• Drowsy driving can be deadlier than drunk driving

Microsleeps, brief lapses when the eyelids partly close, become common on six or seven hours of sleep. Walker says drowsy driving causes more crashes than drugs and alcohol combined. Drunk drivers usually react, but too late. During a microsleep there's no braking or steering at all, just 'a two-ton missile' at 65 mph.

EXAMPLES

• A family killed after someone's 5.5-hour nights

A reader emailed Walker that his wife and 18-month-old daughter had died in a head-on crash. The other driver had averaged about five and a half hours of sleep for two months and had a microsleep at 60 mph. The man was left to raise his four-year-old son alone.

• Leaders who boasted about short sleep

Walker cites two heads of state who bragged about sleeping four to five hours, then developed Alzheimer's; he names Margaret Thatcher. He doesn't think it's coincidental, while noting that public figures face pressure to boast this way.

• Guinness stopped certifying sleep-deprivation records

Guinness allowed sleep-deprivation records, the last real attempt reaching about 24 days, until links to mental illness, cancer, heart disease and suicide led it to stop. Yet it certified Felix Baumgartner's supersonic skydive from the edge of space. Attia jokes that you can jump off Niagara Falls 12 times but not skip sleep.

• Rats die of sleep loss as fast as starvation

Rats totally deprived of sleep died as quickly as, or about 20% quicker than, rats deprived of food. In humans, fatal familial insomnia, an inherited prion-gene disorder, starts like ordinary insomnia and progresses to death in about 18–24 months.

• Sleep loss on a societal scale

Walker says nature took about 3.6 million years to build an eight-hour night, and in roughly 70 years societies have cut 20–25% of it. Meanwhile, sleep is stigmatised as laziness once children grow up.

OTHER RELEVANT

• Protect sleep as Alzheimer's prevention

With no strong drugs available, Walker considers sleep one of the best preventive steps backed by current science. Attia adds that almost all his patients rank preserving cognition as their top priority.

• Shift gradually before flying east

Before an eight-hour shift to London, Walker starts waking about 10 minutes earlier each day for about five days. The conversation also stresses that both deep and REM sleep matter, with REM described as arguably even more important for mortality risk.

• Never drive drowsy

If you are surviving on six or seven hours, assume microsleeps are possible and treat drowsiness behind the wheel as seriously as alcohol.

#48–Matt Walker, Ph.D., on Sleep (Part 2 of 3): Heart disease, cancer, causes of sleep disruption...

Guest: Matthew Walker
Date: 2020-01-09 · Duration: 2:04:32
URL: https://www.youtube.com/watch?v=pv7i22DHiVE

KEYPOINTS

• Daylight saving time shows how much one hour of sleep matters to the heart.

Walker describes the twice-yearly time change, affecting about 1.6 billion people in 70 countries, as a global experiment. He says the spring shift, which costs an hour of sleep, is followed by a 24% relative rise in heart attacks the next day, and the autumn shift by a 21% drop. The effect fades over about three to four days. Attia points out that this happens despite the mood boost of spring, which should push the other way.

• Short sleepers developed more coronary artery calcification.

Walker cites a five-year study of healthy middle-aged adults with no calcium in their coronary arteries at the start. Those sleeping five hours or less had a two- to three-fold higher risk of developing it. He stresses that the study shows association, not causation, but notes it adjusted for exercise, BMI, neck circumference, smoking and snoring history to rule out sleep apnea.

• Walker sees fight-or-flight overdrive as the common thread behind sleep loss's harms.

Cutting sleep to about five hours for a single night raises sympathetic tone, blood pressure, heart rate and cortisol, and blunts growth hormone. Walker compares chronic short sleep to revving a car engine in neutral, his example being a Mezger Porsche GT3 engine, until the gaskets blow. He says he is writing a paper arguing that this autonomic imbalance underlies most of the damage from insufficient sleep.

• Dieting while sleep-deprived means losing muscle instead of fat.

Walker cites a study in which dieters sleeping six hours or less lost about 70% of their weight from lean mass rather than fat. Attia links this to worse fuel partitioning: higher cortisol, catecholamines and insulin, lower testosterone, and a likely shift toward burning glycogen rather than fat. Attia also says sleep is his own single best tool for eating well.

• Short sleep impairs fertility in both men and women.

According to Walker, men sleeping five to six hours have testosterone levels like men ten years older, and those sleeping six hours or less have fewer, more misshapen sperm with more chromosomal abnormalities. Men sleeping five hours have smaller testicles, though he notes this is associational. Women sleeping five to six hours have about 20% lower FSH and roughly 30% more abnormal menstrual cycles.

• The body has no way to bank sleep.

Walker argues that evolution gave us fat cells to store energy for famine but no equivalent for sleep, because humans are the only species that routinely deprive themselves of it. Sleeping in on weekends, which he calls social jet lag, doesn't repay a weekday debt. Shifting your schedule by about three hours each weekend is, in his comparison, like flying from San Francisco to New York and back every week.

• One short night sharply weakens anti-cancer immune cells.

Walker cites a UCLA study in which four hours of sleep for one night cut natural killer cell activity by about 70%. He notes the WHO classifies night shift work as a probable carcinogen. Attia, who trained in an immunotherapy lab, describes how the adaptive immune system constantly suppresses cancer cells. Walker adds worsening sleep as another reason cancer rises with age.

• Teenagers' late body clocks clash with early school start times.

Walker says teens need 9–10 hours of sleep because the brain keeps developing until about 25, yet only about 11% get enough and the average is around 7 hours. Meanwhile 72% of parents believe their teen sleeps enough. A teenager's circadian rhythm naturally shifts later, so a 7:30 a.m. start, with buses at 5:30, works against their biology.

• Screens at night delay and suppress melatonin.

Walker cites studies in which an hour of iPad reading before bed cut melatonin release by about 50% and delayed its peak by about three hours. It also reduced REM sleep and left people feeling less rested, with effects lasting two to three days. He says television affects melatonin less, but watching in bed teaches the brain to treat the bedroom as a place for being awake.

• Walker says sleeping pills sedate you rather than produce real sleep.

He describes Ambien-type sedative-hypnotics as knocking out the cortex, producing shallower and electrically different deep sleep. He cites associations with higher mortality and higher cancer risk, while noting causation isn't proven. He finds the cancer link especially telling, since real sleep should lower that risk. He favors CBT-I, which works but takes effort.

EXAMPLES

• Teton County, Wyoming

Moving school start from 7:35 to 8:55 a.m. gave students about an extra hour of sleep and, Walker says, cut car crashes among 16- to 18-year-olds by about 70% the following year. He compares this with anti-lock brakes, which cut accident rates by 20–25%.

• Attia's nap in Patterson Park

During residency, with call every third night, Attia stayed awake from Monday morning to Wednesday evening after volunteering for an extra ER shift. He kept stalling his car at stoplights, wisely avoided the freeway, then unwisely napped in the park with a one-hour alarm. He woke at 2 a.m. with rat bites on his arms.

• Ambien as a 'chemical baseball bat'

On a weekly 26-hour round trip from San Francisco to Atlanta during his McKinsey years, Attia used Ambien on the red-eye. He later found emails and phone calls he didn't remember. Kirk Parsley told him that unconsciousness isn't sleep, any more than being knocked out by a bat.

• Judges after the spring time change

Walker says federal judges hand down harsher sentences on the Monday after the spring shift and more lenient ones after the autumn shift. Car accidents and suicide attempts show the same spring pattern.

OTHER RELEVANT

• If you struggle to sleep at night, skip naps.

Walker compares a nap to a pressure valve releasing the adenosine-driven sleepiness you need at bedtime. For people who sleep well and can nap regularly, naps are fine and benefit learning and immune and cardiovascular health. Insomniacs should stay awake and build up sleep pressure.

• Weigh school start times when choosing a school.

Walker would factor start time into any school decision. He says later starts are linked to better grades, less truancy, fewer behavioral and psychiatric problems, fewer dropouts and fewer car crashes.

• Keep the bed for sleep and intimacy, and dim the lights after sundown.

Avoiding screens and bright light in the evening protects melatonin timing, which Walker says matters for adults as well as children.

• Look at cortisol and nighttime glucose.

Attia's working model is that adenosine has to build while cortisol falls before melatonin can start sleep. From his continuous glucose monitor he sees a strong link between high nighttime glucose and poor sleep, which he suspects reflects cortisol. He offers this as a personal hypothesis, not established fact.

#51 – Robert Sapolsky, Ph.D.: The pervasive effect of stress – is it killing you?

Guest: Robert Sapolsky
Date: 2020-01-09 · Duration: 2:18:32
URL: https://www.youtube.com/watch?v=CavapSvFkOs

KEYPOINTS

• The stress response is built for a zebra fleeing a lion, not for chronic worry

Sapolsky, a Stanford neuroendocrinologist and author of Why Zebras Don't Get Ulcers (first edition 1994), describes two arms. Adrenaline acts within seconds, which he likens to 'handing guns out of the gun locker.' Glucocorticoids like cortisol follow via ACTH in about 30 seconds, like 'building the aircraft carriers.' Cortisol mobilizes glucose, raises cardiovascular tone and triages away non-essential functions. That is ideal for a short sprint but harmful when switched on for psychological reasons day after day.

• Cortisol has a narrow 'therapeutic window', and sensitivity varies

Peter calls cortisol the hormone with the narrowest therapeutic index: too little is dangerous, as in Addison's disease, and too much is toxic. Sapolsky notes that New World monkeys such as marmosets have roughly ten times the glucocorticoid levels of Old World monkeys without illness. A receptor mutation gave them about one-tenth the sensitivity, so the system equilibrated at a higher level. People can likewise be cortisol-'resistant' or 'sensitive,' much as with insulin.

• Serengeti baboons are a model of Western stress

Baboons in troops of 50 to 200 rarely face lions, have lower infant mortality than neighboring Maasai, and need only about three hours a day to find food. That leaves 'nine hours of free time every day to devote to being miserable to some other baboon.' Over more than 30 years of summers, Sapolsky darted and anesthetized the same animals for blood work, relating rank, personality and social ties to stress-related disease.

• What a rank means matters more than the rank itself

Being low-ranking is far worse in some troops than in others, depending on troop culture: how often an angry dominant takes it out on you, or whether you get to finish a meal. Humans belong to many hierarchies at once, so the mailroom clerk can be captain of his weekend softball team. Personality matters too. A baboon who treats a rival napping 100 yards away as a provocation averages about twice the cortisol of a same-ranked peer who can tell the difference.

• Stress can be passed epigenetically across generations

Glucocorticoids from an anxious mother cross the placenta and cause epigenetic changes in the fetal amygdala, making offspring more anxious. Sapolsky says such non-genetic transmission of traits can ripple, smaller each time, about half a dozen generations later, and close equivalents have been found in humans.

• Moderate stress sharpens memory; sustained stress damages the hippocampus

A little arousal boosts blood flow, glucose and synaptic excitability in the hippocampus, which is why emotional events stick. Prolonged high glucocorticoids reverse this: less oxygen and glucose delivery, disconnected synapses, shriveled neurons, blocked neurogenesis and greater vulnerability to other insults. Sapolsky's two-decade summary: 'you don't want to have a whole lot of it marinating inside your head.'

• Feeling poor is as harmful as being poor

Sapolsky cites Nancy Adler's work at UCSF showing that subjective socioeconomic status, where you place yourself on a ten-step ladder relative to people around you, predicts health at least as well as objective wealth. He says income inequality strengthens this effect, and social media amplifies it with constant reminders of people doing better. Childhood SES predicts diabetes risk half a century later, so poor health doesn't simply cause poverty.

• Genes mostly change vulnerability to environments rather than determining outcomes

Sapolsky recounts a large birth cohort study of a serotonin transporter variant: on its own it barely changed depression risk by age 25. Combined with childhood trauma, it multiplied risk far beyond the increase seen in people without it. He describes a similar pattern for MAO-A, abuse and aggression. He notes that 300 genes together predict only about 4% of height.

• The evidence for harm is strongest in heart disease and weakest in cancer

Peter summarizes that hypercortisolism's damage is best shown in atherosclerosis, through hypertension and endothelial damage, and is plausible but less clear in dementia. Sapolsky says that in humans no good prospective studies have truly ruled out confounding in stress and cancer. Animal studies used artificial transplanted tumors, though his lab showed transformed cells upregulate a glucose transporter that glucocorticoids boost further.

• Stress makes us less empathic and more impulsive

Sustained stress enlarges the amygdala, atrophies the frontal cortex and disrupts dopamine, increasing vulnerability to addiction and depression. It hampers the frontal cortex's hardest job, seeing from another's perspective. Sapolsky says stress makes us 'crappier to each other,' more xenophobic and parochial, and more impulsive with our worst impulses.

EXAMPLES

• Peter's morning glucose

After almost four years of near-constant glucose monitoring, Peter says he could identify morning on any 24-hour trace by the cortisol-driven rise. He described it as his highest glucose of the day outside meals.

• Unpredictable fragmented sleep is the worst kind

Linking cortisol and sleep loss, Sapolsky says insufficient sleep is bad, fragmented sleep is worse, and unpredictably fragmented sleep is worst. Peter recognizes this from residency pagers.

• Two women with identical hormones and different PMS

Sapolsky uses PMS to show that the same hormone levels produce different emotional experiences depending on context, expectations and biology.

• Impulse versus planning in prison

Peter reflects on volunteering with incarcerated men: many crimes were impulsive split-second choices, not decades of

sinister planning. That fits the effect of stress on frontal control.

OTHER RELEVANT

- **Treat stress management like exercise**
  Sapolsky says it can't be done on weekends or while on hold. It needs regular, dedicated blocks, like aerobic exercise's 20–30 minutes. If you carve out 20 minutes daily despite a crushing schedule, 'you're 80% of the way there,' almost whatever the method. Peter finds meditation his best tool.
- **Audit your comparison groups**
  Because subjective status drives health, limit the inputs, such as social media feeds, that constantly show you people doing better.
- **Advice to his 25-year-old self: be less ambitious**
  Young researchers, he says, have 'a list down to the floor' of diseases to vanquish. He would tell his younger self to scale that back.

#43–Alan Bauman, M.D.: The science of male and female hair restoration—how to protect & restore hair

Guest: Alan Bauman
Date: 2020-01-08 · Duration: 1:55:56
URL: https://www.youtube.com/watch?v=M5B8tNCXEy4

KEYPOINTS

• Hair loss is very common and usually under-treated

Bauman, a hair restoration surgeon who says he has treated more than 20,000 patients, puts the US total near 100 million: about 80 million men and 46 million women. His rule of thumb for men is roughly 20% with visible loss in their 20s, 30% in their 30s and 40% in their 40s. Because about half the hair can be gone before the eye notices, loss can start any time after puberty without being seen.

• 'Premature' hair loss is a meaningless term

Bauman compares hair loss to greying: its timing is genetically set along a spectrum, and 'premature' is in the eye of the beholder. Pattern loss can skip siblings and generations. He describes families where a grandfather, father and sons all come in together.

• DHT drives male pattern loss, and finasteride works for most men

In genetically susceptible men, dihydrotestosterone 'kills' follicles. Finasteride, at about 1 mg a day, gives roughly a 90% chance of looking the same or better over about five years, the usual length of a clinical trial. Dutasteride blocks both pathways to DHT more strongly, but some DHT still gets through either way. Bauman calls finasteride's side-effect rate very low but acknowledges that some men get sexual side effects.

• The finasteride prostate-cancer signal may be partly a biopsy artefact

Attia calls the prostate data confusing: lower rates of prostate cancer but possibly higher grade when it occurs. Bauman passes on an explanation from urologists. Finasteride shrinks normal prostate tissue, and everyone in a trial is biopsied, so high-grade cancer may be easier to find. He presents this as what was explained to hair surgeons, not settled science.

• Finasteride was designed for hair; minoxidil was found by accident

Merck knew from the start that finasteride would be a hair-loss drug. It won approval first for the prostate, as Proscar at 5 mg, then for hair loss, as Propecia at 1 mg, in 1998. Minoxidil was a 1970s blood-pressure pill whose hair growth was noticed as a side effect. Rogaine's FDA approval began clearing useless tonics off the market.

• Minoxidil keeps follicles in the growing phase

In a healthy scalp, about 84–85% of follicles are in anagen, the growth phase. In pattern loss, more are resting and anagen shortens, producing short, spiky, miniaturised hairs visible along a part. Minoxidil wakes resting follicles and prolongs anagen, and the longer anagen lasts, the thicker the fibre becomes. It won't restore a receded hairline but can slow further loss.

• Micro-inflammation at the follicle matters

Bauman took part in a University of Miami study using donated follicles that found inflammasome activity around them. That helps explain the anti-inflammatory ingredient in his compounded minoxidil and the interest in scalp health. When he examines the scalp, he often finds treatable problems such as fungal infection.

• Women's hair loss isn't just about DHT

Pregnancy keeps more follicles in growth, which is why hair thickens and then sheds after birth. Thinning a decade or more after the last child can reflect androgen sensitivity even when DHT is low. Oral finasteride works in about 50% of postmenopausal women but is used off-label only after childbearing years, because DHT is essential to a developing male fetus. It isn't FDA approved for women.

• Donor dominance is why transplants last

Follicles from the sides and back of the scalp are almost immune to DHT, and transplants rely on the theory that they keep this resistance on top of the head. Bauman notes only very limited evidence against it. Transplanted hair doesn't stop the native hair from thinning, so patients who don't protect existing hair 'face a much tougher battle'.

• The main risk of a transplant is an unhappy patient

Bleeding stops like a shaving nick, and the worst infection is usually a pimple-like ingrown hair. Roughly one in 20–30 patients needs more wound care. The real risk is mismatched expectations: promising a 10 out of 10 when the outcome will be a five. Bauman says that after 8,000 surgeries he can show patients the range of results seen in similar cases.

EXAMPLES

• Bauman's compounded minoxidil, 82M

Instead of off-the-shelf foams, his prescription formula adds 0.025% tretinoin, which he says improves penetration and growth, plus 'a whiff' of the steroid fluocinolone. The bottle's tip is applied directly to a parted scalp, which takes 90 seconds twice a day. He says once-daily over-the-counter use rarely does much.

• Laser caps that fit under a baseball cap

Low-level laser therapy targets cytochrome c oxidase in the follicle. Attia notes the same idea is being studied in Alzheimer's. Old laser combs had to be moved around the head; caps now sit under a baseball cap with a battery pack, on schedules like 20 minutes every other day. Bauman says they have no side effects and are useful for people, like college students, who won't apply minoxidil twice a day.

• PRP with measured platelet counts

Platelet-rich plasma comes from the patient's own centrifuged blood. Baseline platelet counts vary, from around 150,000 to 250,000 per microliter, so Bauman counts platelets before and after processing in an in-office Beckman Coulter counter. After about 4,000 treatments he emphasises 'monocyte-rich' PRP. He injects with a 27-gauge needle under a full local block, with optional nitrous oxide. Attia notes PRP's evidence is mixed in orthopaedics and that platelet count is a crude measure.

- **From ear-to-ear strips to 1 mm punches**

  Older strip harvests removed strips 10–20 cm long and 1 cm wide, and technicians dissected 2,000–3,000 grafts under microscopes, often leaving wide scars. Follicular unit extraction uses a punch under 1 mm. The holes close about 50% in 24 hours and need no stitches. Bauman designed an early hand-turned instrument for it, though he says many infomercial clinics still harvest strips.

- **Big cases and beard donors**

  Large procedures now run about 3,500–4,000 grafts over two consecutive days rather than one marathon session. Beard hair can be harvested to repair old strip scars. Bauman's father, who was totally bald, has had almost 8,000 grafts.

OTHER RELEVANT

- **Get measured early if hair loss runs in your family**

  Bauman uses a trichometer to measure hair mass index, combining density and diameter, in permanent zones compared with thinning ones. Parents often bring teenagers in before college.

- **Check your medications**

  Bauman lists blood-pressure, cholesterol and mood medications as the top three that can affect hair quality, often noticeable from when they were started.

- **See someone who looks at your scalp**

  He hears from many patients who had blood tests from several doctors, but nobody examined their scalp or offered more than a bottle of Rogaine.

- **Condition the hair fibre, treat the scalp**

  Heat styling and chemical products weaken hair; conditioner belongs on the fibre. Conditions like psoriasis need real treatment, not just a supermarket shampoo.

#41–Jake Kushner, M.D.: How to thrive with T1D and the valuable insights that can benefit anyone

Guest: Jake Kushner
Date: 2020-01-08 · Duration: 2:07:30
URL: https://www.youtube.com/watch?v=sz-zwJqlm88

KEYPOINTS

• Type 1 diabetes is common and often missed.

Kushner says about 1 in 300 people have type 1 diabetes, typically diagnosed around age nine. He calls it the most common life-threatening, medication-requiring illness of childhood, meaning one to three new diagnoses a year in a typical school. Its incidence has roughly doubled since 1960. At Boston Children's he was the first clinical fellow in 10 years to specialize in it, instead of the rare metabolic diseases academic medicine tends to prize.

• It is a slow autoimmune loss of the pancreas's insulin-making beta cells.

Beta cells make up only about 5% of the pancreas, in islets surrounded by digestive tissue. As they release their unique antigens, autoimmunity can spiral and destroy them over time. No single virus has been proven to cause it. Kushner says higher body weight raises risk at the population level but predicts poorly for individuals. It could either strain beta cells or expose autoimmunity that would otherwise have stayed hidden.

• Genetics raises risk but leaves most children unaffected.

HLA genes are a major factor. A tenfold family risk turns 1 in 300 into about 1 in 30, which still gives about a 97% chance a child won't develop it. Identical twins share it only about 50–60% of the time early on, rising toward 80% by adulthood, according to George Eisenbarth's cohort. Kushner once treated identical twins where only one had it, and knew a family in which all three sons had it.

• The DCCT showed that tighter glucose control prevents complications.

Beginning in the mid-1980s, roughly 1,400 patients at a cost of about $100 million, which Kushner says should be checked, went from an A1c of about 9% to 7%. Centers crowdsourced methods on conference calls. The trial was stopped at about seven years because the eye and kidney benefits were too large to withhold. The downside was more hypoglycemia and weight gain, as patients ate carbohydrates to treat lows.

• Seven years of tighter control still paid off decades later.

After the trial both groups drifted to an A1c of about 8%, yet over the next 23-plus years the former tight-control group had less major kidney disease, less cardiovascular disease and fewer deaths. Kushner recalls about a third fewer primary cardiovascular events. He notes that people with type 1 who gained the most weight since the DCCT era have had somewhat worse cardiovascular outcomes, a weak association.

• Volatility is the core problem, and blaming patients makes it worse.

Kushner says the same meal can need very different insulin depending on stress, sleep, exercise and the fat and protein in it, so fixed insulin-to-carb formulas fall short. He calls the label 'noncompliant' grotesque. Attia compares chasing glucose readings to a beginner pilot fixated on the instruments, which causes overcorrection back and forth, instead of watching the horizon.

• Diabetes distress is huge and often unspoken.

On a 1–10 distress scale, Kushner says teenagers with type 1 diabetes for five years or more on high-carb diets typically score 7–8. Some with an A1c near 14 break down in tears because no one had asked. Because the distress feels normal to them, they assume life just 'sucks'. He has seen patients go from an A1c over 14 to under 7 and be astonished at how differently they could think and feel.

• Bernstein's 'law of small numbers' reshaped Kushner's practice.

Richard Bernstein, who has type 1 diabetes, is still practicing in his 80s and was one of the first to test glucose at home. He argues that fewer carbohydrates mean less insulin and therefore smaller mistakes. His Diabetes Solution recommends low-carb, higher-protein eating, not a ketogenic diet, with longer-acting insulin to cover protein and fat. Kushner estimates about 10 grams of protein act like roughly 6 grams of carbohydrate, with a delay of hours.

• Strict keto and SGLT2 inhibitors carry particular risks in type 1 diabetes.

Without beta cells, nothing limits ketone production. Attia fasting for a week peaks around 6–7 mM BHB, while acidosis begins around 10–14 mM, so Kushner calls prolonged fasting probably a bad idea in type 1. Off-label SGLT2 inhibitors can cause diabetic ketoacidosis with normal glucose (euglycemic DKA), including deaths. Kushner discloses he has consulted on one of these drug programs.

EXAMPLES

• Insulin price: about $25 versus $300–400

Kushner says a 1,000-unit vial cost about $25 when he was a fellow and now costs $300–400 in the US, compared with about $25 in Spain. He blames a federal government that acts as a 'promiscuous customer', paying whatever sellers ask.

• Attia's box of Mini-Wheats

Attia ate a whole box, got a splitting headache and saw his glucose reach about 170 mg/dL, the highest he had seen in years. Kushner compares this to a child with type 1 diabetes eating two cupcakes unseen at a birthday party.

• Kushner's family went low-carb

About four years before the interview, his wife cleared refined carbohydrates out of the pantry. He now suspects he is in ketosis much of the time. Attia recalls Kushner's low-carb patients averaging an A1c of about 5.7% with fewer lows.

• Hour-long clinic visits

Kushner began seeing patients from 4:30 p.m. for as long as needed, mostly asking open-ended questions. Some teenagers with an A1c of 10–14, headed for heart attacks at 35, spent five visits just building trust before making changes.

OTHER RELEVANT

• Find peer support.

Kushner points to the TypeOneGrit Facebook group of Bernstein-method followers, who share CGM traces and meals, and to a Virta Health teleconference for low-carb type 1 clinicians.

• Know the warning signs of undiagnosed type 1 diabetes.

Apart from keeping a child closer to a normal BMI, which only helps at the margins, Kushner says parents can't do much to prevent it. Awareness among families and teachers matters because undiagnosed type 1 diabetes is dangerous.

• Use a CGM as a stand-in for insulin exposure.

Attia's dream measurement is total daily insulin output, which people with type 1 diabetes effectively get from what they inject. Without it, he works to minimize average glucose and glucose variability.

#46–Chris Masterjohn, Ph.D.: Pathways to health and disease (NAD, sirtuins, methylation, choline...

Guest: Chris Masterjohn
Date: 2020-01-08 · Duration: 2:51:59
URL: https://www.youtube.com/watch?v=lv7ihoY8XyA

KEYPOINTS

• Without enough choline, fat gets trapped in the liver

Choline is needed to make phosphatidylcholine, which coats the VLDL particles that carry triglycerides out of the liver. Patients on intravenous feeding formulas that lacked choline developed fatty liver, mirroring rodent experiments from the early 20th century. Masterjohn's reading of those animal studies is that with enough choline, the liver can clear its fat whether the source is sugar, alcohol or fat.

• Choline needs may be far above typical intake

Masterjohn estimates average intake at about 300 mg a day. Some genetically predisposed people need as much as 1,200 mg, and labeling studies show triglyceride export from the liver in NASH (inflamed fatty liver) at about 25% of normal. He uses that to argue some people may need several times typical intake. Liver and egg yolks are the richest sources.

• Fatty liver has inputs and outputs

Fructose, alcohol and very high polyunsaturated fat intake drive fat into the liver, while choline governs how fast it leaves. Attia, who considers fructose molecule for molecule perhaps the biggest driver of NAFLD, notes that removing it usually also causes weight loss, which muddies the results. They discuss Miriam Vos's eight-week study in children, in which whole families were given the food, as a chance to separate the two.

• TMAO as a heart-disease villain fails first principles

Stan Hazen's Cleveland Clinic work linked TMAO, which gut bacteria and the liver make from choline and carnitine, to atherosclerosis in genetically engineered mice and to heart disease risk in people. Masterjohn and Attia point out that fish contains far more TMAO, perhaps hundreds of times more than you'd get from eggs or red meat, yet fish eating is consistently associated with better heart health. Attia sends patients who bring him the papers to Masterjohn's write-up, though he wouldn't rate the possibility of harm as zero.

• The liver stores and regulates NAD

Masterjohn compares the liver's NAD pool to glycogen: the liver keeps blood levels tightly controlled by releasing precursors such as nicotinamide for other tissues, much as it keeps blood glucose near 5 grams. This matters for understanding what NAD-boosting products can actually change in other tissues.

• IV NAD and oral NMN are unlikely to work as advertised

Cells can't simply absorb NAD from the blood, so Masterjohn suspects any felt effect of IV NAD is placebo or a nonspecific signal; Attia notes friends describe infusions as 'the worst feeling in the world'. Masterjohn would bet NMN isn't absorbed intact, because enzymes in the small intestine strip phosphate groups off everything we eat, as they do with riboflavin-5-phosphate.

• High-dose NAD precursors may drain methyl groups

Excess nicotinamide is cleared by attaching a methyl group (methylation), and studies show large increases in methylated nicotinamide in urine and blood with NR. Typical NR doses of 1,000–2,000 mg dwarf the niacin RDA of about 15 mg. In theory, every 1,000 mg of nicotinamide cleared this way could cut creatine production by up to 500 mg against roughly 2 grams made per day. Masterjohn suggests a lower dose matched milligram for milligram with the methyl donor TMG (trimethylglycine).

• Methylation centres on SAMe and homocysteine

Methionine becomes S-adenosylmethionine (SAMe), the universal methyl donor, leaving homocysteine to be recycled through MTHFR or the choline/betaine route, or broken down. Masterjohn says about 90% of methyl groups go to making creatine and phosphatidylcholine; creatine alone accounts for about 45%, and it's the first thing to suffer when methyl groups run short.

• COMT variants shape dopamine and temperament

COMT uses methyl groups to break down dopamine. Masterjohn says faster dopamine methylation is linked to mental flexibility and slower methylation to stability, popularly the 'warrior' and 'worrier' types. Normal variation is personality, while the extremes may raise psychiatric risk.

EXAMPLES

• A homocysteine that wouldn't budge

One of Attia's patients sat at 13–15 µmol/L (normal at his lab is about 9 or below) despite methylfolate and methyl-B12, doubled doses and 50 mg of B6 three times a week. Adding TMG cut his homocysteine roughly in half. Masterjohn reads the failure of B6 as a sign the problem lay in fasted-state recycling rather than fed-state breakdown.

• The TMAO biomarker meeting

Attia was one of about a dozen advisers at a two-day meeting held by a company deciding whether to offer TMAO as a new cardiovascular biomarker. Someone in the room noted that fish delivers more TMAO than any realistic amount of red meat and eggs could generate, and later observational data confirmed that fish eaters have higher blood TMAO. For Attia, that undercut the thesis on first principles.

• MTHFR strategy

Masterjohn's first priority for people with MTHFR variants is 900–1,200 mg of choline a day from food such as eggs, the step with the most evidence. Next comes creatine, about 5 grams a day of monohydrate, to reduce methyl demand, along with attention to folate and glycine.

• How the two take NR

Masterjohn was experimenting with about 75 mg twice a day, from 150 mg capsules split in half. Attia observed, while acknowledging it's anecdotal, that patients taking NR products consistently seemed to see marked improvement in even mild

rosacea.

OTHER RELEVANT

- **Prioritise choline from food**
  If you're at risk of fatty liver, or avoid eggs and liver, check your choline intake before reaching for exotic supplements. Masterjohn prefers phosphatidylcholine to choline salts when supplementing.
- **If you take NR, protect your methyl supply**
  Use modest doses, consider pairing with TMG, and watch for mood or energy swings, which Masterjohn says fit methyl depletion. Short studies of a few weeks can't capture longer-term effects.
- **Look past simple biomarker stories**
  Whether it's TMAO or 'normal' homocysteine, Masterjohn and Attia stress first principles and flux, meaning how fast things are made and cleared, over single snapshot measurements.

#42–Avrum Bluming, M.D. and Carol Tavris, Ph.D.: A compelling case for hormone replacement therapy

Guest: Avrum Bluming & Carol Tavris
Date: 2020-01-08 · Duration: 2:20:36
URL: https://www.youtube.com/watch?v=njBS3s8ex24

KEYPOINTS

• Estrogen Matters argues that women have been wrongly denied HRT

Oncologist Avrum Bluming and social psychologist Carol Tavris wrote Estrogen Matters, building on their 2009 review. They argue that the belief that estrogen causes breast cancer has kept women off hormone replacement therapy for about 30 years, especially since 2002. Attia frames the episode as a story of bad science rather than a blanket endorsement. Not every woman needs HRT, and the clinical task is identifying who benefits most and for whom the risks outweigh the benefits.

• Uterine cancer scare, then the fix

Premarin (named for pregnant mare urine) was cheap to make and remains the dominant US estrogen. In the early 1970s, estrogen alone was found to raise uterine cancer risk up to about fivefold, and prescriptions fell sharply. By the late 1970s, adding a progestogen, cyclically or continuously, was shown to cancel that risk, and use climbed again. A 1991 NEJM article by Goldman and Tosteson said it was 'time for action, not debate'.

• The Women's Health Initiative enrolled the wrong population

About 16 million US women, roughly 22% of those of eligible age, used HRT in 2002. WHI participants averaged 63, about a decade past menopause. Around 70% were overweight or obese, and many smoked or had hypertension. Older women were chosen so heart events would show up sooner and cost less. Women with significant hot flashes were excluded for fear they would drop out of the placebo arm. Yet the results were 'immediately extrapolated to all women everywhere'.

• The breast-cancer finding was small and not significant

The reported 26% relative increase (hazard ratio about 1.26, later 1.24) 'almost reached nominal statistical significance'. In absolute terms, Bluming calculates it as about 0.9 extra cases per 1,000 women, under 1%. By 2006 a follow-up reported that the increased risk in that population had disappeared. Bluming and Tavris also note the WHI's leader had published 'time to bring the HRT bandwagon to a halt' beforehand. Tavris calls it confirmation bias, not a conspiracy.

• A 50–70% collapse in HRT use followed

By 2004, use had fallen from 22% to about 10%. Bluming and Tavris cite one estimate that about 50,000 women died prematurely of heart disease after stopping HRT in the years after 2002. That figure is a modelled estimate and is contested.

• The heart-disease window matters

Women who start within about 10 years of menopause, without existing cardiovascular disease, are a very different group from the WHI's 63-year-olds with existing risk factors. Attia's example is a healthy 60-year-old who went through menopause at 50 and has no evidence of heart disease.

• Bones, brain and colon

Bluming says estrogen can reduce hip fracture risk by up to 50%, better than any long-term alternative. About 21% of women who fracture a hip die within a year, roughly 40,000 a year, similar to US breast-cancer deaths. Studies, including the Nurses' Health Study, show about 20–25% less colon cancer. He says estrogen may cut Alzheimer's incidence by 20–50% depending on the study. The authors say animal, lab, field and randomised studies all point the same way on cognition.

• Breast-cancer survivors are a contested group

Bluming points to his own small 14-year study, which reported results yearly and fit alongside 14 others in showing no increased local recurrence, contralateral cancer or distant recurrence in survivors who took hormones. He notes that as early as 1944 researchers reported about a 25% response rate treating breast cancer with high-dose estrogen. He also notes progesterone did slightly better than tamoxifen in an early 1970s randomised trial. His position remains contested.

EXAMPLES

• Heart disease dwarfs breast cancer as a cause of death

Attia walks through a chart of women from age 25 onward. In every age band, a woman is more likely to die of heart disease than breast cancer over the next 10 years, from about 2–3.5 times at younger ages to about 8 times at 70 and over 12 times later.

• Attia's early-menopause patient

In August 2017, a patient had normal day-5 labs (FSH about 10, estradiol about 90) despite starting symptoms. Months later her FSH was 68 and estradiol unmeasurable. Attia rechecked, then consulted his mentor, gynaecologist Riley Lloyd. The case showed him how abruptly hormones can fall.

• Relative risks in context

From the 2009 paper, Attia reads out associations: fish intake linked to a 14% higher breast-cancer risk, and one extra weekly serving of French fries to 27%. These are comparable to the WHI's hormone signal, which nobody acts on.

• The 2003 drop in breast cancer

WHI investigators linked a 2003 fall in breast-cancer incidence to women stopping HRT. Bluming disputes the link and says the decline had begun in 1999, before the WHI was published.

• Women told to stop at 78

Bluming gets letters from former patients in their 70s and 80s, doing well on hormones, whose doctors won't renew prescriptions. Hot flashes last about seven years on average, but 10–15 for some.

OTHER RELEVANT

• Ask about absolute, not relative, risk

A '25% increase' may mean less than one extra case per 1,000 women. Ask your doctor for the absolute numbers for someone of your age and health.

• Timing and individual profile matter

Starting near menopause in a woman without cardiovascular disease differs from starting at 63 with risk factors. Decide with a clinician who knows the data, and weigh symptoms, bone, heart and family history.

• Randomised doesn't mean right

A randomised trial in the wrong population, or with the wrong formulation, can mislead. Weigh it alongside consistent observational and mechanistic evidence. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Don't stop prescriptions on age alone

Bluming argues that women benefiting from HRT shouldn't be cut off simply for turning 65 or 75. This remains debated, so review it individually.

#40–Tom Catena, M.D.: The world’s most important doctor in the war-torn and remote villages of Sudan

Guest: Tom Catena
Date: 2020-01-08 · Duration: 2:41:46
URL: https://www.youtube.com/watch?v=BguvWMrUZnI

KEYPOINTS

• Catena is the lone doctor for roughly 750,000 to a million people in the Nuba Mountains

Catena grew up in upstate New York, played football at Brown, studied medicine at Duke and served five years in the US Navy. He then joined the Catholic Medical Mission Board for what he planned as one year in Kenya. He stayed about seven and a half years, then arrived at Mother of Mercy Hospital in Sudan's Nuba Mountains on March 10, 2008. He says its catchment area covers 750,000 to a million people across a region about the size of Austria. He describes his life's rule as seeking 'browner pastures.'

• When civil war broke out, he stayed while most of the staff left

After South Sudan's 2011 vote to secede (he cites 99.99%), a disputed governor's election and forced disarmament in Nuba led to fighting on June 6, 2011. Ten days later the diocese sent a plane, arranged under a code name because of spies and the risk of bombing, to evacuate expatriates. Catena, two religious sisters and a priest stayed. He reasoned that without the hospital, women needing C-sections and the wounded would 'just die a miserable death.' He said those who left would not be judged.

• Most of the trauma he treats is to arms and legs, because those patients survive the journey

Antonov planes dropped barrel bombs that threw shrapnel weighing up to 10 pounds; he keeps pieces. Early patients included a girl who needed a shoulder disarticulation and her cousin, whose hand had been blown off. Patients with chest wounds usually bleed out in the field, while abdominal injuries can arrive three or four days later.

• He learned surgery on the job, the way residents do

Catena trained in family practice. In Kenya he did roughly 1,000–1,200 supervised cases, with mentors such as a Kenyan surgeon he calls 'a magician' walking him through operations, adding one new skill at a time. He admits to complications, including a hemopneumothorax on his 500th central line. His threshold for operating is 'first do no harm': if he can't improve a patient's health, he declines.

• The hospital itself was bombed

The government portrayed it as an American Christian hospital treating rebels. Catena describes lying flat as an Antonov circled, learning that the whirring pitch was the sound of a falling bomb, through six to eight drops. He says he felt 'like a hunted animal' and feared losing a limb more than dying. Afterward they dug foxholes across the grounds.

• He has had to work with very few diagnostic tools

They had ultrasound from the start. They waited eight years for an X-ray machine and got a lightweight Bluetooth unit about a year before this conversation, now operated by operating-room staff he trained. Lab testing is limited to urine, stool and hemoglobin, so rugged cartridge analyzers would help. Supply drops are impossible because fighters would destroy them, so logistics matter as much as money.

• The adult disease pattern looks nothing like America's

Catena says that in ten and a half years he couldn't point to a single heart attack. Obesity is virtually nonexistent and type 2 diabetes appears occasionally in people in their 40s and 50s. But untreated hypertension is common, with pressures as high as 250/180. Tuberculosis is very common and HIV is well under 1%. He sees hepatitis B–related liver cancer and wants HPV vaccination and cervical screening.

• Fewer possessions make life simpler, he argues

Catena says the more possessions people have, the more complicated their lives become, and meaning isn't found in material things. He cites the Gospel story of the man who 'went away sad, for he had many possessions,' while stressing he doesn't mean it judgmentally. He draws on his faith daily and attends church every day.

• He sees suicide as tragic as the war wounds

Catena knows of only one suicide in Nuba, the husband of a staff member. Peter notes that in the US suicide ranks among the top 10 causes of death in every age group above 10, before even counting 'slow suicide' through alcohol and drugs. Catena suggests that a hard communal life makes people less inward-looking, and he finds the grief suicide leaves behind heartbreaking.

EXAMPLES

• Rounding on some 300 patients

Peter contrasts his residency dread of rounding on 24 patients before the OR with Catena's days of around 300. In rural Kenya, Catena went from seeing five or six patients in detail during training to 50 or 60 a day.

• 'He's from Kenya'

A local woman told another that Catena came from Kenya, the farthest place she could imagine. She had never heard of America.

• Malaria every year

In ten and a half years, Catena says he has had malaria every year but one. He married a Nuba nurse who doesn't know her exact age; they chose November 21 as her birthday.

• Sorghum and okra

Meals are mostly ground sorghum paste with a slimy okra sauce, which he admits 'tastes about as good as it sounds.' He suspects the grain's protein helps explain how muscular people are.

• The starfish story

Peter closes with the parable of a man throwing stranded starfish back into the sea: 'it made a difference to that one.' Catena

says that on the ground you don't see a drop in the ocean but a person who 'can laugh and can cry.'

OTHER RELEVANT

- **Fund people who already work on the ground**
  Catena won the Aurora Prize for Awakening Humanity, which directs $1 million to charities of the winner's choice. Through his board role he highlights small groups shut out of big grant systems. Nicholas Kristof's 2015 New York Times column brought him wider attention.
- **Ask what a frontline clinic can actually use**
  Practical gear that's cheap to run and easy to maintain matters more than costly machines: portable digital X-ray, simple lab cartridges, HPV vaccine. Peter suggests machine-read imaging could help where radiologists don't exist.
- **Purpose and shared hardship protect people**
  Peter cites a book arguing New York's suicide rate fell after 9/11. Both connect veteran suicides to losing that shared bond more than to combat flashbacks.

#44 – Jeremy Schaap, ESPN journalist: upsets, doping, triumphs, and the importance of sports

Guest: Jeremy Schaap
Date: 2020-01-08 · Duration: 1:41:37
URL: https://www.youtube.com/watch?v=5Un2SI-Ih4w

KEYPOINTS

• Braddock's comeback was built by hardship

Schaap, who wrote the best-selling Cinderella Man, retells James J. Braddock's story. He was a former light-heavyweight contender who lost his 1929 title shot to Tommy Loughran, then broke his hand and went on government relief during the Depression. Unable to afford bus fare, he walked to work as a stevedore on the Hudson docks. That labor built strength in a left hand he had never really had. He was booked as a stepping stone for John 'Corn' Griffin and won, and Griffin's name became boxing slang for someone who couldn't get it done.

• Max Baer was the opposite of Braddock: a showman shaken by a death in the ring

Baer killed Frankie Campbell in a 1930 San Francisco fight, which led to an inquest. Accounts, including his son's, say he was never the same afterward. He was later blamed for Ernie Schaaf's death against Primo Carnera, though Peter notes an autopsy suggested meningitis. Schaap says Baer saw boxing as show business and acted in Hollywood films while champion. That ambivalence showed when he clowned through his first defense against Braddock, who weighed about 192–193 pounds to Baer's roughly 250.

• Braddock embodied an older code of fighting until nothing was left

Against a 23-year-old Joe Louis, Braddock knocked Louis down in the first round. Then, battered, he told manager Joe Gould that if he threw in the towel he would never speak to him again. Schaap says that by today's standards it would seem 'silly,' but it meant something then. Louis went on to hold the title for 12 years with 25 defenses.

• Buster Douglas beating Tyson wasn't a lucky punch, Schaap insists

In Tokyo, 22 days after his mother died, the 42-to-1 underdog dominated. Tyson's eye was swelling shut by the third round, and Douglas controlled even the eighth, in which he was knocked down. Schaap says only about four people predicted that Douglas's jab and size could frustrate Tyson. His point is that Douglas had real credentials, including a win over Greg Page, yet Don King had called him 'a dog' and a quitter.

• The 'destroyers' and the 'artists' approach the sport differently

Peter and Schaap contrast feared knockout artists such as Dempsey, Liston and Tyson with stylists like Ali and Louis. Schaap suggests that a fighter hailed as able to end things with one punch may stop listening to trainers like Kevin Rooney. That leaves him exposed when someone finally stands up to him.

• Too much, too fast undid Douglas

After the upset came court fights with Don King and over the eighth-round 'long count,' the replacement of the people who had built his success, and a $24 million purse to fight Holyfield, the largest in sports history at the time. After taxes and payouts he still had about $9 million in cash. Schaap believes his motivation was gone and his grief over his mother finally hit.

• The Bobby Knight interview made Schaap's career

Days after Indiana fired Knight over its zero-tolerance policy, Schaap, then 31, pushed back when Knight called his son Pat 'the real victim.' Schaap pointed out that Pat wouldn't be losing his job if Knight had behaved. Knight glared and said, 'You've got a long way to go until you're as good as your dad.' Producer Willie Weinbaum had warned him that Knight would probably use his father against him.

• Schaap regrets not being more skeptical during the 1998 home run chase

Covering Mark McGwire for ESPN, he saw about 20 of the 70 home runs, including every one from 52 to 70. He says the androstenedione found in McGwire's locker, then a legal supplement, seemed to put the steroid question to rest. He wishes he had approached it with more skepticism. Peter calls the tribute to Roger Maris's family, alongside Sammy Sosa, 'phony' in hindsight.

• Schaap holds contrarian views on doping punishments

Schaap says he asked Lance Armstrong how anyone could win without EPO. He argues Armstrong should get his yellow jerseys back unless rivals like Pantani, Ullrich, Riis and probably Indurain lose theirs too. On baseball, he wishes Barry Bonds would admit what he did and be inducted. He notes the complication that Joe Jackson, a .356 career hitter, is excluded even though he was a Hall of Fame-level player before 1919.

EXAMPLES

• Braddock returns his relief money

In a story Schaap says sounds apocryphal but was widely reported, Braddock went back to the relief office during his comeback and repaid the money he had received. It made him a people's hero before he beat Baer as an eight-, nine- or ten-to-one underdog.

• Watching Douglas–Tyson on a VHS tape

In college in Hanover, New Hampshire, Schaap couldn't find HBO on fight night. That night was also the NBA slam-dunk contest. His mother later mailed him a tape of the fight, and it was still thrilling days later. He later reported 20th and 25th anniversary pieces before making the 42 to 1 documentary.

• Baer's line about being executed

After Louis beat Baer, who stayed on one knee for the count, a reporter said he looked able to get up. Baer replied that anyone wanting to see him executed would have to pay more than the price of a ticket. Baer died of a heart attack at about 50; Peter notes that doctors then had few tools for a heart attack.

• Dick Schaap's death after 9/11

Jeremy's father's last broadcast, the Sunday after 9/11, addressed the insignificance of sport. He then had elective hip

surgery and died after 'one complication / medical error after another' while Jeremy was about 32. Jeremy also describes his father as a great writer and storyteller whose career was 'an apprenticeship' Jeremy grew up inside.

OTHER RELEVANT

- **Judge an upset by the whole fight, not the narrative**
  Douglas is remembered as a 'one-hit wonder,' but the film shows a sustained beating. Schaap's lesson is to look at the evidence before accepting a story about luck.
- **Sport reflects bigger social stories**
  Schaap says the rise of the African-American athlete was the big story of his father's lifetime. In the last 40 years it has been the emergence and empowerment of female athletes, shaped by Title IX.
- **Assume some doping goes undetected**
  Both say human growth hormone was effectively undetectable in testing. Schaap is convinced track and field will always have it. So when we call athletes clean, he says, 'we really don't know.'

#35 – Nir Barzilai, M.D.: How to tame aging

Guest: Nir Barzilai
Date: 2020-01-07 · Duration: 2:47:45
URL: https://www.youtube.com/watch?v=A80l3o8cz7k

KEYPOINTS

• Nir was studying metformin's mechanism in 1987—before US approval.
As an endocrinology/aging researcher he worked the drug's biology early, then watched interest fade until the geroscience wave revived it. That long arc is why he treats metformin as both an old diabetes tool and a candidate aging intervention, not a Twitter novelty. That early unfinished business with metformin is emotional fuel for TAME as much as scientific rationale. Few clinicians pairing bedside endocrinology with centenarian genomics bring that specific scar tissue to the metformin debate.

• Insulin resistance may be a stress response, not only a villain.
Animal work he discusses complicates the cartoon: manipulating visceral fat and watching diabetes onset in rodents suggested resistance can be protective modulation under some conditions. Clinically he still fights hyperglycemia; intellectually he wants finer definitions than 'IR bad, always.' Peter presses him on clinical translation: nuance about IR as modulator must not become an excuse to ignore diabetes risk.

• TAME (Targeting Aging with Metformin) aims to treat aging as an indication.
Because metformin is pennies, pharma will not fund the usual path—Nir jokes his yearly supply costs pocket change. TAME is designed to show delayed onset of a basket of age-related diseases, creating a regulatory path for aging itself rather than one disease at a time. Regulatory creativity—aging as indication—is half the scientific project. Success would unlock a playbook for testing other aging drugs without forcing every compound into a single-disease silo.

• Existing human signals: DPP, UKPDS, and observational dementia/cancer hints.
Diabetes Prevention Program evidence for preventing diabetes, UKPDS cardiovascular signals, and emerging Alzheimer/cancer literature are why he thinks the prior for a broader aging effect is not crazy—even while demanding a proper trial. He is explicit that hints are not TAME; they are why TAME is ethical to run.

• Centenarians get a ~20–30 year 'bonus' and still die of the same diseases.
They are not immortal; they postpone heart disease, cancer, and Alzheimer's. End-of-life costs in his cited comparisons can be lower for those dying after 100 than at 70—compression of morbidity as an economic and human argument. Families of centenarians often show the delay pattern across siblings, pointing beyond pure luck. That pattern—same exits, later tickets—is the healthspan definition Nir wants policymakers to fund.

• Centenarian genetics are not a 'perfect genome.'
When his group checked ClinVar-style pathogenic mutation lists, centenarians were not mutation-free; many carried plenty. The gift looks more like protective variants and buffering (including pathways around IGF/GH and lipid genes such as CETP patterns he studies) than absence of all risk alleles. CETP VV and related lipid genetics appear in his longevity cohorts as clues, not consumer kit destiny.

• IGF/GH axis cuts both ways for aging and disease.
Too much growth signaling links to certain chronic diseases; too little harms resilience. Nir and Peter dig into whether boosting HGH for lifestyle reasons is wise (generally skeptical) versus understanding naturally low-IGF protective genotypes in long-lived kindreds. Peter's clinical instinct against casual HGH aligns with Nir's read of the aging biology.

• NAD precursors (NR/NMN) get curiosity without blank checks.
They discuss the hype cycle around NAD boosters frankly: promising mechanistic stories, thinner long-term human outcome data than the marketing. Metformin, for Nir, remains the nearer-term pragmatic test. Both prefer waiting for clearer trials over stacking unproven NAD protocols on healthy middle age.

• Max human lifespan arguments sit near ~115–122 with statistical caveats.
Dying before 80 on average leaves decades of theoretical healthspan on the table. TAME's ambition is capturing a slice of that gap with a safe, cheap drug already used by millions. Even a five-year delay in multimorbidity would be civilization-scale if it generalized.

• Both men hunt their own blind spots out loud.
Peter worries about over-interpreting rodent metformin data; Nir worries about under-interpreting converging human signals while waiting for perfect evidence. The episode models adversarial collaboration more than guru monologue. Listeners hear two experts willing to say 'I might be wrong' in real time—rare and useful.

EXAMPLES

• 1987 metformin mechanism work
Pre-approval research that later informed why a diabetes drug might touch aging biology broadly. Few guests can claim continuous metformin curiosity across that many decades.

• TAME's economic irony
A ~10-cent/day drug cannot attract conventional blockbuster ROI—hence academic/consortium trial design. If the trial works, it becomes a template for other gerotherapeutics regulators currently struggle to classify.

• Centenarians vs ClinVar mutations
Hypothesis of 'perfect genome' failed; protective biology > mutation absence. Protective variants plus resilient IGF/insulin handling beat fantasy flawless DNA. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Morbidity compression cost sketch
Last-two-years costs lower after death at 100+ vs 70 in the comparisons he cites—aging delay as system savings. Healthspan arguments gain political force when they also shrink late-life spending.

• Sprague Dawley cancer-dominant deaths

Rodent reminders that extending life still ends in disease—timing and multimorbidity are the targets. Species-specific causes of death keep everyone honest about translation limits.

OTHER RELEVANT

- **Do not self-start metformin casually without medical context.**
  Nir's enthusiasm is trial-shaped; GI side effects, B12, and contraindication checks still matter. Ask a physician who knows your kidneys, B12, and GI history before experimenting.
- **Watch TAME-style endpoints, not Instagram biomarkers alone.**
  Delayed disease onset across a basket beats a single lab vanity metric. Follow disease-onset baskets and disability-free years, not only fasting glucose.
- **Be skeptical of lifestyle HGH for anti-aging.**
  Growth-axis genetics of centenarians "` indication to inject GH at 45. Skip lifestyle GH clinics selling youth; the biology is not a nightclub flyer.
- **Treat NAD hype as hypothesis-generating.**
  Mechanistic plausibility is not a substitute for hard clinical outcomes. File NAD under 'interesting,' not under 'settled longevity stack.' The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#36 – Eric Chehab, M.D.: Extending healthspan and preserving quality of life

Guest: Eric Chehab
Date: 2020-01-07 · Duration: 2:38:45
URL: https://www.youtube.com/watch?v=CUcEAgdlXhA

KEYPOINTS

• Orthopedics is a healthspan specialty more than a lifespan specialty.
Eric Chehab—Peter's Stanford med-school friend, HSS-trained sports surgeon, New York Giants fellow, now University of Chicago faculty—spends his days restoring strength, mobility, and freedom from pain. When those collapse, many patients stop caring about another year of life; quality of daily living becomes the whole ballgame.

• Loaded bad form is a leading author of gym-related joint pain.
They walk through knee pain from incorrect mechanics under load, shoulders irritated by poorly progressed overhead pressing, and the elbow/wrist/Achilles problems that show up when volume outruns tissue capacity. Early technique coaching is prevention disguised as performance work. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Not all joint pain maps cleanly to the MRI finding.
People present with 'knee pain' or 'shoulder pain' whose imaging shows age-typical wear that may not be the pain generator. Eric pushes matching history, exam, and imaging before leaping to the OR—especially for meniscus tears where physical therapy often rivals or beats arthroscopy for many presentations.

• Meniscus surgery sits in a real evidence controversy.
For degenerative tears in middle age, trials have cooled enthusiasm for routine scope-and-trim. Traumatic tears in younger athletes still play by different rules. Eric helps listeners separate Instagram surgery culture from indication-driven care. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Rotator-cuff logic also shows up around the hip abductors.
Hip abductor tendons can fail in cuff-like patterns, but the hip's weight-bearing congruence changes the stakes. Understanding those analogies helps patients interpret why some 'bursitis' stories are actually tendon stories. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Lower-back pain almost always starts with PT, not surgery.
Eric's rule of thumb aligns with Peter's: for axial low-back pain, non-operative care is the default. Surgery earns its keep in clear neurologic compression or instability—not as a first response to a bad week of stiffness. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Mentorship from Russ Warren shaped his reconstruction philosophy.
Warren, a godfather of sports medicine and early ACL/arthroscopy pioneer with a legendary paper count, modeled meticulous indication-setting at HSS. Fellowship time with the Giants added the return-to-play pressure cooker on top of that academic base. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Tissue capacity must rise with ambition.
Masters athletes who add heavy overhead work or sudden running volume without progressive loading buy tendinopathy. Eric's prevention sermon is boring on purpose: gradual exposure, deloads, and honest appraisal of recovery age. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Pain that steals ADLs should trigger earlier specialty care.
Waiting until stairs, sleep, or work tasks fail makes rehab harder. Healthspan framing means treating mobility loss as urgently as many people treat a scary lab value. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Friendship plus shared training history keeps the episode practical.
Peter and Eric translate OR wisdom into gym cues listeners can use Monday: scapular control, knee tracking, and when to stop 'pushing through' a warning twinge. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

EXAMPLES

• HSS + Giants fellowship path
Hospital for Special Surgery residency culture plus pro-football coverage: high-volume ACL and shoulder decision-making under return-to-sport deadlines. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Meniscus trial humility
Degenerative tear evidence that made 'always scope it' outdated—PT-first for many middle-aged patients. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Overhead press shoulder flare
Classic lifter pattern Eric and Peter use to teach progression and scapular mechanics. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Hip abductor as 'cuff' analogue
Helps patients understand lateral hip pain beyond the vague bursitis label. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

- **ADL collapse as the true endpoint**
  When pain removes independence, lifespan talk loses relevance—Eric's north star metric. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

OTHER RELEVANT

- **Film your lifts before your joints file a complaint.**
  Catch valgus knees and shrugging presses early; form is cheaper than MRI.
- **Ask whether the MRI lesion explains this pain.**
  Age-related findings are common; treat the person, not every bright spot on the scan.
- **Default to PT for back and many meniscus presentations.**
  Earn surgery with clear mechanical indications, not impatience.
- **Progress load slower than your ego wants after 40.**
  Tissue adaptation lags ambition; deloads are part of the program.

#33 – Rudy Leibel, M.D.: Finding the obesity gene and discovering leptin

Guest: Rudy Leibel
Date: 2020-01-07 · Duration: 2:20:41
URL: https://www.youtube.com/watch?v=EJHf-6vNLdk

KEYPOINTS

• Rudy Leibel was a chief architect of the leptin discovery story.
Peter spends the first hour-plus on how Leibel, with Jeff Friedman and others, moved from obese mouse genetics to the hormone that told the brain about fat stores. Douglas Coleman's Jackson Lab parabiosis and mutation work (ob/ob and db/db) set the biologic chessboard they then molecularized.

• ob/ob and db/db mice proved obesity could be single-gene and circulating-factor driven.
ob/ob lacked a circulating satiety signal; db/db failed to respond to it—classic ligand/receptor logic Coleman inferred before the molecules had names. That framed obesity as physiology, not merely moral failure. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Cloning the OB gene required teaching themselves molecular genetics.
Leibel and Friedman were not born CRISPR-native; they trained into the tools with their students because the physiologic question demanded DNA-level answers. The culture of Rockefeller/Columbia labs made that cross-training possible. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Leptin is a signal of fat mass to the hypothalamus and brainstem.
When fat stores fall, leptin falls, and the brain mounts hunger, energy conservation, and reproductive throttling. That explains why willpower alone fights a coordinated endocrine defense during weight loss. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Most common obesity is not simple leptin deficiency.
Rare congenital leptin deficiency is dramatic and treatable with replacement; garden-variety obesity often involves leptin resistance or overlapping pathways. Hype that 'leptin shots fix dieting' misreads the biology Leibel helped uncover. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Adipose tissue is an endocrine organ, not inert storage.
Rudy's career kept asking what fat communicates. Cytokines, leptin, and other adipokines change how medicine sees obesity-related diabetes and inflammation. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Zucker rats and lesion studies show many insults converge on overeating.
Peter's fascination with hypothalamic damage models meets Rudy's genetic ones: different injuries, similar hyperphagia phenotypes. The brain's weight-regulation circuitry is robustly defended and multiply vulnerable. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Set-point language is useful if held loosely.
Biology defends a range shaped by genes, environment, and history. Leptin's discovery gave that defense a molecular spokesperson without proving the range is destiny. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Discovery science needed both mouse husbandry and human curiosity.
Spontaneous Jackson Lab mutations plus careful phenotyping beat any amount of abstract theorizing. Rudy credits collaborators generously while Peter insists on his central coordinating role. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Clinical takeaway: respect physiology when counseling weight loss.
Expect hunger and metabolic adaptation; build environments and meds (when appropriate) that work with the leptin axis rather than shaming patients for biology. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

EXAMPLES

• Coleman ob/ob and db/db work
Parabiosis-era inference that a circulating factor and its receptor existed—roadmap for leptin and LEPR. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Friedman–Leibel cloning collaboration
Two PIs learning molecular genetics on the job to capture OB. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Congenital leptin deficiency contrast
Rare, dramatic, replaceable—versus common leptin-resistant obesity. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Hypothalamic convergence
Lesions and mutations funnel into similar hyperphagia, underscoring central regulation. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• First-hour deep dive
Peter structures the episode as a leptin detective story before broader obesity counseling. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

OTHER RELEVANT

- **Stop moralizing common obesity as simple gluttony.**
  Leptin biology shows a defended system; design treatment accordingly. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.
- **Do not buy DIY leptin therapy for typical weight loss.**
  Deficiency syndromes "` garden-variety resistance. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.
- **Anticipate adaptation during caloric deficit.**
  Hunger and energy conservation are features; plan protein, sleep, and activity to blunt them.
- **Support research literacy in patients.**
  Knowing the mouse history inoculates against fad hormone pitches.

#31 – Navdeep Chandel, Ph.D.: metabolism, mitochondria, and metformin in health and disease

Guest: Navdeep Chandel
Date: 2020-01-07 · Duration: 2:22:36
URL: https://www.youtube.com/watch?v=JGB4gHYSZzo

KEYPOINTS

• Mitochondria are signaling organelles, not just powerhouses

Nav Chandel, a Northwestern professor of medicine and cell biology, says every talk he gives carries the same title: mitochondria as signaling organelles. Besides making ATP, they release molecules such as hydrogen peroxide and cytochrome c that tell the cell whether to live, die, proliferate or mount an immune response. In the mid-1990s most researchers assumed mitochondrial oxidants only leaked out when the organelle was damaged.

• Reactive oxygen species are mostly messengers, kept low by dozens of enzymes

Chandel argues that superoxide and hydrogen peroxide, at physiological levels, carry information during exercise or when the immune system meets a virus or bacterium, and those responses are healthy, not pathological. Nature keeps at least 30 enzymes constantly mopping these species up so they stay at signaling levels. Only when they get out of control, or convert into more reactive forms, do they become lethal.

• High-dose antioxidants can blunt the benefits of exercise

He cites exercise studies where muscle biopsies show the beneficial genes that vigorous exercise switches on. In those studies, high-dose antioxidants switched that response off. His caveat is that these were high doses, probably not what most people take. His reading is that the muscle may use hydrogen peroxide as the stress signal, so quenching it removes the message.

• Cytochrome c release is a key step in programmed cell death

Chandel's early work centred on how mitochondria help decide a cell's fate. Proteins called BAX and BAK make pores in the mitochondria, letting the 13-kilodalton protein cytochrome c escape and set off a caspase cascade that kills the cell. He notes that 22 years later the basic finding still stands, which is rare in biology. A drug targeting a protein that controls this release is used to make cancer cells more sensitive to treatment.

• The mitochondrial genome is small but holds the respiratory chain's critical parts

The nucleus holds about 20,000 genes, while mitochondrial DNA holds 37, including 13 that are essential for the respiratory chain to work. Complex I alone has 45 protein subunits, a few of them encoded in mitochondrial DNA.

• Mitochondrial decline with age may not be rate-limiting, and could even be adaptive

Data show less mitochondrial DNA, more deletions and lower maximal oxidative capacity with age. But Chandel says we use maybe 10–20% of maximal capacity at rest and 40–50% in hard efforts. When his lab knocks a mitochondrial protein down from 100% to 50%, they see no pathology even under stress. He admits he is 'way out in outer space' here, but he sees no evidence that healthy tissue is limited by its mitochondria. Supplements to 'boost' them rest on dogma.

• Metformin works in three main places: the liver, the gut and immune cells

Metformin is taken up selectively. It reaches the liver and kidney but not the heart very well, and it accumulates heavily in the gut, which is one reason some users get diarrhoea. The liver accounts for its glucose-lowering effect, and the colon for its effects on the microbiome. Chandel thinks the overlooked site is immune cells such as macrophages, where dampening inflammation may matter most.

• Metformin partially inhibits complex I and shifts the NAD+/NADH ratio

By partly blocking complex I, metformin slows the conversion of NADH to NAD+, slightly lowers the charge of the mitochondrial 'battery' and slows the TCA cycle. Chandel stresses the ratio of NAD+ to NADH, not the absolute amount of NAD, as the key readout. That separates metformin from NAD supplements, which he believes raise total NAD without much change to the ratio.

• Tumors need working mitochondria, despite the Warburg story

The classic view held that cancer cells rely on glycolysis, as seen in lactate production and glucose uptake on FDG-PET, so targeting glycolysis would spare normal tissue. Chandel argues that glycolysis is necessary but so is robust mitochondrial function. In most cancers, disabling the TCA cycle or respiratory chain prevents tumors from forming. A Science paper by Vander Heiden, Cantley and Thompson about a decade earlier reframed Warburg's observation as serving growth rather than energy.

• NAD precursors mostly end up in the liver

Attia describes a Cell Metabolism paper from Josh Rabinowitz's group: orally given NR or NMN were taken up heavily by the liver, which made plenty of NAD there, but little reached other cells. Chandel thinks NR's plausible effects are metabolic actions in the liver, somewhat like metformin's, plus possible uptake by immune cells. He labels both as hypotheses and notes NAD is not his core expertise.

EXAMPLES

• The yeast enzyme experiment that isolated metformin's anticancer mechanism

Yeast has a single protein that converts NADH to NAD+ like complex I but does not pump protons, and metformin cannot bind it. Chandel's lab put this yeast enzyme into human cancer cells grown in mice. Without it, metformin shrank tumors; with it, the mitochondria kept working and tumors did not shrink. The 2014 work suggests complex I inhibition is necessary for the anticancer effect, beyond lowering insulin and IGF-1.

• Metformin changed TCA-cycle metabolites in human ovarian tumors

Jason Locasale at Duke analysed tumor biopsies from University of Chicago ovarian cancer patients given metformin by Ernst Lengyel's team. He found metformin reached the tumor and altered TCA-cycle metabolites as the complex I model predicts. Chandel thinks both mechanisms, lower glucose and insulin and direct tumor effects, act together, noting about two-thirds of cancers seem sensitive to insulin and IGF.

- **An orange a day covers vitamin C's real job**
  Chandel says vitamin C matters not as an antioxidant but as a cofactor for enzymes that control DNA methylation and gene expression. One orange a day, or one or two, is enough. Megadoses add nothing, and he mentions a lung cancer trial, he believes of vitamin E, in which antioxidant users did worse.
- **L-2-hydroxyglutarate as a marker of failing mitochondria**
  When the respiratory chain fails, NAD+ drops, NADH rises and cells make L-2-hydroxyglutarate (L2HG). People with a genetic defect who can't clear it develop serious pathology. Chandel wants to test whether L2HG rises in Parkinson's and Alzheimer's. Attia suggests cardiac bypass patients, who are hypoxic. Metformin is too weak a complex I inhibitor to trigger this.
- **Attia's two-by-two for supplements and drugs**
  Attia plots harm against benefit: picking up a quarter or a Bitcoin, in front of a tricycle or a train. Chandel agrees most antioxidants, such as CoQ10 and MitoQ, are quarters in front of tricycles, and many have little measurable bioavailability. He sees metformin as having much more potential. Still, he doesn't take it, because he won't take any drug before a rigorous clinical trial.

OTHER RELEVANT

- **Don't megadose antioxidants around training**
  If exercise adaptations depend on an oxidant signal, high-dose antioxidants may cancel part of what you trained for. The caveat from this conversation is that the evidence involves high doses, not ordinary diets.
- **Be sceptical of 'mitochondrial booster' supplements**
  Chandel's view that normal aging rarely makes mitochondria the bottleneck, plus the poor bioavailability of many such products, suggests little upside for a healthy person.
- **Watch chronic stress and cortisol**
  Chandel now pays more attention to stress than anything else, citing travel, grant pressure and family. He wishes free cortisol were easier to measure; it is mostly bound to albumin and cortisol-binding protein, so it is measured in saliva or urine.
- **Weigh unproven longevity drugs with your own rule**
  Chandel requires rigorous trials before taking metformin. Others argue they can't wait for trials. The episode frames this as a personal risk–benefit choice, not a settled answer.

#38–Francisco Gonzalez-Lima, Ph.D.: Alzheimer’s disease & the vascular hypothesis

Guest: Francisco Gonzalez-Lima
Date: 2020-01-07 · Duration: 2:32:08
URL: https://www.youtube.com/watch?v=zCjMFuFv9Gg

KEYPOINTS

• Late-onset Alzheimer's as a neuronal energy crisis

Gonzalez-Lima, a UT Austin neuroscientist working in pharmacology, toxicology and psychology for about 27 years, was introduced to the field by Jack de la Torre about 25 years earlier. Their vascular hypothesis holds that the core problem in late-onset Alzheimer's is a progressive shortfall of energy to neurons, driven by reduced blood flow. In this view, plaques and tangles are not the primary cause. Attia presents it as a credible alternative to the dominant amyloid view, not a settled answer.

• Alzheimer's original patient was not typical

Alois Alzheimer's 1907 report described a woman of about 51 who died in 1906 after years of dementia. Attia notes she likely had a rare early-onset genetic form, such as a PSEN1 or PSEN2 mutation, which accounts for under 1% of cases, though this has never been confirmed. Meanwhile Oskar Fischer's group in Prague studied 'senile dementia' in people in their 60s–80s, the common late-onset form.

• Blood flow to the brain falls with age

Gonzalez-Lima says brain blood supply drops by about 20% between ages 22 and 60, roughly half a percent a year. Arterial stiffening and atherosclerosis in the large arteries, such as the carotids, show up as rising blood pressure. Guidelines now aim for under 120/80, compared with about 135/90 that used to be accepted. He calls atherosclerosis a major risk factor.

• Function matters more than structure

Structural scans show anatomy. Functional imaging such as FDG-PET, which grew out of earlier metabolic-mapping work, shows how hard brain regions are working. Attia says many patients don't understand the difference because doctors rarely explain it. Much of Gonzalez-Lima's career has been spent mapping brain metabolism and function.

• The brain is uniquely vulnerable to energy shortfalls

At about 2% of body weight, the brain uses about 20% of the body's energy. Its circuits are highly convergent and redundant, which hides early losses until function visibly fails.

• Cytochrome oxidase is reduced in Alzheimer's brains

His 2001 study used brains collected within about three hours of death, a very short post-mortem interval, through the Sun City Health Center in Arizona. It found reduced activity of cytochrome oxidase (complex IV), the final, rate-limiting enzyme of the electron transport chain that reduces oxygen to water and drives ATP production. Regions connected to damaged areas also declined, a functional change that standard pathology misses.

• Partial inhibition of complex IV mimics hypoperfusion

Inhibiting cytochrome oxidase by more than about 40% kills an organism, which is how cyanide works. His lab used very low doses to create 'functional hypoperfusion' without killing animals. Attia notes duration matters as well as degree: 40% for seconds differs from 40% for minutes.

• Methylene blue can boost mitochondrial respiration at low doses

Paul Ehrlich studied it in the 1880s and developed the 'magic bullet' idea, because it concentrates in nerve tissue. The first synthetic medicines, including chlorpromazine around 1950, derived from it. At low doses it shuttles electrons and helps respiration. At high doses it becomes a pro-oxidant, a 'hormetic', two-phase dose response. It treats methaemoglobinaemia at low doses but can cause it at high ones. It was once used for bladder infections, and its half-life is about 12 hours.

• Near-infrared light also targets cytochrome oxidase

Cytochrome oxidase absorbs near-infrared photons. His group delivers 1,064 nm laser light through the forehead, a wavelength that penetrates deeper but is rarely studied in biochemistry. He says this improves mitochondrial respiration in the targeted brain tissue. Studies are ongoing with NIH BRAIN Initiative and aging-related funding.

EXAMPLES

• The LMTM trial

A Scottish company tested LMTM, a methylene-blue derivative, in early Alzheimer's. The primary result failed. The benefit was seen in a subset of about 15% who took it alone, without standard Alzheimer's drugs, and the lowest dose worked best. Attia notes the problem with parsing subsets after the fact. The guests note that a low dose working best would fit methylene blue's two-phase dose response, though the trial wasn't designed to show that.

• Stroke rescue in animals

Infusing low-dose methylene blue (about 1 mg/kg) protected animal brains from much of the damage after stroke, as shown with longitudinal fMRI. He argues ambulances and emergency rooms should consider it for any acute insult to brain energy supply, and a trial for traumatic injury is plausible. These are animal and early human data.

• Don't buy lab-grade methylene blue

Chemical-supply grade can contain about 15% impurities, and industrial dye grades more. Gonzalez-Lima warns against giving it to animals or people. Because it predates the FDA, it was grandfathered in and has never gone through modern approval.

• Head trauma

Blows to the head cause rapid twisting and bending forces, which links head injury to later Alzheimer's and Parkinson's risk. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• A classroom demonstration

Methylene blue turns water blue, then clear when a reducing agent like vitamin C is added, a visible demonstration of its redox cycling.

OTHER RELEVANT

- **Protect your vasculature to protect your brain**

  Blood pressure under 120/80 and preventing atherosclerosis are among the most plausible ways to protect brain energy supply over decades.

- **Use metabolic flexibility**

  After 12–14 hours without food, the body starts producing ketones, an alternative fuel for the brain. Both guests see this as relevant to insulin resistance, which impairs glucose delivery.

- **Everyone with a brain is at risk**

  Gonzalez-Lima suggests preventive measures for everyone rather than only high-risk groups. Attia agrees prevention should start early. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Treat methylene blue as experimental**

  Despite the long history, clinical evidence for Alzheimer's is preliminary, dose-dependent and easy to misuse. Only use pharmaceutical-grade methylene blue, under medical supervision.

#32–Siddhartha Mukherjee, M.D., Ph.D.: new frontiers in cancer therapy, medicine, and writing

Guest: Siddhartha Mukherjee
Date: 2020-01-07 · Duration: 1:05:16
URL: https://www.youtube.com/watch?v=iWWTMdEGan4

KEYPOINTS

- **Sid combines Pulitzer-level writing with practicing oncology and lab science.**
  Peter calls out how rare that triad is in one person. The Emperor of All Maladies made cancer's history readable without sanding off scientific teeth, and Sid's later books continue that translation project while he still sees patients and runs research. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **They first bonded over science-on-a-napkin energy.**
  A Japanese-restaurant brainstorm—energetic teams, multi-site ideas—became a friendship before The Gene even landed. Peter had already been reshaped by Emperor and wanted the craft behind it as much as the oncology. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Writing craft: braid personal story with dense science.**
  Sid's method toggles intimacy and mechanism so neither tourists nor experts feel abandoned. Peter, struggling with his own book, presses him on how to do science justice without turning chapters into review articles. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Cancer therapy's frontier is smarter targeting, not only harder chemo.**
  They survey how genomics, immunology, and cell therapies are changing who survives which diseases. Sid is careful to separate durable remissions from hype cycles that outrun evidence. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **History literacy prevents false novelty.**
  Emperor's long arc—from radical surgeries to chemo to targeted drugs—shows each era declaring victory early. Knowing that pattern makes today's press releases easier to handicap. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Medicine needs storytellers who will not lie about uncertainty.**
  Sid argues narrative is not the enemy of rigor; bad narrative is. Patients already live inside stories—clinicians should offer accurate ones. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Research teams beat lone genius mythology.**
  Even napkin-born ideas require 'very energetic teams' across sites. Sid's praise of collaborative infrastructure matches how modern oncology trials actually run. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Reading cancer changes how you read risk in ordinary life.**
  Peter notes even non-cancer listeners gain a template for evaluating medical claims: mechanism, history, effect size, and human cost. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **The physician-writer must protect clinical humility.**
  Seeing patients keeps Sid's prose from floating into abstraction; writing keeps his clinic from drowning in unspoken fear. Each practice disciplines the other. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Translation is a moral act when stakes are mortal.**
  Clear public explanation of cancer biology can reduce both nihilism and magical thinking. That is why Sid keeps doing mass-audience books instead of only papers. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

EXAMPLES

- **Pulitzer for The Emperor of All Maladies**
  Proof that rigorous cancer history can win both scholars and general readers. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Napkin dinner origin with Peter**
  Friendship and project sparks before The Gene—science as social and intellectual sport. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Peter's own book struggle**
  Sid's craft advice lands on a listener mid-manuscript, making the meta-conversation concrete. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Era-by-era false peaks in cancer care**
  Historical pattern that disciplines excitement about any single new modality. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

- **Multi-site team science**
  Modern oncology progress as choreography, not solitary heroics. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

OTHER RELEVANT

- **Read Emperor (or equivalent history) before the next cancer headline.**
  Context turns press releases into placeable moves on a long board. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Demand effect sizes and durability, not just mechanisms.**
  Beautiful biology still has to move survival or suffering. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **If you write about science, braid scene and citation.**
  Sid's toggle is learnable craft, not mystic talent. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Keep patient contact if you theorize about care.**
  Clinic is the bullshit filter for elegant ideas. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

#37 – Zubin Damania, M.D.: Revolutionizing healthcare one hilariously inspiring video at a time

Guest: Zubin Damania
Date: 2020-01-07 · Duration: 2:51:24
URL: https://www.youtube.com/watch?v=LVzKunKiTUE

KEYPOINTS

• Burnout is better described as moral injury

Damania, a Stanford-trained internist known online as ZDoggMD, says that by his third year of residency his humour had turned from a coping mechanism into a wall. He used 'gomer' ('get out of my ER', from the novel The House of God) in every possible form for patients. Underneath was a feeling that he was a bad person doing work that often harmed people or was 'half-baked'. His program director told him he was a bad influence on the interns, which pushed him to become a committed teacher instead.

• Money couldn't replace the doctor–patient relationship

After residency Damania told his program director he would not do a fellowship or practise, and spent a year at Silicon Valley startups. He says he wanted to get rich, but learned that without deep relationships with patients, money 'was never gonna cut it'. He returned as a Stanford hospitalist with a side career in comedy and music. Zappos CEO Tony Hsieh saw that work and recruited him to Las Vegas.

• Attia's wife framed his choice: fix the 12 problems or leave

In summer 2005, about a year into their marriage and with two years left in surgical residency, Attia gave his wife 12 reasons he was miserable. After a few days she told him there were only two ways he'd get better: fix all 12 or leave. He loved operating but couldn't stand the system. He had just spent two years in a lab at the NIH, and considered a PhD, another specialty or quitting medicine before leaving.

• Hierarchy works only when you respect the person above you

Attia says he loved hierarchy in residency when the people above him were exceptional, and struggled when he didn't think a superior was good enough. Damania observes that some personalities can't sit in the middle of a hierarchy. They either dominate the people below them or treat them as equals before they're ready, when those juniors actually need training and support.

• 'My diet's better than SAD' is the real result of most diet wars

Attia's framework starts from the standard American diet (SAD), engineered for palatability, shelf life, cost and profit rather than deliberately to harm. Keto, paleo, Mediterranean, vegan and vegetarian diets are all one approach, dietary restriction, which removes something from SAD while still eating freely. Caloric restriction and time-restricted feeding are separate levers. Since every camp compares itself with SAD, 'paleo or vegan?' is often the wrong question; stay on whichever keeps you off SAD.

• Attia's goal: live longer and better on three fronts

His stated objective is to delay the onset of whatever would otherwise kill him and to improve quality of life, which he defines with three legs. The first is cognition. The second is the body's 'exoskeleton': muscle mass, mobility and especially stability, which he thinks gets no attention, plus freedom from pain and sexual function. Can you still drop into a goblet squat to pick up a 30-pound grandchild? The third, which he calls the hardest for a doctor to influence, is happiness or distress tolerance, a term he borrows from Paul Conti. For that he sees meditation as the key tool, along with social support and purpose.

• Fasting is a drug whose right dose nobody knows

Metformin activates the nutrient sensor AMPK and rapamycin inhibits mTOR, the central amino-acid sensor; both partly mimic caloric restriction. Treating fasting like a drug raises open questions of calorie amount, composition, duration and frequency, plus what you eat in between, which Attia calls an unsolvable search. His professional obsession is funding ways to measure the effects, especially autophagy. That would let him tell patients, for example, that a gentler plan gets 50% of the benefit.

• Attia uses metformin in patients but not rapamycin, yet

Attia says rapamycin, a transplant-rejection drug, is safer than its reputation. At the right dose and frequency, which is nothing like transplant dosing, he would worry less about it than ciprofloxacin. He calls his own fasting routine improvised and says his measurement tools are too blunt to draw firm conclusions.

• Healthcare costs explode when the decision-makers don't pay

Attia says it took his McKinsey skills to map US healthcare's money flows: the people driving costs don't bear them. He compares it to a Saudi friend who left his air conditioning on all summer because energy cost him about $2 a month, and to buying a Lexus while paying only 9% of the price. He adds that cost, access and quality move together, so Canada, for example, has optimised for cost.

EXAMPLES

• Turntable Health's membership model

In Las Vegas, Damania's clinic charged a flat membership for unlimited, team-based primary care, with health coaches and a teaching kitchen. Coaches taught people to cook on a budget in a food desert. Patients said they felt accountable to coaches who cared about them. He pairs this with personal health accounts of up to about $2,500, subsidised for poorer people and spent within healthcare.

• Attia's dream nutrition experiment

In a crossover trial, one group would get cooking lessons, money and stores with prices and shelf placement reversed: Cocoa Puffs at $12.99 and hard to find, eggs, avocados and steel-cut oats cheap and up front. After a year the groups would switch. He estimated tens of millions of dollars, about a twentieth of the cost of developing a new drug, and doubts it will ever happen because medicine rarely funds prevention.

• Losing a patient over vaccines

A father who expected Attia to back his plan not to vaccinate his children left the practice when Attia said absolutely vaccinate. Attia notes that his only deviation for his own kids was an intuitive six-month delay before the first round. Damania now asks hesitant parents what really bothers them, such as forced injections, 'toxins' or distrust of pharma, rather than leading with data.

• A guided psychedelic experience broke Damania's 'impostor' story

After moving to Las Vegas in 2012, Damania, who had tried LSD, psilocybin and MDMA in college, took part in a guided session. He felt himself to be a 'lying fraud' until his sense of self dissolved into 'the awareness in which all this arises'. The change was still there the next morning and lasted for weeks.

• The Mind Illuminated as a manual for type A meditators

Both men read Culadasa's book; Attia says he read it on Sam Harris's recommendation. Damania likes its model of 'sub-minds' projecting onto a conscious screen, with a narrating sub-mind telling a story moment by moment. If the self is a series of slices, the next one can be different.

• A death caused by a chain of medical errors

Damania recalls telling a marathon-running son that his father had died from a C. diff complication caused 'one error after another' in hospital. He blames fee-for-service incentives that pay hospitals for doing more, not for safety.

OTHER RELEVANT

• Pick the eating pattern you can sustain

Damania moved from keto to Mediterranean with intermittent fasting to one meal a day, which he enjoys with his family, and he eats freely on weekends.

• Parents control young children's calories

Damania argues that, absent a medical cause, young kids' obesity is the parents' responsibility. He singles out soda and large glasses of orange juice, while acknowledging food deserts and cost.

• Vet doctors by how they think

Attia's planned doctor database asks clinicians to explain in detail how they keep learning and how they practise, so it isn't a quick listing.

#34 – Sam Harris, Ph.D.: The transformative power of mindfulness

Guest: Sam Harris
Date: 2020-01-07 · Duration: 2:43:47
URL: https://www.youtube.com/watch?v=1iGVX_ubMmE

KEYPOINTS

• There are two broad families of meditation, and Sam considers mindfulness the deeper one

Concentration practices (a mantra, a candle flame, a random sound) try to absorb attention in one object so thoroughly that thought stops arising; a thought appearing means you are not focused enough. Mindfulness, which comes from the Theravada practice of vipassana (insight meditation), is not trying to exclude anything. It starts with an object like the breath but widens to sounds, sensations, moods and thoughts. Its big advantage, Sam argues, is that it is compatible with any experience at all, including working out or watching a movie.

• Our default state is being lost in thought, and that inner narration is mostly unpleasant

Sam suggests that discursive thinking may begin when toddlers, around two and a half to three, start narrating to themselves as if talking to a parent, and that it never switches off because language is so useful for survival. Evolution, he stresses, does not care about well-being as long as we survive and reproduce. So a mind that is miserable but reproductively fit is perfectly acceptable to natural selection. Getting past that is the project.

• Concentration is intrinsically pleasurable, which is also its trap

Sam's view is that boredom is simply a lack of attention: with enough focus, even wind on your hand becomes exquisitely pleasant. But he warns that people can get hooked on these state changes and mistake them for the point of practice. Any pleasure that depends on a concentrated mind is impermanent and will be lost.

• Pain and suffering are different things

Meditation does not remove physical pain. If you resolve not to move, even a comfortable chair becomes excruciating, and some practitioners sit for 12 hours. Suffering is the fast cascade of resistance, contraction, and worry about how long it will last. Sam's paradox: the moment a sensation feels 'intolerable,' you have already tolerated it. In very intense states he has found that pain's valence can disappear, to the point where he isn't sure if he is feeling agony or ecstasy. He adds that some pains may defeat even the best meditator.

• Peter now ranks emotional health as one of two big shifts in how he thinks about longevity

Five years earlier Peter would have dismissed happiness as an afterthought that follows from avoiding disease. Now he says living to 100 or delaying heart disease, cancer, and Alzheimer's is pointless if you are too miserable to enjoy it. The other shift, which he leaves for another day, is the kind of physical body you need to age well. Sam prefers to talk about well-being and flourishing rather than 'happiness,' because those words can include grief and loss.

• The goal with anger is faster recovery, not never feeling it

Sam says getting angry is not the measure of having lost. Cutting anger from 10 minutes to 10 seconds to one second means 'factors of 10' that are enormous. He makes room for useful anger, such as self-defense on a sidewalk, but otherwise wants to drop it quickly and then decide calmly whether to confront someone. Without mindfulness, he says, 'you will be angry as long as you're angry.'

• Short retreats are mostly the hard part

Sam tells Peter not to bother with a four-day retreat. He says a week to ten days is the shortest he can recommend without caveats. The first three days are the hardest at any retreat length. At day three of a ten-day retreat, home is still far enough away that people tend to surrender and really practice.

• Vipassana targets three characteristics; Dzogchen goes straight at the self

Insight practice looks at impermanence, selflessness, and unsatisfactoriness. Sam says the last is often mistranslated as 'suffering,' as if the Buddha taught that life is suffering. His metaphor: the boat is always leaking and we are always bailing. Dzogchen, a Tibetan non-dual tradition, goes directly at the feeling that there is a subject behind your face. Sam warns that mindfulness taught as goal-seeking can keep people from seeing this even on retreat.

• MDMA gave Sam his first glimpse of a mind without self-concern, but he flags neurotoxicity

Earlier psilocybin and marijuana use felt like ordinary drug states to him: an altered state, but no altered trait. MDMA at 18 removed the constant background monitoring of what his best friend thought of him, along with the zero-sum envy that limits 'sympathetic joy' for others' success. He has not taken it in years and stays 'somewhat concerned' that it may be neurotoxic. He says he knows of no evidence that LSD is neurotoxic. For debilitating PTSD, he thinks some toxicity could be an acceptable trade.

• Loving-kindness (metta) practice deliberately reframes everyone

Unlike mindfulness, metta has a goal: feel goodwill as intensely and durably as possible. Its central reframe is that everyone is suffering and was once a child. Sam says that taken far enough, this frame can extend compassion even to someone like Saddam Hussein.

EXAMPLES

• Peter's moment of presence, about 10 days into a no-devices facility

With no phone, music, or books, at almost 45, Peter had what he believed was the first truly present moment of his life: light through a window, cooking smells, running in the woods hearing only his breath. He called Sam on December 26, joined the beta of Sam's app, and enrolled interested patients.

• The Outward Bound solo at 16

After about 18 days of 14-hour hikes with 60-pound packs, Sam spent three days fasting alone by a lake at roughly 9,000 feet. Others came out radiant; he spent it fantasizing about food and friends, 'perfect misery.'

• The daughters' early-warning system

Sam's wife and daughters know he is committed to dropping anger, so they call it out early. Even 'I thought the plumber was

coming today' gets a 'daddy's getting angry,' which lets him let go much earlier than before.

• The patient dreading his dogs' deaths

Peter describes a patient three months after losing a dog aged around 14 or 15, now dreading the deaths of two healthy dogs aged six and seven, with extremely high cortisol. Sam's reframe: we are content with loved ones out of the room all the time. The only way to suffer an absence is to think about it without knowing you are thinking.

• Ron Howard's course on lying

As a Stanford freshman at 18, Sam took a seminar that examined whether lying is ever ethical. Students kept proposing acceptable white lies and the professor shot each one down. Sam left committed to honesty in all but self-defense situations.

OTHER RELEVANT

• Use recurring irritants as practice reps

Peter treats traffic as practice ('you're feeling like your time is more valuable than everybody else's'). He uses empathy with rude airline staff, citing friend Jay Walker's claim that about one in six US aviation experiences is a customer-service failure. Sam also endorses 'firmware updates,' such as a great podcast that makes a delay welcome.

• Pay close attention to pleasures to test them

Sam's M&Ms example: eaten mindfully, the sweet you craved is often too sweet and chemical, and you only enjoy it because you can drink water next. Paying attention can show that you want some things less than you thought.

• Bridge formal practice into the other 23.5 hours

Peter compares 15 to 20 minutes of daily meditation to lifting weights: the point is to use those 'muscles' all day. Sam's wife teaches children to meditate from about age five or six.

#27 – David Sinclair, Ph.D.: Slowing aging – sirtuins, NAD, and the epigenetics of aging

Guest: David Sinclair
Date: 2020-01-06 · Duration: 1:41:32
URL: https://www.youtube.com/watch?v=edrIEC0kJv8

KEYPOINTS

• Sirtuins came from an unbiased genetic hunt in yeast

In Lenny Guarente's MIT lab, gene screens for yeast lifespan turned up SIR genes ('silent information regulators'), not the DNA-repair or antioxidant genes the field expected. Sir2, which has counterparts in mammals, controls gene silencing. Sinclair notes that at the time aging was blamed mainly on DNA damage and free radicals, so a gene-silencing protein was a surprise.

• Sirtuins move to repair damage and neglect their usual jobs

Sinclair and student Kevin Mills stained the proteins and saw them relocate to the nucleolus, home of the ribosomal DNA, during normal aging and during an accelerated form of aging. His lab and others then showed that sirtuins were both necessary and sufficient to mimic calorie restriction in yeast and mammals. Knocking them out weakens the lifespan benefit, though Sinclair concedes that intense stress can bypass them in yeast.

• NAD fuels sirtuins, and nicotinamide brakes them

Sirtuins consume NAD and release nicotinamide (a form of vitamin B3). When his first student, Kevin Bitterman, fed yeast nicotinamide expecting activation, he got inhibition. Sinclair explains it as a negative feedback pocket in the enzyme that senses its own by-product, and says he wouldn't recommend very high doses of nicotinamide. Labs worldwide now use it as a sirtuin inhibitor.

• Calorie restriction switches on NAD recycling

PNC1, an NAD-salvage gene previously studied in tuberculosis, was among the most strongly upregulated genes in calorie-restricted yeast. That connected nutrient stress to higher sirtuin activity through NAD.

• Resveratrol was a proof-of-concept activator, not a drug

In 2003, Konrad Howitz at Biomol screened compounds and found plant molecules that appeared to activate human SIRT1. The two labs spent about six months trying to disprove it, because true allosteric activators are rare. What convinced Sinclair was that the molecules extended yeast lifespan only when the sirtuin gene was present. Even so, he calls resveratrol 'a terrible molecule' because it dissolves so poorly.

• Mouse results depended on diet and absorption

In his 2006 study, middle-aged mice on a high-fat, high-sugar 'Western' diet given resveratrol (about 200 mg/kg/day, by his recollection) lived roughly 20–25% longer than equally fed controls. The NIA's Interventions Testing Program later found no lifespan extension with resveratrol mixed into standard chow, which Sinclair says matches his own data and reflects absorption. He says fat improved blood levels in his studies, so he takes it with oil or yogurt.

• His personal regimen comes with explicit uncertainty

Sinclair takes about a gram of resveratrol, reasoning that if it doesn't work at a gram it won't work at more. He also takes metformin at a low dose because the pathways overlap and stacking compounds is 'unknown territory', plus NMN. He doubts resveratrol will add even five years to his life, but believes it may delay cardiovascular disease.

• Aging as loss of analog information

Sinclair previewed an unpublished 'unifying theory'. DNA is digital and stays largely intact in old animals, he says, while the epigenetic pattern of which genes are switched on is analog and degrades like a scratched CD. Using Waddington's 1950s landscape, he describes cells as marbles jostled out of their valleys until neurons and liver cells lose their identity. His lab was writing up experiments in which manipulating the epigenome produces hallmarks of aging.

• Old eggs may suffer from low NAD

Sinclair links egg aneuploidy to faulty spindles. He describes a kinase that controls spindle quality, regulated by the NAD-dependent sirtuin SIRT2, and says giving NAD precursors to older mice produced healthier, more numerous eggs. Whether this applies to sperm is untested. This is mouse work, not a human fertility treatment.

EXAMPLES

• The 10-gram resveratrol trials

Worried about poor absorption, clinical researchers dosed people at about 10 grams a day. A couple of late-stage cancer patients developed kidney failure, which Sinclair notes happens anyway in such patients, but the company decided it wasn't worth pursuing for a would-be blockbuster.

• Starting at the equivalent of age 70

Sinclair says unpublished work from his lab extends mouse lifespan even when treatment begins after 600 days, roughly 70% of the way through life, and hinted that NMN given in drinking water to normal mice was involved.

• The 5,000-person trial he'd fund

With unlimited money, Sinclair would give metformin, rapalogs or NAD precursors to about 5,000 people in their 70s for three to four years and look for a change in the mortality hazard ratio. He puts the cost in the tens of millions against potential savings in the trillions. Attia compares the design to Nir Barzilai's metformin (TAME) trial, which focuses more on healthspan.

• A grandmother who never lied

Sinclair traces his focus on mortality to his grandmother Vera (who insisted on being called by her first name) answering his childhood question honestly: everyone he loved, his cat and he himself would die. He notes that children typically grasp death between four and seven, then bury the thought until around 50.

OTHER RELEVANT

- **Products using Sinclair's name aren't endorsed by him**

  He says nothing sold over the counter carries his name with his or Harvard's permission, and that he has sent many cease-and-desist letters. Be skeptical of supplements marketed with his name.

- **Don't megadose B3 to boost NAD**

  Because nicotinamide inhibits sirtuins through feedback, Sinclair advises against very high doses. Precursors like NR and NMN, he says, are still early, and we don't yet know which tissues take them up preferentially.

- **Introduce compounds one at a time**

  Following Sinclair's caution about overlapping pathways, if you combine metformin, resveratrol or NAD precursors with your doctor's oversight, start low and add one thing at a time rather than stacking full doses.

#30 – Thomas Seyfried, Ph.D.: Controversial discussion—cancer as a mitochondrial metabolic disease?

Guest: Thomas Seyfried
Date: 2020-01-06 · Duration: 2:48:21
URL: https://www.youtube.com/watch?v=6PJfOFTaYow

KEYPOINTS

• Seyfried argues cancer is primarily a mitochondrial metabolic disease, not a genetic one

Following Otto Warburg, Seyfried, a Boston College professor, says there is 'only one primary cause' of cancer: chronic damage to cellular respiration. Mutations are downstream effects. Peter frames the episode as controversial and repeatedly presses for experiments that could settle it. Seyfried notes estimates that only about 5–6% of cancers stem from inherited germline mutations.

• His interest in cancer grew out of epilepsy research and calorie restriction

At Yale, Seyfried studied glycolipids, epilepsy and lipid storage diseases, and an internal grant to study ketogenic diets was rejected. Years later, a student pointed him to a ketogenic diet meeting connected to Jim Abrahams' Charlie Foundation. In his mouse work, seizure control and tumor shrinkage tracked with calorie restriction: lower blood sugar plus higher ketones. He says children on ketogenic diets can get breakthrough seizures when blood sugar spikes, a visible signal that tumors don't give.

• Seyfried says the 'Warburg effect' everyone cites is only the secondary feature

Warburg saw tumor slices produce lactic acid even in 100% oxygen. He concluded respiration was defective, so cells had to ferment. Seyfried says Warburg himself called aerobic glycolysis a secondary, environment-dependent phenomenon. He argues that cell-culture findings of 'normal' oxygen uptake mislead, because uptake in tumor cells is uncoupled from ATP production.

• His proposed 'missing link' is mitochondrial substrate-level phosphorylation fueled by glutamine

Substrate-level phosphorylation makes ATP by moving a phosphate directly from a molecule onto ADP, for example at the succinyl-CoA step of the TCA cycle, without the electron transport chain. Seyfried argues most cancer ATP comes from this pathway inside the mitochondria, driven by glutamine, with glucose fermentation in the cytoplasm. The heart can do this briefly under stress, he says, but normal cells can't sustain it. Warburg couldn't have known about it.

• He points to structural defects: abnormal cristae and cardiolipin

Seyfried says cardiolipin, the signature lipid of the inner mitochondrial membrane, has been abnormal in every tumor his lab has examined. He cites Peter Pedersen's lifetime of work showing abnormal mitochondria and accuses top journals of ignoring it. He compares this to the Church refusing to look through Galileo's telescope. Peter pushes back that this looks like a stalemate between bodies of literature and calls for collaborative new experiments.

• Metastasis may come from macrophage–cancer cell fusion

Seyfried cites early observations of tumor cells fusing with immune cells and becoming more aggressive. He also cites John Pawelek's Yale work suggesting malignant melanoma behaves like a macrophage. He offers this as why some plant tumors with damaged respiration never metastasize: plants have no immune system.

• His 'press-pulse' strategy: press glucose, pulse glutamine

Press means steadily lowering glucose with a calorie-restricted ketogenic diet, drugs, and stress reduction, since anxiety raises corticosteroids and blood sugar. Pulse means intermittently targeting glutamine, with DON (6-diazo-5-oxo-L-norleucine) working best in his hands. It is pulsed because T cells, macrophages and other immune cells also depend on glutamine and are needed to clear dead tumor cells. He also proposes hyperbaric oxygen at about 2.5 atmospheres as an oxidative-stress 'pulse' to replace radiation.

• The 'therapeutic ketosis' target is a glucose-ketone index near 1.0 or below

His group published the GKI, a ratio of blood glucose to ketones. He adds that in his experience women reach the target more easily than men, and that Dom D'Agostino's ketone supplementation can help.

• Seyfried claims a 50% drop in cancer deaths within 10 years, and Peter calls it bold

Seyfried says stopping 'half of the stuff we're doing' and treating cancer by its metabolism could cut deaths by more than 50%. Peter notes age-adjusted mortality had fallen only about 3% in 50 years by his figure. His dream trial adds the missing arm: metabolic therapy without standard of care, compared against standard care alone and standard care plus metabolic therapy. Peter notes a practical barrier: GBM usually presents with mass effect that requires urgent surgery or steroids.

EXAMPLES

• Peter's near-blackout at Stanford

After three years on a ketogenic diet, Peter underwent an insulin suppression test, which in roughly 400 non-diabetic subjects had produced steady-state glucose no lower than about 79 mg/dL. Peter's glucose fell to about 31, and his ketones dropped from about 2.5–3 mM to under 1. He drenched in sweat, nearly seized, and the IV dextrose infiltrated his arm. His wife didn't even know he'd flown there.

• Sequencing tumors with no pathogenic mutations

Seyfried says his lab sequenced the whole genomes of five independently derived mouse cancers and found no pathogenic mutations. He uses this to argue cancer can exist without driver mutations.

• Mouse fasting isn't human fasting

Mouse metabolism runs about seven to eight times faster. One day of water-only fasting in a mouse roughly equals seven days in a human, and 35–40% calorie restriction in mice approximates therapeutic water fasting in humans.

• A GBM case and radiation necrosis

A glioblastoma patient in a published case report spent three weeks in therapeutic ketosis before debulking surgery and deferred standard care for three months. He lived 30 months, far longer than typical, but at his death the tissue showed radiation necrosis rather than tumor. Seyfried argues against brain radiation. He also cites Andrew Scarborough, a stage 3 astrocytoma patient who refused radiation and chemotherapy, and admits these are anecdotes.

• Avastin in brain cancer

Seyfried calls the roughly $100,000-a-year anti-angiogenic drug 'despicable' for GBM. He argues starving vessels worsens hypoxia, which fermenting cells tolerate, so scans look better while survival stays 'abysmal.' He says GBM survival resembles the 1926 Bailey and Cushing paper.

OTHER RELEVANT

• Don't try extreme glucose lowering alone

Seyfried insists 'our goal is to kill the tumor cells,' not ourselves. Drugs must be used strategically by people who know what they're doing. Peter's hypoglycemic episode shows the danger.

• Treat this as a hypothesis awaiting trials

Peter's stance throughout is curiosity plus a demand for rigorous head-to-head trials. The only setting where mainstream medicine accepts ketogenic diets as legitimate first-line therapy is drug-resistant epilepsy.

• Question both camps' evidence

Seyfried notes that up to 50% of papers in top journals can't be reproduced. Peter counters that both sides can explain away each other's data, which is why new collaborative experiments matter.

#29–Apolo Ohno: Olympic medalist—extreme training, discipline, pursuing perfection, and adversity

Guest: Apolo Ohno
Date: 2020-01-06 · Duration: 3:38:29
URL: https://www.youtube.com/watch?v=kx2j8l-QZ5g

KEYPOINTS

• Apolo Ohno won eight Olympic medals across 2002, 2006, and 2010 in short-track.
Short-track's chaos—packs, blades, instantaneous DQ risk—made his results a masterclass in controlled aggression. Peter stacks race video in the show notes because the sport's violence and precision are hard to grasp from stats alone. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• A single immigrant father raised him with intense, detailed involvement.
Not a vague 'dad believed in me' slogan: logistics, standards, and emotional weather through wins and public controversies. That partnership is central to how Apolo understands drive. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Early talent stopped being enough; then the switch flipped to monastic work.
He coasted on gifts until he chose all-in discipline—training routines so extreme peers still trade the videos. Once flipped, work ethic became the identity, not a mood. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Passing rules put a huge onus on the overtaking skater.
At the time, contact while passing could DQ the passer even when packs compress. That rule set rewards spatial IQ and patience as much as raw lap speed. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Salt Lake 2002 at 19, post-9/11, delivered his first Olympic medal (silver).
The home Games pressure cooker included rival rumors—Korean teams joking about NASA-grade tech—because they could not parse his race craft. First-medal night locked the loop between preparation and podium. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Mental training was as programmed as intervals.
Meditation, breathing, written positive self-talk, visualization: tools he treated as trainable skills. Sport psychology was not an accessory; it was how he entered the start gate. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Cross-training fame (Dancing with the Stars win) showed the same switch.
Peter and Apolo laugh that DWTS did not make the episode despite dinner stories—yet it proved the identical obsessiveness transfers when the arena changes. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Adversity public and private forged selective toughness.
Judging controversies, injuries, and the loneliness of travel forced a thicker skin without fully hardening him against coaching and fatherly feedback. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Inline-to-ice and short-vs-long track transitions taught skill transfer limits.
Some engines carry; some techniques fight you. Apolo's career is a case study in what to keep and what to rebuild when the surface changes. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Perfectionism is fuel until it becomes poison—he learned to steer it.
The same trait that polished technique could also spike anxiety. Structured mental skills kept perfectionism pointed at process cues rather than at identity annihilation after a bad heat. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

EXAMPLES

• Eight medals, three Games
Longevity at the top of a sport that ends many careers with one crash. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• First medal: Salt Lake silver at 19
Home Olympics, geopolitical emotional load, arrival on the biggest stage. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Clean-pass DQ rule pressure
Spatial discipline as a scoring skill, not merely etiquette. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Father as high-resolution coach-partner
Immigrant single dad logistics as competitive advantage and emotional complexity. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

• Visualization + breath stack
Documented mental routine parallel to physical periodization. The conversation keeps returning to concrete mechanisms and

lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.

OTHER RELEVANT

- **Flip the work-ethic switch before talent plateaus in public.**
  Apolo's career hinged on choosing monastic training while medals were still optional. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Train the mind with the same calendar seriousness as intervals.**
  Breath, visualization, and self-talk are reps, not posters. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Know the rulebook that decides your sport's fairness.**
  Short-track passing law is a metaphor: constraints define excellence. The conversation keeps returning to concrete mechanisms and lived examples so readers can carry the idea into Monday decisions without needing the full multi-hour listen.
- **Aim perfectionism at cues, not at your worth.**
  Process goals survive bad races; identity goals shatter.

#22 – Tom Dayspring Part III of V: reverse cholesterol transport, CETP inhibitors, & apolipoproteins

Guest: Thomas Dayspring
Date: 2020-01-01 · Duration: 1:04:19
URL: https://www.youtube.com/watch?v=3ZWLxElxIBg

KEYPOINTS

• Most cholesterol is made by peripheral cells, and it has to get out

Dayspring says the liver makes only about 20% of the body's cholesterol. The rest is made by cells throughout the body. A cell that accumulates too much must export it or die. Cells push free cholesterol out through transporters such as ABCA1 to apoA-I, the HDL protein. Lipid-poor 'baby' HDL particles are especially good at picking it up. Attia says that of all seven hours with Dayspring, he learned the most from the HDL and CETP discussions.

• Reverse cholesterol transport has more than one route

HDL can deliver cholesterol directly to the liver, small intestine, adrenal glands, ovaries or testes. It can also hand cholesterol to apoB particles via CETP (cholesteryl ester transfer protein), and the liver then clears those through LDL receptors. Red blood cells and albumin (one albumin molecule can carry up to 17 cholesterol molecules) also move cholesterol. Even excretion is leaky: the gut reabsorbs about 90–95% of bile salts.

• Remnants are cleared by apoE; LDL lingers

As VLDL and chylomicrons lose their core triglycerides, they become remnants. Dayspring compares it to being 'a remnant of my former self' after losing an arm. Remnants carry apoE, which binds both LDL receptors and LDL-receptor-related proteins, so they are cleared quickly. LDL relies on apoB-100 alone, so it can 'hang around forever' until an LDL receptor clears it. Some people carry more apoE on their LDLs.

• ApoC-III makes particles more atherogenic

An LDL particle that carries apoC-III is 'intensely more atherogenic' than one with apoB-100 alone, because apoC-III impairs clearance. Drugs targeting apoC-III were in development at a San Diego company. Dayspring considers triglycerides above about 130 mg/dL a sign of a problem.

• In insulin resistance, most of the added apoB comes from LDL

When triglycerides rise, VLDL particle numbers can double or triple, for example from 30 to 90 nmol/L. Because LDL starts from a much higher base (about 1,000 rising to 3,000 in the example given), the extra 300–400 nmol/L of LDL dominates the risk. A big relative change in VLDL can be a small share of the total apoB.

• VLDL-C is a crude marker

Dayspring once estimated VLDL remnants with VLDL cholesterol. He now calls it 'a very crude estimation that's almost useless', which he says annoys his lipid colleagues. He still tells patients to aim for VLDL-C under 15 mg/dL when nothing better is available.

• 'Good cholesterol' is a misnomer

HDL can transfer its cholesteryl ester to an LDL particle (about 95% of apoB particles are LDL). That LDL can end up in a macrophage in the artery wall. HDL particles also swap lipids with each other. Dayspring tells doctors that calling HDL-C 'good cholesterol' is 'mis-educating patients'.

• Low HDL-C is mostly a proxy for high apoB

In the Framingham-era data, low HDL-C and high triglycerides travel with very high apoB in almost everyone not on drugs or a strict diet. Dayspring says that if those studies had adjusted for apoB or LDL particle number, which they couldn't, low HDL-C would likely disappear as an independent risk factor. Insulin-resistant patients' disease is ultimately apoB-driven.

• HDL-C doesn't tell you whether HDL is working

Low HDL-C could mean poor pickup of cholesterol or fast delivery of it. High HDL-C could mean good pickup or a failure to drop cholesterol off. HDL particles carry about 200 identified proteins, and their protein and phospholipid signatures likely matter more than their cholesterol content. Functional HDL assays are still largely research tools.

EXAMPLES

• ApoA-I Milano

People in a small northern Italian village had HDL-C of only 5–10 mg/dL yet lived long lives, which contradicts Framingham's 'low HDL, you're out of here'. Their variant apoA-I was highly functional at moving cholesterol. Infusions based on it showed better-looking arteries on imaging, but Dayspring warns there are '217 ways to be fooled by an angiogram'.

• Torcetrapib's sudden end

Attia was at a 2006 meeting in San Francisco, sure the CETP inhibitor would succeed and send Pfizer stock soaring. At 11:30 that night he saw that Pfizer had terminated torcetrapib. Later CETP inhibitors raised HDL-C anywhere from 20–30% to 80–100%, without the expected benefit.

• Mendelian randomisation

Around 2010–2011, genetic studies showed that variants raising HDL-C don't protect against heart disease. That confirmed what the failed CETP trials suggested, but the drugs had been developed long before that data existed.

• A CETP inhibitor that worked, but won't be sold

One trial was stopped for futility. Merck continued its own large trial and showed a benefit. But Merck decided not to market the drug because it stays in the body for years. It still isn't clear why one CETP inhibitor works and another doesn't.

• Very high HDL-C as a warning

Dayspring had shared a case with unusually high HDL-C. Dayspring notes that oversized HDL particles may fail to bind the proteins they should carry. Treatment in such cases still comes down to lowering apoB.

OTHER RELEVANT

- **Focus on apoB, not HDL-C**
  For risk assessment and treatment, apoB or LDL particle number is the target. HDL-C should not reassure or alarm you on its own.
- **Use triglycerides as a metabolic clue**
  Triglycerides above about 130 mg/dL, especially with low HDL-C, suggest insulin resistance and rising apoB, a prompt to address diet and metabolism.
- **Be cautious about 'HDL-raising' claims**
  Raising HDL-C with drugs hasn't reliably reduced events. Judge any therapy by hard outcomes, not by HDL numbers or angiogram images. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't drop a good drug over a few bad signals**
  Using Vioxx's withdrawal as the example, they argue that restricting a drug for everyone because of risk in a small subgroup deprives many patients. Better to identify who is at risk.

#20 – Tom Dayspring, M.D., FACP, FNLA – Part I of V: an introduction to lipidology

Guest: Thomas Dayspring
Date: 2020-01-01 · Duration: 1:14:35
URL: https://www.youtube.com/watch?v=PllTHYgWpuw

KEYPOINTS

• Attia calls Dayspring 'the mentor to the mentors' in lipidology

This first part of a roughly seven-hour, five-part conversation introduces Dayspring. He practised internal medicine in New Jersey for just under 40 years, has given about 4,000 lectures including over 600 accredited medical-education programmes, and received the National Lipid Association's 2011 President's Award. Attia calls him his single most important clinical mentor and 'a national treasure'. This episode is the gentler warm-up before the technical parts.

• At 72, Dayspring lost 67 pounds in 11 months with monthly low-calorie weeks

Dayspring had lived for years with obesity, insulin resistance, fatty liver, gallbladder removal, a hip replacement and several spinal surgeries. After watching a talk Attia gave at MIT on longevity, he took on Attia's modified fast: one week a month of 700 calories or less with significant carbohydrate restriction. Attia's colleague Nicole helped plan the meals. Dayspring says days two and three were the hardest. Eleven months later he was 67 pounds lighter.

• His lab report went from red and yellow to all green

Working for a lab company, Dayspring tests nearly every cardiometabolic marker on himself. A report that was largely yellow and red a year earlier was 100% green. He also feels his orthopaedic symptoms are about 90–95% better. He can walk to dinner, where a year before he had to stop after a short block. He suspects the fasting did more than weight loss alone, but offers this as personal experience.

• Fear of cognitive decline was a big motivator

Dayspring says his biggest worry was cognitive impairment as he aged, with fatty liver and other problems 'sneaking up'. Seeing 'the light at the end of the tunnel', with US average life expectancy around 80, plus wanting to be around for his son, turned years of ambivalence into an all-in switch. Attia notes that once Dayspring commits to something, he never wavers.

• Coronary care has changed dramatically since the 1970s

As a resident in a 700-bed hospital, Dayspring might admit a dozen coronary care patients in one night. He saw transmural heart attacks with Q waves and pulmonary oedema, and patients 'dropping dead before your eyes'. A 50-50 survival chance was common. Attia's concierge-practice colleague says he can't remember his last Q-wave heart attack. Dayspring still believes early prevention could all but end the disease.

• He taught himself lipidology over a decade

Frustrated by middle-of-the-night heart attack calls, Dayspring moved into prevention: smoking, weight and aggressive blood-pressure control. After trials such as Framingham and MRFIT pointed to cholesterol, he says it took about 10 years of serious reading, often not understanding what he'd read for the first five, before it 'all made sense'. Early influences included Dan Rader, Virgil Brown, Allan Sniderman and Ron Krauss.

• His diagrams made complex lipid biology teachable

Dayspring says he can't draw a person beyond a stick figure, but he learned to build detailed, animated lipoprotein diagrams in PowerPoint. Attia, who learned PowerPoint at McKinsey, assumed a professional illustrator made them. Dayspring also wrote Lipidaholics Anonymous, a free weekly newsletter of real case discussions read by several thousand people. He jokes that what he wrote in 2002 is 'mostly all wrong' now.

• Facts have half-lives, including 'high HDL is good'

Attia contrasts very long-lived facts, like a round Earth, with the Framingham-era belief that high HDL cholesterol is protective, which he now calls grossly oversimplified and possibly incorrect. Dayspring goes further: no one should judge cardiovascular risk from HDL cholesterol or think raising it achieves anything. He considers it worth listing only for calculations like non-HDL cholesterol.

• Lipoproteins mainly carry energy and phospholipids, not cholesterol

Dayspring stresses that almost every cell makes all the cholesterol it needs. The bigger problem is cells making too much, which can crystallise and kill them, so cells have powerful ways to export it. Lipoproteins mostly deliver triglycerides, fatty acids for fuel, to muscle or for storage in fat cells. They also deliver phospholipids, which make up their outer shells.

EXAMPLES

• Phospholipids: the overlooked lipid

Lipids are water-insoluble molecules. Triglycerides are three fatty acids on a glycerol backbone. Phospholipids have two fatty acids plus a phosphorus-containing head that is water-friendly, which lets them form both lipoprotein surfaces and cell membranes. Most are made in the liver and small intestine. Dayspring calls them the glyceride nobody looks at.

• Shrinking 'dump trucks' feed HDL

Large chylomicrons from the gut and VLDL from the liver have the most surface area. When lipoprotein lipase in muscle and fat strips their triglycerides, the particles shrink and shed surface phospholipids. Phospholipid transfer protein hands those to cells or to immature apoA-I particles, helping them grow into large HDL.

• Fat structure shapes cell membranes

Attia explains that saturated fatty acids have no double bonds, monounsaturated have one and polyunsaturated have two or more. Dayspring adds that straight saturated chains make membranes rigid, while multiple double bonds take up space. That changes 'lipid rafts', the membrane zones where receptors such as the LDL receptor can sit, and he expects it to explain much of HDL function.

• Paterson firefighting and a 1962 Rangers game

The son of a Paterson, New Jersey fire chief, Dayspring built one of the most-visited historical fire department websites in the

US and a large collection of firefighting antiques. A high-school friend took him to the old Madison Square Garden around 1962, where the bright ice and helmetless New York Rangers turned him into a lifelong hockey fan.

OTHER RELEVANT

- **Don't judge heart risk by HDL cholesterol**
  Both men treat HDL-C as an outdated measure; later episodes focus on particle number and HDL function.
- **It's never too late to start**
  Dayspring's transformation at 71–72 came after decades of ignoring his own risk. He credits support from his wife, who prepared meals, and Attia's team.
- **Learn visually**
  Dayspring's own method, drawing what you read, is offered as a way into dense subjects; his diagrams are shared on Twitter at @Drlipid.

#21 – Tom Dayspring, M.D., FACP, FNLA – Part II of V: Lipid metrics and cholesterol regulation

Guest: Tom Dayspring
Date: 2020-01-01 · Duration: 1:27:02
URL: https://www.youtube.com/watch?v=bQCXbtvZrhY

KEYPOINTS

• Lipids do not float free in plasma—they ride inside lipoproteins.
Dayspring credits physicist John Gofman (the transcript sometimes says 'Hoffman') with mid-century ultracentrifuge work showing hydrophobic lipids must be packaged. Learn that first, he says, or every later cholesterol debate will be confused. Plasma is water; triglycerides and cholesteryl esters are not. Without apolipoproteins and phospholipid coats, the cargo would oil-slick out of solution.

• There are separate lipoprotein lineages, not one maturation ladder.
You do not climb chylomicron !' VLDL !' IDL !' LDL !' HDL as a single sequence. Chylomicrons are gut-derived triglyceride carriers; VLDL/LDL are liver-apoB lineage; HDL is its own system. Mixing those stories produces nonsense clinical advice. Dayspring is emphatic about that semantic hygiene because patients hear 'LDL turns into HDL' folklore that no pathway diagram supports.

• LDL-C measures cholesterol cargo; LDL-P / apoB count the ships.
A 'direct LDL-C' assay quantifies cholesterol inside LDL particles. NMR LDL-P reports particle concentration in nmol/L. ApoB counts apoB-containing particles. Discordance—low cholesterol per particle but high particle number—is exactly where risk hides from a standard panel. When particles are cholesterol-poor but numerous—common in insulin resistance—LDL-C underestimates risk and apoB corrects it.

• Ultracentrifugation is the conceptual gold standard almost nobody uses clinically.
Separating fractions and measuring cholesterol in each is too slow for routine care, so chemistry assays and NMR shortcuts evolved. Framingham-era HDL assays were an early practical win; modern NMR still cannot perfectly distinguish a huge chylomicron from a huge VLDL by size alone. Chemists built direct assays precisely because nobody could centrifuge every patient sample the way research labs once did.

• Sterol vocabulary matters: cholesterol, stanols, zoosterols, phytosterols.
Cholesterol has a double bond at carbons 5–6 and a hydroxyl at carbon 3. Saturating that bond yields a stanol. Plant foods bring dozens of phytosterols (campesterol, stigmasterol, and others). Those markers help sort synthesis vs absorption stories in advanced testing. Mislabeling a stanol as cholesterol on a slide is the kind of error that still shows up in papers Dayspring referees, which is why he drills structure.

• ABC transporters move sterols in and out of cells and gut lumen.
ABCA1 helps seed nascent HDL; ABCG5/G8 efflux sterols (including plant sterols) back into the gut. People vary widely in sterol absorption—Dayspring cites ranges from modest (~20%) to very high (reports into the 60%+ range)—so the same diet is not the same internal exposure. If ABCG5/G8 is sluggish, phytosterols accumulate; sitosterolemia is the extreme teaching case for why efflux genes matter.

• The brain makes its own cholesterol; plasma LDL is not its delivery truck.
Neurons and glia synthesize what they need behind the blood–brain barrier. That fact reframes why crashing plasma LDL pharmacologically is not the same as starving the CNS of cholesterol. That disconnect also explains why neurologic fear-mongering about 'low cholesterol starving the brain' usually misunderstands compartmentalization.

• Acute illness wrecks a lipid panel's meaning.
Peter noticed HDL plunging in ICU patients under extreme stress and kept rechecking it. Inflammatory and metabolic shifts move lipids transiently—so never make chronic risk decisions off an admission panel. Steroidogenic tissues still need cholesterol for hormones, but an ICU draw is the wrong moment to invent a lifelong HDL deficiency story.

• Cholesterol synthesis pathways (Bloch / Kandutsch–Russell) are not trivia.
Multiple routes and crossovers exist; cells still end at the cholesterol molecule they need. Understanding synthesis vs absorption helps interpret precursor sterols on advanced panels and why some drugs hit production while others hit gut uptake. Nobel politics aside (Bloch/Lynen vs later pathway workers), clinicians mainly need to know production and absorption can be independently high or low.

• This Part II is the 101 before later clinical application episodes.
Dayspring is one of Peter's core lipid mentors. The episode deliberately stays on structure, measurement, and vocabulary so later talks about residual risk, remnants, and therapy have a shared language. Listeners should treat this installment as vocabulary bootcamp before Parts III–V get more applied.

EXAMPLES

• Gofman ultracentrifuge insight
A physicist's centrifuge work reframed plasma 'fat' as organized lipoprotein particles—foundation for everything that followed in lipidology. Once you see lipids as passengers, 'cholesterol in my blood' stops sounding like dissolved grease and starts sounding like traffic counting.

• LDL-C vs LDL-P discordance
Same person can look fine on cholesterol concentration and be high-risk on particle number; NMR/apoB resolve that. Peter returns to this distinction constantly with patients who were told their LDL was 'fine' on an outdated panel.

• Phytosterol panel as absorption clue
Elevated plant sterols suggest hyper-absorption phenotypes that diet and ezetimibe-class strategies target differently than pure over-producers. Pair them with triglycerides and HDL to see the whole remodeling neighborhood, not a single villain molecule.

- **ICU HDL collapse**
  Peter's repeated inpatient observations: severe stress acutely tanks HDL—another reason timing of labs matters. Inflammatory cytokines and altered CETP activity are among the plausible acute movers.
- **ABCG5/G8 efflux**
  Pumping sterols back into the gut lumen is a major, not minor, pathway—and a big source of person-to-person variability. Combined with ABCA1's role launching nascent HDL, transporter talk becomes clinical rather than alphabet soup.

OTHER RELEVANT

- **Ask for apoB or LDL-P when stakes are high.**
  If family history, diabetes, or surprising events exist, cargo-only LDL-C is not enough. Guidelines have been moving this direction for years; Dayspring was early and loud about it.
- **Do not interpret lipids drawn during acute illness.**
  Wait until the inflammatory storm settles before rewriting a prevention plan. Recheck fasting lipids weeks after recovery when you need numbers for prevention.
- **Learn lineage before supplements and internet protocols.**
  Chylomicron vs VLDL vs HDL confusion is how people mis-blame 'cholesterol' for triglyceride problems and vice versa. If a thread cannot say which particle lineage it means, ignore the protocol.
- **Match therapy to synthesis vs absorption phenotype when data exist.**
  Advanced sterol markers plus apoB give a clearer lever than total cholesterol folklore. Hyper-absorbers and hyper-producers are not moral categories—they are levers.

#19 – Dave Feldman: stress testing the lipid energy model

Guest: Dave Feldman
Date: 2020-01-01 · Duration: 3:10:33
URL: https://www.youtube.com/watch?v=kRxeyaNWmHw

KEYPOINTS

• Peter opens already mostly unconvinced by Dave's lipid-energy model.
He estimates he entered ~20% open to being persuaded and left unconvinced. His null hypothesis remains the lipid/apoB causal framework, even while granting Dave's n-of-1 experiments are interesting and technically earnest. He repeatedly separates respect for Dave's curiosity from assent to Dave's clinical conclusions.

• Dave's personal 'catharsis' was a late-2015 lipid spike on low-carb.
About seven and a half months into the pattern, total cholesterol hit roughly 329 mg/dL with LDL-C around 200–250. That shock launched the software engineer into systematic self-experimentation and the 'cholesterol code' public project. Friends on similar diets had milder moves; Dave's magnitude made denial impossible and launched the public 'drop roll call' community.

• Lean mass hyper-responders are the phenotype under debate.
Lean people on ketogenic/low-carb diets who show very high LDL-C/LDL-P with high HDL and low triglycerides. Dave hypothesizes energy trafficking via lipoproteins explains the rise; Peter doubts the triglyceride-export math can account for the extra cholesterol mass and particle counts. Peter also argues that even garden-variety type 2 diabetes does not generate the LDL burden people casually attribute to 'energy delivery,' weakening the model's scaling claim.

• Inversion experiments: huge dietary fat can drop LDL short-term.
Dave reports multi-day high-fat runs where LDL-C fell ~73% and LDL-P dropped on the order of ~1,000+ nmol/L in three days. Peter finds the phenomenology striking but insufficient to overturn chronic risk models built on apoB exposure over years. If fat influx acutely lowers measured LDL, Dave reads that as particles being used; Peter reads it as an acute redistribution that still fails the decades-long apoB risk literature.

• Mass balance is Peter's first objection.
Where does the extra cholesterol in all those LDL particles come from if not synthesis or delayed clearance? Without a closed account of cholesterol flux, the energy model feels incomplete to him—even if Dave later refined answers after the taping. Until synthesis, absorption, and clearance are quantified together, a storytelling model remains a hypothesis.

• Genetic FH lessons cut against 'exclude my phenotype' special pleading.
Peter notes ~2,000 vaguely identified genetic routes to familial hypercholesterolemia phenotypes. He is unwilling to throw out that causal body of evidence for a low-carb subgroup that has not yet shown clean outcome data. Excluding those mutations from the debate because they are 'genetic' while treating diet-induced highs as a different species of LDL is, to Peter, special pleading.

• PCSK9 and receptor biology still dominate his clinical priors.
Even on max-dose atorvastatin (80 mg), some patients need more particle-lowering. PCSK9-related FH subsets (~3–5% in his framing) and receptor pathway genetics keep him anchored to apoB reduction as the lever with outcome trials. Fourier and ODYSSEY-type PCSK9 outcome data sit in the background of that prior even when cost-effectiveness is a separate argument.

• Dave wants atherosclerosis imaging and more stratified cohorts.
He argues trouble should show up as rising CAC or carotid intima-media thickness before panic, and that studies stratifying high HDL/low TG alongside high vs low LDL-C are the fair test. Peter agrees better data would help while refusing to treat absence of powered studies as reassurance. Dave grants imaging lag and noise; Peter answers that waiting for plaque to prove a hypothesis is a harsh experiment to run on yourself.

• Composition experiments (SFA cuts, mono swaps) are practical middle ground.
In one early case with Tom Dayspring, a keto loyalist with extreme LDL-P was urged to cut saturated fat toward ~25 g/day and lean on mono sources (olive oil, macadamia)—hard to do without creeping carbs. Lipid-P moved; ideology was the obstacle. Olive-oil-and-macadamia thought experiments show how hard pure mono eating is at weight-stable calories without sneaking carbohydrate back in.

• Remnants, oxidized LDL, and kinetics remain measurement gaps.
Both admit clinical labs poorly resolve true remnant particles without apoC-III-aware methods, and oxidized LDL assays are imperfect. Those gaps cut both ways: they limit Dave's reassurance and Peter's mechanistic certainty in any single blood draw. Better assays would help both men; they would not, by themselves, rewrite Mendelian and trial evidence favoring lower apoB.

EXAMPLES

• November 2015 panel: TC ~329
Dave's inflection point from curious low-carb eater to full-time lipid experimenter. From that lab printout came years of inversion diets, sterol panels, and public spreadsheets.

• Three-day fat load !' ~73% LDL-C drop
Inversion pattern central to his talks; Peter calls it interesting phenomenology, not outcome evidence. Directionality is clear in his logs even when exact assay ceilings (some LDL-P assays top out near 3,500) complicate extreme readings.

• Patient on 80 mg Lipitor still above particle goal
Peter's clinic reminder that max statin "` max apoB control for everyone. Add ezetimibe or PCSK9 inhibition when diet and statin leave residual particle risk.

• SFA ~25 g/day keto rescue attempt
Dayspring/Attia advice for a hyper-responder who refused to leave ketosis—diet composition as a lever inside the low-carb constraint. The case is an existence proof that composition changes can move LDL-P without abandoning low carb entirely.

• Quebec / stratified HDL-TG studies Dave cites
He wants bets settled by apoB-aware cohorts with high HDL and low triglycerides, not slogans. Peter would take the same

bet structure if apoB were measured and follow-up long enough—data he says still are not in.

OTHER RELEVANT

- **Keep apoB/LDL-P on the table even if you love low-carb.**
  Peter's closing posture: phenotype pride does not replace particle burden when lifetime risk is the question. High HDL and low triglycerides are good signs for insulin sensitivity; they are not a force field against apoB.
- **Use imaging as additional data, not a permission slip.**
  CAC/CIMT can inform urgency, but a zero CAC at 40 does not prove a 3,000 nmol/L LDL-P pattern is safe forever. Repeat imaging and lipids on a schedule; do not interpret one reassuring scan as a lifetime waiver.
- **If you stay keto with extreme LDL-P, change the fat composition.**
  Cut saturated fat hard, emphasize monos, recheck particles—before arguing on Twitter that causality is canceled. Recheck advanced lipids after 4–8 weeks of the swap before declaring victory or defeat.
- **Separate curiosity from clinical null hypotheses.**
  Dave's experiments are worth watching; they have not, in Peter's view, earned a new default for patient care. For clinicians, that means continuing to treat elevated apoB seriously in lean low-carb patients until outcome evidence says otherwise.

#24 – Tom Dayspring, M.D., FACP, FNLA – Part V of V: Lp(a), inflammation, oxLDL, remnants, and more

Guest: Tom Dayspring
Date: 2020-01-01 · Duration: 1:29:47
URL: https://www.youtube.com/watch?v=ttQY5J98Iok

KEYPOINTS

• Lp(a) is an LDL-like particle carrying an extra protein, apo(a), and the name matters.
Dayspring insists on saying 'little a', because Lp(A) with a capital A would point to apoA-I, the main protein on HDL. Lp(a) is an apoB particle with apolipoprotein(a) attached, and he calls it potentially highly atherogenic. He reminds listeners that it was covered in depth in an earlier episode and gives only a two-minute recap here.

• Measuring Lp(a) by mass is crude, and particle number is better.
Most labs report Lp(a) mass, the weight of the whole particle including cholesterol, triglycerides, phospholipids and proteins. Because the molecular weight of apo(a) varies so much between people, Dayspring calls mass a nearly useless metric unless it is very high. A particle count requires separating lipoproteins by electrophoresis and staining the Lp(a) band for apoB, which gives 'Lp(a)-P'. He stresses that this is not an NMR test, and discloses that he works for True Health Diagnostics, which owns the assay.

• Statins don't lower Lp(a), probably because apo(a) hides the receptor binding site.
Dayspring thinks LDL receptors are the main way Lp(a) is cleared. Statins increase LDL receptors, but those receptors grab ordinary LDL first, and apo(a) may hide the part of apoB that the receptor binds to. He also notes that Lp(a) levels are driven mainly by how much apo(a) the liver makes, not by clearance. So the real fix is blocking its production.

• Niacin and PCSK9 inhibitors lower Lp(a), but there is no outcome proof yet.
Niacin lowers Lp(a) by about 20%, and PCSK9 inhibitors lower it to varying degrees, but insurers won't cover a PCSK9 inhibitor for Lp(a). Any benefit could be credited to lowering LDL and remnants instead. Dayspring doesn't use niacin for this, though he notes Sam Tsimikas does. The decisive test will be an antisense drug from Ionis that blocks apo(a) production, then in phase 3 in high-Lp(a) patients who already had heart disease.

• Inflammation is 'necessary but not sufficient' for heart disease.
The anti-IL-1 drug showed fewer events but costs about $30,000 and slightly raised cancer risk, so Dayspring doubts it will ever be approved for routine prevention. Low-dose methotrexate and colchicine trials were still awaiting results. Attia argues that these drugs make sense only for patients whose problem is actually inflammation. Someone with low CRP and fibrinogen whose issue is high LDL particle number wouldn't benefit.

• The 'oxidized LDL' blood test measures something other than what its name suggests.
Truly oxidized LDL, the kind macrophages take in to become foam cells, forms inside the artery wall, not in plasma, which is full of antioxidants. The blood test detects aldehydes on apoB, a sign of 'minimally oxidized' particles, usually about 5% of the total. Dayspring uses it, myeloperoxidase (MPO), or preferably urinary F2-isoprostanes to flag a pro-oxidative state and to motivate changes in diet.

• Dayspring advises against relying on Lp-PLA2.
The FDA cleared it only for screening in primary prevention. Mendelian randomization shows its levels don't track outcomes, and two large trials that sharply suppressed Lp-PLA2 reduced no events. Attia and Dayspring have both largely stopped using MPO. Attia still finds Lp-PLA2 somewhat informative when Lp(a) is also high, and Dayspring explains why that pairing might matter inside the artery wall.

• ADMA and SDMA may give a window into endothelial function.
Both are byproducts of protein breakdown that reduce arginine available for making nitric oxide, so high levels suggest endothelial dysfunction. Dayspring notes that high homocysteine slows ADMA clearance, a plausible mechanism for homocysteine's link to heart disease. He would use these markers to push a borderline primary-prevention patient toward aggressive diet changes, or to justify more apoB lowering in someone already on maximal therapy.

• Remnants matter, but LDL particles still deliver most of the cholesterol.
VLDL particles are two to three times larger and carry more cholesterol each. LDL particles vastly outnumber them, though, so most cholesterol entering the artery wall is still LDL-delivered, 'a thousand guys versus one', as Dayspring puts it. Estimates of VLDL cholesterol, from triglycerides divided by five or non-HDL minus LDL cholesterol, often disagree and don't identify true remnants. All approved apoB-lowering drugs clear remnants too.

EXAMPLES

• An Lp(a)-heavy patient on a statin
One man had an LDL particle number of about 1,600 nmol/L, about 600 of which were Lp(a) particles. A statin only acts on the roughly 1,000 non-Lp(a) particles, so total particle number may fall less than expected.

• Earl, Dayspring's best friend
His high school friend in Paterson, New Jersey, took him to his first hockey game and became a firefighter. Despite high cholesterol and repeated invitations to come in for free care, Earl avoided doctors. He died of a sudden heart attack in his mid-50s while watching TV, and Dayspring calls it a needless death.

• Prescription EPA and omega-3 delivery forms
Dayspring says omega-3s lower apoB by about another 8–10%. He was expecting positive results from a prescription EPA trial on top of statins due that November. He points out that most supplements are esterified forms that need pancreatic enzymes to be absorbed, and that krill oil phospholipids carry only one omega-3 per molecule.

• JP and first principles
Attia recalls an engineering student who taught him to derive formulas rather than memorize them. Attia wrote only F = ma on his exam cheat sheet. He contrasts this with biology, where, as a physicist-turned-biologist once lamented, you keep getting out

of the bath to look up one more fact.

OTHER RELEVANT

- **Test red-blood-cell omega-3s, not plasma levels.**
  An RBC omega-3 index reflects about 60–90 days, much like A1c, while plasma levels reflect your last meal. Dayspring says Bill Harris might aim for about 14%. He says he has seen no data showing harm at high levels and doesn't know of omega-3s causing clotting problems, though he notes this would have to be tested.
- **Use oxidation markers to guide diet changes, not to justify drugs.**
  Since lowering apoB itself reduces inflammation, Dayspring treats oxidative markers mainly as a reason to push diet: carbohydrate restriction for insulin resistance, and fasting. Very high-risk patients, such as someone just out of bypass surgery, need both diet and medication from day one.
- **Don't put off checking your lipids.**
  Dayspring's point from Earl's story is that heart disease is the most delayable of the major killers. Many early deaths come from people never getting checked or being judged on the wrong metrics.

#23–Tom Dayspring Part IV of V: statins, Zetia, PCSK9 inhibitors, niacin, cholesterol & the brain

Guest: Tom Dayspring
Date: 2020-01-01 · Duration: 2:00:15
URL: https://www.youtube.com/watch?v=xJ6X81Gn83Y

KEYPOINTS

• Early cholesterol drugs proved that lowering cholesterol reduces events, and then the field fixated on cholesterol numbers.

Before statins there was immediate-release niacin, which most people couldn't tolerate, and an antibiotic that disrupted cholesterol recirculation through bile. Then came bile acid sequestrants, whose long outcome trial showed modest benefit. Dayspring calls the result a tragedy: for 20–30 years drug companies chased cholesterol numbers, including sequestrants' trivial one- or two-point rises in HDL cholesterol.

• Statins began with a fungus and were proven in patients with familial hypercholesterolemia.

Dayspring credits Japanese mycologist Akira Endo, who he says deserves a Nobel Prize. Lovastatin was approved in 1987. The first outcome trials enrolled people with LDL cholesterol around 180–190, likely familial hypercholesterolemia: Swedish heart-attack survivors on simvastatin, then Scottish men without prior events on pravastatin in the West of Scotland trial. Both cut events by about 25%, with Dayspring recalling a number needed to treat of roughly 40–50 for West of Scotland.

• Five-year trials underestimate a disease that develops over 50 years.

Attia credits Allan Sniderman for teaching him that lipid trials give a drug about five years to change the course of a disease that began at birth. Because statins work, it is now unethical to withhold them from high-risk patients. New drugs therefore get tested on top of statins, which, as both point out, raises the bar for showing benefit.

• Ezetimibe works in both the gut and the liver.

Dayspring explains that NPC1L1, the transporter ezetimibe blocks, sits on intestinal cells and on the liver's bile-facing surface, where the liver can reclaim cholesterol from bile. Blocking both drains liver cholesterol and switches on LDL receptor production through SREBP. Attia admits this weakens his habit of reserving ezetimibe for people who over-absorb cholesterol, though Dayspring says plant-sterol over-absorption still matters.

• Ezetimibe was hurt by trials that measured the wrong thing.

Dayspring says early imaging studies measured artery wall thickness (carotid IMT), which in his view was the wrong surrogate, and ignored the extra reductions in apoB, triglycerides and CRP. That led cardiologists to write the drug off. He also points to aortic stenosis trials that could test ezetimibe without a statin.

• PCSK9 inhibitors cut events even in patients who were already low.

Attia calls the FOURIER trial one of the most remarkable results in cardiovascular medicine. Patients on statins with an average LDL cholesterol of 92 mg/dL, around the 10th percentile of the Framingham population, still had fewer events with Repatha within about 2.2 years. Amgen's stock was hammered because the cost per life saved looked like $1 million or more. Attia stresses that this is a separate question from the science.

• Gemfibrozil has outcome data on its own, and its benefit tracked particle numbers.

The VA-HIT trial in veterans with heart disease, low HDL cholesterol and roughly normal LDL showed event reductions as large as any statin trial, despite only about a 1.5-point rise in HDL cholesterol. Dayspring says James Otvos's post hoc NMR analysis explained the benefit by lower LDL particle counts and higher HDL particle counts. Fenofibrate trials missed their primary endpoints, which he blames partly on many participants also taking statins.

• Dayspring regards niacin as having failed every rigorous test.

In the 1960s Coronary Drug Project, niacin did not improve its primary endpoint, mortality, and trended the wrong way. Other arms of that trial gave men estrogen, which triggered heart attacks, and thyroid hormone, which killed people. A follow-up a decade or more later claiming a mortality benefit is, he says, a post hoc analysis that 'would be laughed at' today. Later trials also failed, and insurers stopped paying.

• Statins and brain cholesterol: a subset of patients may be at risk.

The brain makes all its own cholesterol, mainly through the desmosterol pathway. Dayspring says blood desmosterol tracks spinal-fluid levels closely, and statins are the leading cause of suppressed desmosterol. Both stress that population data do not show statins causing dementia. Attia's concern is patients with unmeasurably low desmosterol, such as someone with LDL cholesterol of 40 and LDL particle number of 500.

EXAMPLES

• Statins and the blood-brain barrier

Lipophilic statins such as atorvastatin and simvastatin enter the brain more easily. Hydrophilic, liver-selective statins such as pravastatin and rosuvastatin need no transporters to enter the liver and have fewer drug interactions. Dayspring notes 5 mg of rosuvastatin is often enough, and pravastatin at 40–80 mg matched the roughly 25% event reduction in outcome trials.

• Fibrate drug interactions

Gemfibrozil raises statin levels and increases the risk of muscle inflammation and breakdown (myositis and rhabdomyolysis), which Dayspring says isn't seen with fenofibrate. Fenofibrate strengthens warfarin, so the warfarin dose has to come down. He prefers fenofibrate and notes it has evidence for small-vessel benefits.

• A $3,000 niacin bill

Attia had a patient billed about $3,000 for prescription extended-release niacin. Dayspring adds that cheap sustained-release niacin is the form with the most liver toxicity.

• Liver enzymes rising on ezetimibe

Attia has seen it at least four times: adding ezetimibe to a statin doubled transaminases, which returned to normal when it was stopped. Dayspring says no package insert calls for monitoring liver enzymes and the rise is inconsequential, but agrees the

decision is individual.

OTHER RELEVANT

- **Don't stop a statin because of creatine kinase (CK) levels alone.**
  Get a baseline first, since exercise and ethnicity can raise CK. Dayspring says stop for muscle aches or weakness, such as trouble getting out of a chair, not for a rise from 50 to 300. Attia still tends to switch to pravastatin if CK rises even without symptoms.
- **Make apoB or LDL particle number the target.**
  Dayspring would use whatever combination lowers apoB, for example a low-dose statin plus ezetimibe if sterol markers suggest over-absorption. He would rather do that than push one drug to its maximum dose.
- **Check whether you convert EPA to DHA.**
  Dayspring says DHA has the stronger effect on apoC-III and triglycerides, while EPA does more for apoB. He measures omega-3 levels, because some people on high-dose EPA don't make enough DHA.
- **Be wary of diets that send apoB soaring.**
  Dayspring warns that diets that raise LDL particle number sharply may be fine for two years. He questions keeping that up for 15 years in a young person, given that genetic and trial data consistently show apoB matters.

#18 – Richard Isaacson, M.D.: Alzheimer’s prevention

Guest: Richard Isaacson
Date: 2020-01-01 · Duration: 2:24:31
URL: https://www.youtube.com/watch?v=Vq_hAXQsB78

KEYPOINTS

• A clinical diagnosis of Alzheimer's is often wrong

Isaacson, who directs the Alzheimer's Prevention Clinic at Weill Cornell, explains that Alzheimer's has traditionally been diagnosed clinically: progressive short-term memory loss plus other changes that impair daily activities. It accounts for about 60–70% of dementia. Ordinary cognitive aging, such as misplacing keys or a word on the tip of the tongue, doesn't disrupt independent living. He cites a study in which 40% of patients clinically diagnosed with Alzheimer's, and receiving anti-amyloid drugs, had no amyloid in the brain.

• 'A-G-E': age, genetics, environment

Isaacson's mnemonic captures the constant tug of war between genes and environment. Age is the top risk factor. Genes such as APOE4, along with others, can make the disease unavoidable for some people despite doing everything right. For others, changing their environment changes how their genes play out.

• About one in three cases may be preventable, and delay matters too

Based on conservative population risk models, Isaacson says one in three Alzheimer's cases may be preventable. For the rest, the goal is delay of two, five, seven or 10 years, long enough that many people die of something else first. Attia frames it as optionality: getting the disease at 78 instead of 69 buys nine years in which much can change.

• APOE4 risk estimates have been revised down

Everyone inherits two APOE copies, making six combinations. About 55–60% of people are 3/3, the neutral baseline. Isaacson has seen only one or two 2/2 patients, a genotype carrying about 20% lower risk. 3/4 covers about 20–25% of the population, with risk once quoted as three to four times higher, now perhaps two. For 4/4, early-2010s literature said about 25-fold. Recent papers say eight to 10-fold, which Isaacson believes overestimates the risk, and Attia unofficially guesses four to six times. Two copies don't guarantee the disease.

• Women may be in the 'express lane' because of menopause

Attia doubts that women's higher risk is explained only by living longer. Isaacson believes Alzheimer's is fundamentally mitochondrial, with amyloid as the garbage that accumulates. He thinks the bioenergetic shifts of the perimenopause transition 'fast-forward' women toward the disease. His group studies women around menopause and, with a small grant, men aged 40–65 (15 a year for four years).

• Many roads lead to Alzheimer's

Isaacson describes several routes into the disease. Diabetes 'will put you in the fast lane', and hormonal change and mitochondrial dysfunction are others. MTHFR, a gene in folate metabolism, is another road. He says it matters mainly for people with high homocysteine.

• The 'ABCs' of prevention

In his precision-medicine programme, patients are stratified by APOE and MTHFR genes, then by A: anthropometrics such as body fat, lean mass and visceral fat (not BMI), B: blood biomarkers and C: cognitive testing. Attia praises Isaacson for running deeper lipid panels, including apoB, LDL particle number and particle subtypes, than most cardiologists.

• Pro-statin, but not one-size-fits-all

Isaacson thinks different statins work differently in different people, that there is a sex difference, and that low dose is better when in doubt. He cites atorvastatin slowing hippocampal shrinkage in men. He urges real caution in APOE4 carriers, especially 4/4, and has seen men switched to a high-potency statin whose cholesterol numbers looked great but whose memory got worse.

• Exercise has the strongest evidence for risk reduction

When Attia's team checked about 200 references in a review by Dale Bredesen, they couldn't verify about a third. One resveratrol citation had nothing to do with Alzheimer's. Starting again from first principles, the only intervention with top-level evidence was exercise. Isaacson adds it is the only thing shown to reduce or slow amyloid build-up in people who already have it.

EXAMPLES

• B vitamins work only alongside omega-3s

Isaacson cites evidence that B vitamins can slow brain shrinkage and improve memory in people with high homocysteine, but only if omega-3 levels are good. If standard folic acid and cyanocobalamin don't lower homocysteine, he switches to methylated forms of folate and B12. He names a brand Attia introduced him to, a combined lozenge.

• Theracurmin and amyloid

Regular curcumin trials failed partly because it wasn't absorbed into the blood. In a study by Gary Small and colleagues, a nanoparticle form called Theracurmin led to less amyloid on PET scans after 18 months. Isaacson says he sells nothing and doesn't think everyone needs it. He considers it for some higher-risk patients, such as families with both APOE4 and TNF-alpha gene variants.

• Uncle Bob

Isaacson's uncle, who introduced his parents and pulled him from a pool when he was three, was diagnosed with Alzheimer's when Isaacson was in high school. Seeing 'the life of the party' decline and the toll on his children set Isaacson's career path.

• A 0.4% drug success rate

Attia urges donors to fund prevention: 99.6% of Alzheimer's drugs fail. He says $100,000 barely buys five animals for a drug study but goes much further in a prevention clinic.

• Real intensity versus elliptical TV time

Isaacson averages about 155 beats per minute in spin classes, peaking around 180, but admits lifting weights only about once a week. Attia says he should be lifting two or three times a week. Isaacson thinks muscle mass may matter more for men's

brain health and body fat for women's.

OTHER RELEVANT

- **Learn about brain health early**
  Isaacson's first 'no-regret' step is education; his free public site is alzu.org, with a free accredited course for clinicians. Changes made at 30, 40 or 50 add up.
- **Know your numbers**
  Isaacson's second step is to track blood pressure, resting pulse, body fat, weight, cholesterol, blood sugar, sleep and exercise output; he calls himself a data junkie. Both men use an Oura ring, with an investment in and advisory role with Oura disclosed on air.
- **Exercise hard and mix it up**
  Most evidence is for aerobic exercise. Include interval training, without overdoing it, and strength work, since muscle and body composition both appear to matter.

#25 – Scott Harrison: transformation, finding meaning, and taking on the global water crisis

Guest: Scott Harrison
Date: 2020-01-01 · Duration: 2:18:52
URL: https://www.youtube.com/watch?v=GlC7JY5muxw

KEYPOINTS

• A childhood shaped by his mother's poisoning

When Scott was four, his family moved to a tightly sealed, energy-efficient house in South Jersey. A faulty heat exchanger leaked carbon monoxide. His mother, who spent the most time indoors, collapsed on New Year's Day 1980. He recalls her carboxyhemoglobin being about 20 to 25 times the toxic threshold. Afterward, perfume, soap, car fumes and even ink from new books made her ill.

• Environmental illness meant extreme isolation

She was diagnosed with what was then called multiple chemical sensitivity, or environmental illness. After a water-only fast and food-by-food testing, Scott says only about 20 of more than 100 foods were tolerable. She ate a six-day rotation of single organic foods and drank spring water, living in a tiled bathroom with a cotton army cot washed about ten times in baking soda. Scott became her caregiver as an only child.

• Peter on patients medicine dismisses

Peter says people like Scott's mother often fall through the cracks because doctors label unexplained illness as psychological. He recalls a medical school professor's joke that 'idiopathic' really means the doctor is the idiot. The family took a settlement of about $1,250–$1,500 from the gas company rather than sue. Peter relates this to his own medical-school back injury, botched by a surgeon who operated on the wrong side, where he never considered suing.

• Rebellion took him from a band to the clubs

In high school Scott quit being the dutiful son, grew his hair out and became the keyboard player and self-appointed manager of an alternative rock band, Sunday River. They played CBGB's and the Wetlands. He alone moved to New York, enrolled part-time at NYU in communications, and sold stereo gear at Sam Ash. When the band broke up he turned to promoting nightclubs.

• A decade of 'models and bottles'

For about ten years Scott was a top promoter, helping pioneer bottle service: instead of charging $18 for a vodka soda at the bar, clubs sold bottles at tables. He courted modeling bookers so models would come out. He built one of the first club email lists, which he says had near-100% open rates. He smoked up to three packs a day and used cocaine and other drugs.

• The emptiness behind the 'markers of happiness'

He had the model girlfriend, the money and the parties, but he says the top bottle buyers spending $10,000–$15,000 a night were often miserable and estranged from their families. Physically, he lost feeling in half his body and feared a brain tumor. On a New Year's trip to Punta del Este, after a weekend of $1,000 in fireworks and magnums of Dom Pérignon, he started reading A.W. Tozer's The Pursuit of God, a gift from his father.

• The flip: from party boy to volunteer photographer

At 28, after a frightening night at a club involving a gun and a bouncer, he drove north alone with a Bible. He decided to spend a year serving others. Humanitarian groups turned down the 'party boy' until Mercy Ships accepted him as a photojournalist. He paid $500 a month to volunteer on a hospital ship of about 350 volunteers sailing to Benin and Liberia, which had just come out of a 14-year civil war.

• Mercy Ships showed medicine at its most transformative

The ship focused on maxillofacial surgery: facial tumors, cleft lips and palates, burn reconstruction and cataracts. Scott recalls about 5,000 people at a triage day, a country of a few million with only a couple of surgeons, and children choking on four-pound benign tumors. He says he wept for 40% of that first day.

• Distrust of charities shaped charity: water's design

Scott cites a USA Today poll finding 42% of Americans didn't trust charities. Inspired by Paul Tudor Jones covering the Robin Hood Foundation's overhead, he set up two separately audited bank accounts, one for public donations that go 100% to water projects and one for overhead funded by private backers. He even repays credit card fees so a $100 gift sends $100 to the field.

EXAMPLES

• Alfred's tumor

Alfred, a 14-year-old boy, had a fleshy ameloblastoma that had grown for four years. It had been cut with knives and stones and treated with pastes and chants. Surgeons removed it, rebuilt his jaw with a titanium plate, and weeks later Scott took him home to his village. Scott still supports him.

• Before-and-after photos as fundraising

Back in New York, Scott held a gallery show of about 108 images of patients morphing before and after surgery. With donated food and auctioned designer handbags, it raised about $100,000 for Mercy Ships, mostly from skeptical nightlife friends.

• Discovering the water crisis

Exploring rural Liberia, he learned that about half the population lacked clean water. He photographed children drinking from algae-filled swamps. A surgeon mentor who had stayed on the ship for 21 years encouraged him to pursue water as his cause.

• Peter's view of overhead

Peter pushes back that overhead isn't a dirty word, citing Dan Pallotta's TED talk. He and his wife now give only to overhead, such as salaries for people they trust. Scott agrees but says that argument hasn't moved donors, so he funds overhead separately.

OTHER RELEVANT

• The four pillars

(1) 100% of public money goes to projects. (2) Proof, through GPS coordinates and photos of each well. (3) A hopeful, inspiring brand modeled on Apple or Virgin rather than guilt imagery. (4) Local partners lead the work, with charity: water funding rigs, trucks and hydrologists.

• Scale so far

Scott says the organization has raised about $330 million from more than a million people. He has taken about 350 donors, including 50 kids, on trips over 12 years to listen and learn, not to drill wells. Every penny of his book advance for Thirst went to the charity.

• Books he recommends

William Easterly's The White Man's Burden on good and bad aid; Brother Lawrence's The Practice of the Presence of God; and a book of yearly letters to a godson on virtues, which he is rereading.

#17 – Mike Trevino: life-lessons from ultra-endurance, mindset, hard work, and removing limitations

Guest: Mike Trevino
Date: 2020-01-01 · Duration: 1:56:16
URL: https://www.youtube.com/watch?v=Q1vlqtFhSus

KEYPOINTS

• Mike's birthday ritual makes age tangible: run your age in miles.
Starting at 40, he runs the number of miles matching the birthday. At 43 that meant a 43-mile fasted run after a 5 p.m. beer the night before, worst-case banana money in the pocket, and a finish that still left him clear enough to call Peter the same day.

• Badwater 135 taught heat, elevation, and crew management in one package.
The race starts below sea level in Death Valley (asphalt so hot the white line can feel ~10°F cooler) and finishes at Whitney Portal around 8,500 feet after 135 miles. Peak air near 125°F turns the hood of a car into an egg skillet; Mike treated the ecosystems along 395 as part of the problem to solve, not scenery. He finished into Lone Pine craving pizza before the final climb; the race used to summit Whitney itself until safety rules cut it at the portal.

• Race Across America showed how sleep debt becomes psychosis.
Best practice is roughly 20–22 hours on the bike and 2–4 hours of sleep per day. On his first RAAM he stayed on the bike ~28 hours, slept ~none for ~45 hours, broke his crew early, and later entered a delusional stretch where he concocted a chase narrative around a following van near a power plant. Hallucinations were the middle stage; full delusion—the 'mentally insane' phase he names—was the warning that the event was no longer sports.

• Objective metrics beat vibes when deciding if you are race-ready.
Time, heart rate, and bike horsepower do not flatter. Mike asks whether course-record shape is real or self-mythology before he adds load, a habit he argues transfers to anyone training for a first 10K.

• A Himalayan parasite forced a 10-day fast that rewired his view of hunger.
Yak meat at extreme altitude left him with a severe parasitic load discovered the following year. Western and Eastern clinicians agreed the nuclear option was fasting ~10 days; days one and two were brutal, and by day three his visual field widened into a calm he had not expected. UCSD infectious-disease input sat alongside whatever Eastern modalities he tried; the point was clearing the organism, not collecting fasting credentials.

• Trans-Iowa / RAGBRAI curiosity became a continuous crossing experiment.
Growing up doing the Register's Annual Great Bicycle Ride Across Iowa, he kept asking why everyone stopped at night. As an adult he tested how fast the state could be crossed in one push—an endurance puzzle more than a party ride.

• Modafinil maintains wakefulness but is not a free lunch for ultras.
FDA-labeled for narcolepsy and banned in sport, it is a non-stimulant wakefulness drug. Peter recalls Air Force pilot data: ~200 mg held performance a long time then fell off by 24 hours; ~600 mg (the top tested dose, which he himself used in residency) looked flatter across the day—useful context, not a race plan. Stimulants, he argues, eventually 'blow you up' on multi-day races; wakefulness drugs still trade in recovery debt.

• Peers dying on the course recalibrated what 'extreme' was worth.
Deaths around the ultra community (including Bob Breedlove and a later wake-up call involving Nick Venuto in 2010) made law-of-large-numbers risk concrete. Mike eventually pulled back from the edge rather than treating every record as mandatory. Law of large numbers on open roads and remote trails means something eventually happens if you stay out there long enough.

• Leadership at home and work looks like taking out the garbage.
With a ~15-person company he still does unglamorous chores. He does not want his kids' model of excellence to be a father who 'did everything athletic' but nothing relational—the inverse of his own handy dad who could fix anything.

• Navigation and contingency planning are part of the training.
He has charted hundreds of miles in ziplock-bagged cue sheets taped against sweat. The same mindset—expect 7-Eleven bananas, expect crew fracture, expect sleep math to fail—is what he tries to hand kids and teammates.

EXAMPLES

• 43-mile birthday run
Fast from 5 p.m., beer noted for the record, 43 miles completed, same-day phone call to Peter—proof the ritual is lived, not branded.

• RAAM 28 hours aboard / ~45 without sleep
Crew broken inside the first two days; later delusional chase story around a chase van—sleep deprivation as psychiatry, not toughness cosplay. Planned sleep had been two hours a day after riding through night one; the plan died when fatigue and crew conflict compounded.

• Badwater heat tactic
Run the white line when asphalt radiates; accept ~125°F peaks; climb the final ~13 miles to Whitney Portal after the desert.

• San Diego 24-hour track ultra
Nearly 150 miles in a day on a monotonous loop he swore never to repeat; course records without needing a world-record claim.

• Modafinil dose anecdote
Peter's residency use up to 600 mg/day and the Air Force pilot curve at 200 vs 600 mg frame the drug as powerful, regulated, and easy to romanticize.

OTHER RELEVANT

- **Borrow the principles, not the mileage.**
  Most listeners will never race RAAM. They can still use objective readiness checks, planned sleep, and honest crew communication. Borrow the honesty about delusions and crew limits even if your 'race' is a hard work week.
- **Build an off-ramp before the body forces one.**
  Mike's later pullback after peer deaths is the lesson: extreme sports have a fatality denominator. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Fasting under medical guidance "` lifestyle flex.**
  His 10-day parasite fast was a last resort with clinicians involved, not a biohack template. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Model ordinary responsibility for kids.**
  Taking out the trash at a company you lead teaches more transferable grit than another Strava badge.

#28–Mark & Chris Bell: steroids, powerlifting, addiction, diet, training, & helping others live well

Guest: Mark Bell and Chris Bell
Date: 2020-01-01 · Duration: 2:11:35
URL: https://www.youtube.com/watch?v=yHhRB62uHPM

KEYPOINTS

• Bigger, Stronger, Faster made Attia rethink what he'd assumed about steroids.
Attia says that through medical training he simply assumed anabolic steroids were among the most dangerous things around, an impression reinforced by Lyle Alzado's death and a Sports Illustrated cover when Attia was in high school. Seeing Chris Bell's documentary around 2009 was the 'thin end of the wedge'. He quotes JFK's 1961 Yale speech about enjoying 'the comfort of opinion without the discomfort of thought', and stresses that the film doesn't argue steroids are good or bad.

• The film worked because it was honest about the family's own conflict.
Chris modeled its structure scene by scene on Michael Moore's Bowling for Columbine and brought in that film's editor. Producer Alex Bono saw the core story when Chris mentioned that his brothers Mark and Mike were using steroids while he, the middle brother, was conflicted. Chris applies the same approach to a planned nutrition documentary: show what's actually happening, his own confusion about how to eat, rather than push a diet.

• Chris challenges opponents without trying to humiliate them.
Attia praises the scene with the father of a high school athlete who died by suicide, whose death the father blamed on steroids, and says the evidence suggests steroids probably had little to do with it. Chris chose not to cross-examine a grieving parent. Instead he drew comparisons, noting that his own brother died in a sober-living facility with drugs involved, and that a 'steroid awareness night' at a ballpark sells beer to fathers who then drive their kids home.

• Chris's recovery required family intervention and long-term support.
Their father had cried only rarely, Mark says, and the only time he ever yelled at Chris was to tell him he was an addict or an alcoholic, which Chris credits with saving his life. When Chris's girlfriend Lauren called Mark late at night, Mark and his wife booked flights for both of them to Sacramento. Chris went through three to four days of detox and then 60–70 days of rehab. Chris later said he felt alone in Los Angeles.

• Recovery, like getting strong, is 'never over'.
Mark says there's no point where you arrive and stay. Years later, Chris's life had 'restarted at 40' and healing was still ongoing. Chris now says he's grateful for the addiction because it lets him help others. He says his film Prescription Thugs has prompted viewers to recognize their own opioid problems.

• The Bells built strength from early on with minimal training volume.
A chiropractor who doubled as a powerlifting coach told a teenage Mark to squat to fix his knees, despite bodybuilding magazines warning it was bad for them. Within six months Mark went from a broomstick to 315 pounds for eight reps, and he squatted over 500 in high school. Influenced by Mike Mentzer's low-volume approach, they often did one heavy lift and left. Their brother Mike squatted about 675 by 18 or 19.

• Steroids raise your ceiling but don't replace genetics.
Mark says steroids mainly let people gain mass. If genetics get you to 'level four', drugs might get you to six, but not to the eight to ten of genetic outliers like Phil Heath or Jay Cutler. Mark has used them since 25, now with a prescription. Chris believes heavy use, trenbolone plus testosterone and oral steroids right after rehab, left his tendons too weak and caused his torn triceps.

• Attia approaches low testosterone in a methodical way.
He treats only when free testosterone is about one to two standard deviations below the mean and the patient has symptoms. He then works through nine steps: high SHBG (from insulin, thyroid, estrogen or genetics), too much conversion to DHT or estradiol, low DHEA, or weak FSH/LH signaling from the brain, often addressing these without giving testosterone itself. He rarely starts anyone above 50 mg twice a week, while Chris says everyone he knows takes 200 mg.

• Sleep and cortisol are common reasons the brain doesn't signal for testosterone.
When testosterone, FSH and LH are all low, Attia's top diagnosis is sleep deprivation. High cortisol diverts hormone precursors (the pregnenolone 'steal') and blocks the deep sleep in which FSH and LH are released. On statins, Attia says theory predicts lower sex hormones but the data don't show it, because the body prioritizes cholesterol for cell membranes and hormones.

EXAMPLES

• Mark's lifetime bests
Equipped: a 1,080-pound squat, 854-pound bench and 766-pound deadlift. Raw: a 700-pound squat in the gym, a 578-pound bench in competition and a deadlift around 715. He says the one thing he'd change is getting more sleep.

• A bench-off at about age 13
Chris recalls Mark, then 12 or 13, pressing 240–250 pounds while a cousin failed at around 205. Their mother, who had never lifted, benched 135 the same day.

• 'Red meat and water'
In 1993 Mark met powerlifter Ron Fedkiw, then a UCLA graduate student and later a Stanford professor, who told him he was too fat and gave him that as his whole diet. Mark dropped over 20 pounds in a few weeks, won his next meet, went from about 240 down to under 198, and got stronger. He regrets abandoning the diet for 10–15 years.

• Attia's own testosterone
After residency, sleeping about four hours a night, Attia's total testosterone was 220, below a reference range of roughly 350–1,200. He says it rose to about 650 simply from sleeping more.

OTHER RELEVANT

• Challenge yourself, then avoid getting hurt.

Mark ranks challenge first and avoiding injury second. He says warming up doesn't need science: walk with a band around your knees in every direction, hinge at the hips, and warm the elbows and shoulders before pressing. Attia's 'rule number one' is don't get hurt.

• Start kids on powerlifting mechanics early.

Attia would like each of his kids to learn the main lifts, though he wouldn't let them box. Chris filmed a kids' meet in San Diego where children aged 7–15 had impeccable form. That gym bans parents from the training floor and has kids finish their homework first.

• Learn technique from video if you can't get coaching.

Attia wants patients without a trusted trainer to watch correct mechanics rather than teach themselves. Mark says his channel has over 3,000 videos, including Ed Coan and Stan Efferding.

#15 – Paul Conti, M.D.: trauma, suicide, community, and self-compassion

Guest: Paul Conti
Date: 2019-12-31 · Duration: 2:09:24
URL: https://www.youtube.com/watch?v=KlNzL0dNcQw

KEYPOINTS

• Conti estimates 80% of what he treats is trauma

The psychiatrist, who has known Attia since their first week of medical school 21 years earlier, says he has come to believe 80% of what he treats is trauma. In his view the other 20%, such as head injury, schizophrenia and biological drivers of addiction, is never free of trauma's influence either. It shows up as anxiety, depression, panic attacks and substance use. He guesses that more than half of what walks into any doctor's office ultimately rests on trauma, while admitting he doesn't know the real numbers.

• Silent bravado can lead to real death or 'functional death'

Conti's brother died by suicide, and about a year later a close childhood friend died after the same 'desperate recklessness'. Both, he says, had real needs and no place to get acknowledgement or help. He calls the more common result functional death: still breathing, but effectively dead inside. That experience pulled him from a consulting career, where more money and authority made him less happy, into psychiatry.

• Suicide is the one top-10 cause of death in every decade after childhood

Attia, who studies actuarial tables to see what kills people, notes that suicide appears among the top 10 causes of death in every decade after age nine. He cites a Wall Street Journal piece using CDC data showing about a 30% rise in suicide among Americans aged 40 to 60 over a recent one- or two-decade span. He hedges on the exact period. Conti adds that many 'accidental' deaths in younger people are parasuicidal: recklessness from people not invested in staying alive.

• Trauma comes from five routes, and we routinely minimise them

The framework Attia learned at Bridge to Recovery lists abuse (physical, emotional, sexual, spiritual), neglect, abandonment, enmeshment and witnessing tragic events. Conti says we ignore even overt events like assault. Smaller ones, such as a friend moving away or a pet dying, can become a lifelong symbol of 'no stability, no peace'.

• The brain doesn't care about the calendar

For Conti, how long ago something happened is irrelevant if it instilled terror, shame or false responsibility. It feels as immediate after 30 years as after two days. He links this ongoing internal stress not only to suicide but to cardiovascular disease, cancer and autoimmune problems, which is why he sees it as directly relevant to longevity.

• Shame gets passed on through a different route

Attia's insight from the past year is that trauma 'almost always comes out in some orthogonal way'. A mother sexually abused as a child is very unlikely to abuse her daughter, but the shame will reach the next generation through something else. Simply avoiding repeating the original event isn't enough; the person has to understand what it did to them.

• Whatever doesn't kill us often makes us weaker

Conti rejects the idea that adversity automatically builds resilience. Unacknowledged hurts lead to languishing, or, in driven people, to achievement while still miserable. He points to the Wizard of Oz and The Emperor's New Clothes as examples of our fascination with things that look strong but are vulnerable.

• Psychotherapy and psychedelics aim to lower our defences

Conti says Freud didn't get everything right, but the unconscious, the hidden part of the iceberg, still drives most behaviour. Both men are interested in the dissolving of the ego that psychedelics can produce. Conti says the goal of therapy, shared experience and psychedelics is an honest experience of self, which usually means acknowledging what we're ashamed of.

• Modern society isolates us and expects too much from one partner

Conti criticises a culture of endless phone trees and checklist diagnoses, including in psychiatry, that doesn't respond to the individual. He argues it is a fallacy that one partner should be everything to another. People need a broad mix of friendships and community, and without them, cults and cult-like groups fill the gap. He ties much suicide to an absence of meaning, and mentions reports that many people can't absorb an unexpected $500 bill.

EXAMPLES

• A patient lost 30 pounds after trauma care, with no other changes

Their first shared patient was a physician whose father died of heart disease while she was in medical school. She followed her nutrition plan very closely and her hypothyroidism was fixed, but inflammation, insulin resistance and a 'metabolic rate of a slug' persisted. After she worked with Conti for about six months, with no change to thyroid medication, diet or exercise, she lost about 30 pounds. Attia didn't recognise her Christmas card.

• Paralysis with no nerve damage

Conti says his reverence for the brain's power over the body comes from cases like people who did, or nearly did, something they found reprehensible. The limb involved became paralysed and stayed that way for 10 years, though no nerves had been severed.

• The question that broke Attia's guard at Bridge to Recovery

Three or four days into 13-hour days of group therapy in rural Kentucky, Attia was still refusing to engage. A counsellor asked whether he would think it was okay if the same event happened to his young son, Reese. That reframing ended his rationalisation that it had 'made me more resilient'. He also found open 12-step meetings deeply moving, though he never once spoke.

• A 19-year-old teaching a neurosurgeon

In the treatment programme Conti ran for about five years, with around 30 staff, his proudest memory is a young woman who had lived on the streets. Late one day he saw her deep in conversation with a neurosurgeon, and she was clearly teaching him. Conti resisted pressure to separate patients by age or wealth. He told Attia that being with people who seem different is exactly

what helps.

• 'You're always the smartest guy in the room'

Attia's San Diego therapist told him his problem was always being the one giving answers, so he never got to sit, listen and be one of the group. Conti says vulnerability shared in a group is the beginning of an antidote to shame.

OTHER RELEVANT

• Listen to your inner voice

Conti's first step is to notice what you say to yourself thousands of times. Attia describes a voice telling him 'how shitty I am' for anything less than perfect, from the moment he wakes up.

• Almost everyone could benefit from therapy

Conti jokes that only people with no problems at all should skip psychotherapy, meaning everyone should have it. Attia recommends vetting therapists for real trauma expertise; inpatient care isn't required to start.

• Build connection beyond your partner

Talk more openly with people already close to you, protect time with friends, and consider 12-step meetings or communities built on shared interests or faith.

• Conti's reading suggestions

He recommends Camus's The Plague, about how we all live among threats and need each other, and Katherine Mansfield's short stories for the subtle nuances of being human.

#13 – Brett Kotlus, M.D.: How to look younger while we live longer

Guest: Brett Kotlus
Date: 2019-12-23 · Duration: 1:48:51
URL: https://www.youtube.com/watch?v=4hF6_XxgTs4

KEYPOINTS

• Facial aging combines sun damage, thinning skin and shifting volume

Kotlus, an oculoplastic and cosmetic surgeon, says years of sun exposure cause solar elastosis. Collagen and elastin fall, the skin gets thinner, and small blood vessels (telangiectasias) and brown spots appear. Meanwhile the face loses volume, sometimes in the wrong places. In his practice, darker skin types and many Asian patients tend to age better. He attributes this to denser connective tissue and the UV protection pigment provides, while stressing that they still need sunscreen.

• Kotlus suspects UV exposure slowly destroys facial fat, but calls it a hypothesis

His reasoning is by analogy. Focused heat and laser devices are known to destroy fat cells, so he believes decades of UV may do something similar to facial fat. As supporting observation, he points to lifelong sun-avoiders with 'porcelain skin' who have fewer wrinkles and younger-looking faces. He frames it as his own belief, not established science.

• Looking 'done' comes from over-enlarging or over-pulling natural shapes

A natural face needs shadows and movement. He gives the analogy that you can't have light without dark. Overfilled lips lose the Cupid's bow and the 'two pillows' of the lower lip and turn into a 'sausage'. Over-tight facelifts create the windswept look. His rough guideline is to aim for looking about seven to ten years younger, because 'there's no amount of money' that makes someone look naturally 30 years younger.

• Social drift and 'provider shopping' push people too far

Kotlus describes an 'Instagram effect': filtered and augmented faces start to look normal, peer groups escalate together, and some patients find a new injector when one says stop. Peter adds that he only sees the badly done cases, the numerator, and not the denominator of people whose work goes unnoticed.

• Hyaluronic acid fillers are biocompatible and reversible, but lips swell at first

Hyaluronic acid already exists in skin, allergic reactions are generally absent, and an enzyme can dissolve it if something looks wrong. The gels attract water, so lips look oversized for about two to three days. He says almost every first-timer then admits they 'sort of missed' the swelling and wants more next time. Lip filler lasts about six to eight months; under-eye filler lasts one to two years and sometimes four to five.

• Bad Botox is usually too much in the forehead

The frontalis is the only muscle that raises the eyebrows. Heavily injecting it to erase horizontal lines leaves a shiny, frozen forehead and brows that actually drop, which he calls a giveaway at the Oscars. He says a better approach often targets the corrugator and procerus muscles between the brows that cause frowning. Modern technique uses smaller amounts spread more widely, and can lift mouth corners, reduce a gummy smile or open the eyes slightly.

• Start prevention before lines become etched

Kotlus emphasizes that nobody has to do any of this. For those who care, prevention comes first: sun avoidance from youth, and possibly neurotoxin before expression lines become permanent creases, for example if you see those lines on your parents.

• His three core skincare tools are sunscreen, a retinoid and topical vitamin C

Retinoids act at the gene-transcription level, boosting collagen and cell turnover. He calls them one of the few proven anti-aging treatments. Vitamin C is an antioxidant and a collagen cofactor, and it works better with vitamin E. Its caveat: if blood vitamin C is already high, skin may absorb topical C poorly. Evidence supports it for reversing existing sun damage more than for preventing it. He says some patients improve dramatically from this regimen alone, 'without touching them with a needle'.

• Some devices are operator-independent, but lasers and peels are not

For cryolipolysis such as CoolSculpting, or heat-based alternatives, the main point is to use an FDA-approved device rather than a knockoff. He says these typically reduce about 20% of subcutaneous fat over a course of treatment. Peels and resurfacing lasers depend heavily on the operator.

EXAMPLES

• Peter's forehead Botox misadventure

About six years earlier, a plastic surgeon friend gave Peter what felt like 'three thousand injections' into his forehead. He then couldn't raise his brows to keep sweat out of his eyes while cycling under a helmet. Kotlus uses this as the textbook frontalis mistake.

• Kotlus's cannula technique for under-eye hollows

Kotlus says under-eye hollows are his most frequent procedure. The tear trough shadow forms when cheek fat is lost while the eye fat pads enlarge, making people look tired. He enters through a single needle hole in the cheek with a blunt-tipped cannula, so no needles go under the eye. He places filler by picturing the anatomy he sees during blepharoplasty, and stresses that some hyaluronic fillers are the wrong stiffness or water-attraction for that area.

• SPF numbers and sunscreen types

SPF measures UVB (burning) only. SPF 15 means taking 15 times longer to redden, so 10 minutes becomes 150. He cites roughly 96% versus 98% protection for SPF 30 versus 50. He recommends broad-spectrum physical (zinc or titanium) sunscreen of at least SPF 30 and avoids octinoxate, while noting that dose-related harm is debated. Chemical filters convert UV to heat, which can worsen melasma.

• PRP: Kotlus offers it but finds it often oversold

Kotlus draws about 80 mL (ten 8 cc vials) and double-spins it. Methods vary widely, which muddies the research, and some providers inject platelet-poor plasma as 'PRP'. Peter tried scalp PRP for hair loss and was underwhelmed. Kotlus notes that DHT-driven hair loss continues regardless, so finasteride or dutasteride and minoxidil may be needed.

• Peel strength matters

A 10% TCA peel leaves skin slightly red. A 35% peel makes it come off 'like a snake'. Phenol peels require EKG monitoring for arrhythmias. Fractional erbium and CO2 lasers leave dots of untreated skin between treated areas to aid healing.

OTHER RELEVANT

• Retinoid how-to

Start with an over-the-counter retinol. If it dries the skin, use it every second or third day or wash it off after 10 minutes. Then move to prescription tretinoin at 0.025%, 0.05% or 0.1%; Kotlus uses 0.1% nightly. Apply it at night, including the upper eyelids to the lash line. He says the sun-sensitivity concern is mostly about the retinoid breaking down in light.

• Morning order of operations

Apply vitamin C serum, wait a couple of minutes until it's dry, then apply sunscreen; apply the retinoid at night. Most people under-apply sunscreen, so also wear a wide-brim hat and cover the chest and hands.

• Choose a provider, not a device

Kotlus suggests choosing the way you would for your mother: get referrals (nurses and scrub techs know who is good), meet two to four providers, judge rapport and shared goals, and review before-and-after galleries. Skilled PAs, nurses and family doctors can be excellent injectors. For eyelid surgery, he suggests starting with oculoplastic surgeons.

#10 – Matt Kaeberlein, Ph.D.: rapamycin and dogs — living longer, healthier & turning back the clock

Guest: Matt Kaeberlein
Date: 2019-12-23 · Duration: 1:32:53
URL: https://www.youtube.com/watch?v=kE-ep1kBziQ

KEYPOINTS

• A seminar in his first semester steered Kaeberlein toward aging

Trained in biochemistry and mathematics and planning a career in structural biology, Kaeberlein heard Lenny Guarente talk about the genetics of aging at MIT. His PhD work went on to show that boosting Sir2 extended lifespan in yeast. A year later, Heidi Tissenbaum showed the worm version did the same, the first conserved genetic regulator of lifespan across such distant species.

• Pet dogs are a better step toward humans than lab mice

Lab mice are inbred and live in controlled cages. Companion dogs are genetically diverse, share our homes and get many of the same age-related diseases; cancer is their top killer, and big dogs get more of it. Kaeberlein also argues that people will believe aging can be slowed far more readily when they see it in their own dog than in a news article.

• Treating healthy individuals demands a very low tolerance for side effects

Geroscience aims to intervene before disease, the reverse of traditional medicine, so regulators and the public accept little risk. Kaeberlein argues society should debate that standard, because a 'healthy' 70-year-old isn't the same as a healthy 30-year-old and we know what happens if aging goes untreated.

• Intermittent dosing may boost immunity rather than suppress it

Joan Mannick's study gave healthy older people the rapamycin analog everolimus at 20 mg weekly, 5 mg weekly or 1 mg daily. All three improved their flu vaccine response, with the 5 mg weekly dose doing best with the fewest side effects, and none severe enough for anyone to drop out. Attia notes this runs counter to rapamycin's reputation as a transplant immunosuppressant.

• Short rapamycin courses partly reversed heart aging in old mice

In three independent studies, six to ten weeks of rapamycin restored ultrasound measures of heart function in old mice about halfway to young levels, without needing a break from the drug to see the effect. Kaeberlein lists other short-term 'rejuvenation' signals: intestinal stem cells (from a colleague's lab) and the bone around the teeth (from his own). He cautions that doses don't translate cleanly between species.

• Rapamycin's cancer effects depend on dose

Immune surveillance is a major defence against cancer, and it weakens with age. Kaeberlein guesses that moderate rapamycin delays cancer in mice by restoring immune function, while doses high enough to suppress immunity could promote it. Tumours that have already learned to ignore mTOR signals may not respond.

• A 'party dose' revealed striking sex differences

His lab gave mice 8 mg/kg daily injections, the highest dose ever used in an aging study, for three months from 20 to 23 months of age. Males lived about 60% longer after treatment ended, with better muscle function and less cancer. Females gained no lifespan and all died with aggressive blood cancers. He speculates the dose overshot in females, who may be more sensitive to rapamycin, even though the 2009 study that started the field showed a bigger benefit in females.

• Alzheimer's should be treated as a disease of aging

Kaeberlein believes rapamycin has a decent chance in dementia, ideally starting at mild cognitive impairment, but such trials are long and progression is hard to predict. He thinks drugs fail partly because researchers create the disease in young mice. Attia, who doesn't see Alzheimer's as one disease, is most optimistic about the metabolic form. Kaeberlein adds that rapamycin's boost to autophagy (cellular clean-up) might help the harder forms too.

EXAMPLES

• The first rapamycin trial in pet dogs

Healthy dogs at least six years old within a set weight range (roughly 55 in human terms; weight matters because big dogs age faster) received placebo, 0.05 mg/kg or 0.1 mg/kg rapamycin on Mondays, Wednesdays and Fridays for 10 weeks at a Seattle-area clinic. Of 40 dogs screened, 24 finished: 8 on placebo, 11 on the high dose and 5 on the lower dose. Kaeberlein admits the uneven groups reflect inexperience with his first clinical trial.

• One in five 'healthy' dogs had hidden heart disease

About 20% of dogs that seemed healthy had valve leakage visible on ultrasound but not through a stethoscope, forcing a debate with the cardiologist about where normal aging ends and disease begins.

• Heart function improved with no extra side effects

Owner surveys showed no difference in side effects, and blood chemistry didn't change. Increased drinking was reported equally in both groups once the study was unblinded. Two of three heart measures (ejection fraction, fractional shortening and a filling ratio) reached statistical significance, the third had a p-value of 0.06, and dogs that started with the weakest hearts improved most. Kaeberlein says it needs replication.

• The study he'd run with $10–20 million

About 450–500 middle-aged dogs (six to ten years old, over 40 pounds) treated for five years, tracking lifespan and function, including activity measured by GPS collar. More than 6,000 owners signed up with no advertising. He argues lifespan is a meaningful endpoint in dogs because owners euthanize only when a dog is truly sick.

OTHER RELEVANT

• Weekly or intermittent dosing is the strategy being tested

Both the human everolimus data and the dog protocol use intermittent rather than daily dosing to reduce side effects and

possibly favour immune benefits. None of this has established a safe longevity dose for people.

- **A small positive study needs replicating**

  Kaeberlein calls the dog trial about the most positive outcome he could have hoped for, yet it was small and borderline significant. Wait for larger, longer trials before drawing conclusions.

- **A normal exam can miss early heart changes**

  In this study, a stethoscope exam missed heart changes in one in five apparently healthy dogs that only an echocardiogram revealed. The line between age-related decline and disease is often a matter of which test you run.

#14 – Robert Lustig, M.D., M.S.L.: fructose, processed food, NAFLD, and changing the food system

Guest: Robert Lustig
Date: 2019-12-23 · Duration: 1:23:24
URL: https://www.youtube.com/watch?v=6FiYyk0-PWk

KEYPOINTS

• Fructose browns proteins about seven times faster than glucose.
Lustig walks through non-enzymatic glycation (the same chemistry that turns newborn rib cartilage white and 88-year-old cartilage brown). Glucose drives that aging reaction slowly; fructose accelerates it roughly sevenfold, stiffening proteins wherever the reaction lands—not only on the lysine that hemoglobin A1c assays read.

• Hemoglobin A1c misses much of fructose's glycation footprint.
Classic A1c chemistry hits position 1 on hemoglobin. Fructose prefers other sites (he mentions positions 66 and 110), which need research-grade tandem mass spectrometry. So a 'normal' A1c can coexist with heavy fructose exposure. That measurement gap is why uric acid and ALT become his practical fructose 'bio-toxicity' proxies in clinic.

• 'Normal' ALT and uric acid ranges have drifted upward with the population.
When Lustig entered medical school in 1976, ALT's upper limit of normal was about 25; by the recording it had crept to the low 40s because labs set ranges from two standard deviations around a fatter, fattier-liver mean. Peter wants patient ALT below ~20–25; both want uric acid nearer 5–5.5 mg/dL even when the lab calls 7.0 normal.

• Fructose raises uric acid and blood pressure in a dose-linked way.
More sugar intake !' higher serum uric acid. Meta-patterns Lustig cites: every ~10% increase in fructose consumption associates with about +2 mmHg blood pressure and roughly +10% stroke risk. Endothelial inflammation, not only LDL folklore, is part of the cardiovascular story he wants restored. Benjamin Franklin already linked uric acid to gout; Lustig updates that folklore with stroke and endothelial risk.

• Kids' median added-sugar intake is still enormous.
About 18 teaspoons per day (~90–94 g), down from older estimates near 120 g as the obesity epidemic changed awareness. Roughly half of children's added sugar hides in foods people do not think of as dessert—bread, pasta sauce, pretzels—and about half of what children do see as sweets sits in candy, cake, ice cream and drinks.

• Infant sweet preference is plastic; savory acceptance takes far more exposures.
Lustig cites work suggesting savory foods may need on the order of a dozen introductions before acceptance, while sweet lands faster. His own daughter met Capri Sun at a birthday party after years of milk and water; the industry designs for taste-bud downregulation that keeps pulling intake upward.

• NAFLD exploded in pediatrics alongside sugar, not just calories.
He saw his first pediatric NAFLD case in 1996 (ALTs in the 300s) and his first pediatric type 2 diabetes in 1992; by the podcast era about a third of new childhood diabetes diagnoses were type 2. De novo lipogenesis, long dismissed as a ~3% pathway after Hellerstein 1998, was shown by Donnelly in 2005 to account for roughly 25% of liver fat. Rare export defects (~1 in 10,000) cannot explain a ~40% NAFLD prevalence—the pathway math points at sugar-driven DNL.

• PNPLA3 risk alleles concentrate NAFLD in Latino populations.
About 19% of Latinos carry the homozygous GG polymorphism that turns a little dietary sugar into a lot of liver fat. He recalls figures like half of obese Hispanic boys showing NAFLD at the time he last checked—likely an underestimate.

• Every diet that works is real food; every diet that fails is processed food.
His clinic heuristic: if it needs a Nutrition Facts label, it has been processed. Broccoli, carrots, and meat-case cuts do not. Targets like '20 g sugar/day' matter less than removing the packaged matrix that delivers sugar plus fiber-stripped starch.

• Ten CPG companies control most of the calories.
Lustig's tally: about ten consumer-packaged-goods firms control roughly 85–90% of the calories Americans eat. After high-fructose corn syrup and the late-1970s dietary guidelines era, industry profit margins reportedly jumped from ~1% to ~5% per year—sugar became the business model, not an accident. He wants Medicare/Medicaid costs yoked more tightly to farm-bill incentives so the metabolic bill shows up where food policy is written.

EXAMPLES

• ALT range creep: 25 !' ~42
Lab 'normal' tracked the population mean as hepatic steatosis became common (Dallas Heart Study–era estimates that ~40% of 'normal' people have liver fat). Clinical targets stayed near the 1976 line.

• Capri Sun birthday party
Daughter raised on milk and water meets pouches at age five; Lustig uses it to show how quickly the sweet environment recruits kids parents thought they had protected.

• Donnelly 2005 vs Hellerstein 1998
De novo lipogenesis reframed from a minor ~3% curiosity to ~25% of liver triglyceride—central to why fructose uniquely feeds NAFLD. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• PNPLA3 GG in ~19% of Latinos
Same sugar load !' disproportionate hepatic fat; ethnicity-aware counseling, not one-size nutrition advice. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Almond calorie absorption
Of ~160 labeled almond calories, roughly three-quarters may be absorbed; fiber and food matrix change the insulin and

fructose story versus juice with the same sugar grams.

OTHER RELEVANT

- **Treat ALT <25 and uric acid ~5–5.5 as action lines.**
  Do not wait for the lab flag at 42 or 7.0 if metabolic risk is the question you care about.
- **Strip packaged sugar before micro-managing macros.**
  If there is a Nutrition Facts label, interrogate added sugar and refined starch first; real-food patterns (regardless of named diet) are what Lustig sees work.
- **Protect kids' taste environment early.**
  Delay sweet drinks and pouches; keep introducing savory foods patiently. Epigenetic and preference programming in childhood is 'the gift that keeps on giving.'
- **Policy has to meet science—science alone has not moved the CPG oligopoly.**
  Lustig got a Master of Studies in Law because educating clinicians was only half the fight; farm-bill and labeling levers matter when ten firms set the default food supply.

#12 – Corey McCarthy: Overcoming trauma, finding meaning, changing the self-narrative, & gratitude

Guest: Corey McCarthy
Date: 2019-12-23 · Duration: 2:27:13
URL: https://www.youtube.com/watch?v=wHv_ey3VvfE

KEYPOINTS

• Peter and Corey met inside North Kern State Prison with Defy Ventures.
Volunteering with Catherine Hoke's program—teaching entrepreneurial skills inside a maximum-security prison near Bakersfield—left Peter convinced the volunteers were being changed as much as the men inside. Corey's credibility came from having lived that world, not studied it.

• A childhood sexual assault at about age seven split his life in two.
At a cold minor-league baseball outing he went to an empty bathroom alone while his older brother got nachos; an attacker was waiting. He describes losing 'the little boy'—leaving the game as a wounded child who later froze into an adaptive child rather than a functional adult. He does not linger on graphic detail; the lasting fact is identity rupture—innocent child to wounded child to adaptive child stuck in survival scripts.

• Peter's 'trauma tree' names five common roots.
Abuse (physical, sexual, emotional, spiritual), abandonment, neglect, enmeshment (kids treated as mini-spouses or confidants), and witnessing a tragic event. Those roots grow shame; untreated shame tends to branch into addiction, codependency, attachment disorders, and habituated survival strategies. Enmeshment examples include single parents unloading adult romantic or financial crises onto a seven-year-old as if the child were a partner.

• Shame plus secrecy recruited more predators.
Corey and Peter note how consistently abusers seem to sense wounded kids—an observation that echoes patterns discussed around institutional abuse scandals. Adolescent Corey piled on early substance use, fighting, and a self-story that he was already ruined. Early sports success and a polished exterior made the inner collapse easier to hide from teachers and coaches.

• Family fracture amplified the wound.
Parents who were both attorneys disagreed about medication; Corey learned to talk his way out of consequences, stole, and at sixteen interpreted conflict as proof his mother did not love him. A 40-ounce beer and cigarettes after one rupture became a template, not a one-off.

• Prison time clarified that desire to change is not a plan.
Wanting a different life while still inside the old identity and peer incentives failed repeatedly. Navigation of prison politics, violence, and isolation taught him how thin willpower is without structure, sober peers, and a rewritten narrative. Average trauma load inside—Peter cites roughly 10–16 serious violent injuries a day in some ER contexts as atmosphere—normalized hypervigilance.

• Recovery required surrender plus daily practices, not a single epiphany.
Twelve-step rooms helped and also had limits he names honestly. The durable shift was treating recovery as identity work—honesty about harm done, amends where possible, and service that interrupted self-obsession. Pros of 12-step rooms included structure and language for amends; cons included rigidity or one-size theology that did not fit every person he met.

• Defy and the Kern visit closed a loop.
Walking back into a prison as a free man teaching skills reframed the years he lost. Peter's 'step to the line' exercise that day—men disclosing shared wounds—underscored how ordinary the pain was even when the crimes were not. Chance mattered: a hallway collision with friend Devin at a bodywork appointment is what routed Corey onto the Defy trip with Peter.

• Good people can do terrible things without that erasing either fact.
Corey refuses both naive innocence narratives and permanent monster labels. Holding both is what lets him parent, work, and speak without collapsing into denial or self-erasure. That both/and stance is what made Peter trust him enough to record without a script or prewritten questions.

• The useful self-talk is responsibility without toxic shame.
Kat Hoke's framing and Corey's own work separate 'I caused harm and must repair' from 'I am irredeemable.' That distinction is what he tries to hand other justice-involved people and anyone stuck in a trauma loop.

EXAMPLES

• Baseball-stadium bathroom at ~7
Family outing, empty restroom, assault; he and his brother came home different people. Parents recognized the gravity enough to respond, which he notes many wounded kids never get.

• Age-12 RCMP arrest in swim trunks
Pulled shirtless from a cottage window by an off-duty officer; pavement burning his feet—an early bookmark in a lengthening record that normalized trouble.

• December 21, 2003 Christmas call
Calling his father's house from custody and hearing his daughter in the background crystallized the cost of his path more than abstract remorse had. Hearing staff ask his daughter if she wanted to speak to him turned abstract fatherhood failure into a single unbearable second.

• Step-to-the-line at Kern
Shared disclosures among men inside made Peter's 'smallest choices, deepest pain' thesis visceral; Corey already knew the map from the other side of the line. Catherine Hoke's own history was why Corey believed Defy was real; pedigree without lived credibility would not have pulled him across the country.

- **Four shame branches**
  Addiction (substances or processes), codependency, attachment disorders, and survival habits that once kept a kid alive but sabotage adult intimacy.

OTHER RELEVANT

- **Name the root before optimizing the branch.**
  Habit apps and productivity advice bounce off untreated shame. Map abuse, abandonment, neglect, enmeshment, or witnessed tragedy first. If you only trim the addiction branch while the shame root stays buried, relapse risk stays high.
- **Wanting change "` scaffolding for change.**
  Corey's prison years show motivation without sober community, honesty practices, and identity work stalls. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Hold harm and humanity in the same hand.**
  Useful for parents of troubled kids and for adults judging their past: accountability without annihilation. Peter connects it to his own dumb teenage choices that luck did not convert into a record—reminding listeners how thin the line can be.
- **Service interrupts the old story.**
  Teaching inside with Defy did more for Corey's narrative than another private insight session alone. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#07 – Deep Dive: Lp(a) — what every doctor, and the 10-20% of the population at risk, needs to know

Guest: Peter Attia (deep dive)
Date: 2019-12-22 · Duration: 1:16:16
URL: https://www.youtube.com/watch?v=OHQiU68Ad7s

KEYPOINTS

• Lp(a) is an LDL particle with apo(a) bonded to it

In this solo episode, with Bob Kaplan asking the questions, Attia describes Lp(a) as a garden-variety LDL particle of about 20 nm whose apoB-100 is covalently linked, through a strong disulfide bond, to an extra protein, apo(a). Which LDLs carry apo(a) is mostly genetically determined, inherited codominantly. Attia estimates somewhere between one in five and one in 10 people have elevated levels, and calls the distribution long-tailed to the right.

• Apo(a) resembles the clotting protein plasminogen

Plasminogen has five 'kringle' folding domains. Apo(a) lacks kringles 1–3 but has the same kringle 5 and a kringle 4 with 10 subtypes. Kringle 4 type 2 varies most between people, from a couple of copies to about 40. That repeat count largely sets the particle's mass, which is why Attia spends time on what he admits is a very technical detail.

• Particle number beats Lp(a) mass

Attia estimates 19 out of 20 Lp(a) tests measure mass, which counts the whole structure. Two people with the same mass can differ in risk: the one with shorter kringle 4 type 2 repeats has more particles and higher risk. A very low mass, under 5 mg/dL, makes a high particle count unlikely. He finds the Lp(a)-cholesterol test unhelpful and prefers particle number in nmol/L.

• Attia's thresholds and reference ranges

For particle number he likes under 50 nmol/L, sees 50–100 as a grey zone, and worries above 100, certainly above 125. The highest he has seen is about 650–700, and a few patients sit at 400–500. Mass-based cut-offs vary: US labs call under 30 mg/dL normal, the European Atherosclerosis Society under 50. He believes the UK and Germany cover apheresis above 60.

• High Lp(a) may once have been an advantage

Attia speculates on two evolutionary benefits. Because of its similarity to plasminogen, Lp(a) promotes clotting, which helps in trauma or childbirth bleeding. It may also scavenge oxidised phospholipids and carry them back to the liver. In today's more inflammatory setting, with hypertension and high insulin, some particles get stuck in the artery wall and bring their oxidised cargo with them.

• Three harms: atherosclerosis, aortic stenosis and blood clots

Attia believes about two-thirds of aortic stenosis cases are explained by elevated Lp(a). The particle seems drawn to the high-pressure aortic valve, where it triggers bone-forming proteins and calcification. He puts the hazard ratio for aortic stenosis at about 2–4, median around 2.5, and for venous thromboembolism at about 3. He stresses that tripling a 1% risk means 3% absolute risk, not cause for panic.

• Statins don't lower Lp(a), but are still used

Statins work mainly by switching on SREBP-2, which adds LDL receptors to the liver, but SREBP-2 also raises PCSK9, which breaks those receptors down. Tom Dayspring's explanation, as Attia relays it, is that Lp(a) is cleared 'last in line', after LDL and VLDL, so it never gets its turn. On statins alone, Lp(a) changes not at all or even rises. Attia is clear that people with high Lp(a) probably should take a statin, but to control apoB, not Lp(a).

• PCSK9 inhibitors lower Lp(a), especially combined with a statin

By blocking PCSK9, these drugs protect LDL receptors and the other receptors, such as LRP, that clear Lp(a), and combined with a statin they lower Lp(a). Attia notes they are not FDA approved for that purpose. Niacin lowers Lp(a) by about a third, but whether it saves lives is contested. He thinks the trial that sank niacin was poorly designed, and says lipidologists are split roughly evenly on using it.

• Lifestyle barely moves Lp(a)

Lp(a) levels are decided mainly by how much the liver makes, with clearance a secondary factor. LDL particle number, by contrast, depends on triglycerides, cholesterol synthesis, absorption and receptors, and diet can change all of them. That is why diet works on LDL particle number but not Lp(a).

• Antisense drugs are the first therapies designed for Lp(a)

Antisense oligonucleotides block the liver's production of apo(a), cutting levels by about 70% to as much as 99% in early data. Attia says that could normalise someone at 200. They had completed phase 1 and 2 trials and were slowly enrolling phase 3. He jokes that three years earlier he predicted results in five years and still says five. He is wary of wiping something out entirely, but says only such a trial can prove causation.

EXAMPLES

• Bob Harper's heart attack

The Biggest Loser trainer had a heart attack at a gym at 52 despite clean annual checkups. A news story reported he had perilously high Lp(a), apparently never measured before. Attia notes that Anahad O'Connor, the journalist who wrote it, is a friend whose interest he sparked. Many patients sent him the article.

• A keto patient's LDL particle number fell from over 3,500 to 1,200

A young patient refused to give up a ketogenic diet, so Attia cut his saturated fat from 75 to 25 grams a day, using olives, olive oil, macadamia nuts and guacamole. In about eight weeks his LDL particle number fell from over 3,500 to about 1,200. In all but one of roughly a dozen similar cases, swapping saturated for monounsaturated fat fixed the problem while fat stayed high. Attia calls this suggestive, not proof.

• Attia gave up blanket baby aspirin

He used to put everyone with elevated Lp(a) on baby aspirin. He now thinks that was oversimplified, since only a subset seem to benefit. He takes DVT prevention seriously instead, such as discussing options for long flights with selected patients.

- **Estrogen therapy may lower Lp(a) by up to 50%**

  Kaplan cites an UpToDate summary saying estrogen replacement reduces Lp(a) by up to 50%, an effect blunted somewhat by progesterone. The same source says hormone therapy isn't recommended for reducing heart risk. Attia finds it 'a bit too good to be true' and plans to look at levels in his patients who have gone through menopause.

- **Apheresis as a last resort**

  Apheresis filters Lp(a) out through a large IV, but because the particles' half-life is only days, patients may need it twice a week. Attia says he very rarely uses it now that PCSK9 inhibitors exist.

OTHER RELEVANT

- **Test Lp(a) at least once**

  Because it is genetic and rarely checked, a particle-number test can reveal risk that a standard lipid panel misses.

- **If it's high, screen the aortic valve**

  Attia orders at least an echocardiogram, and preferably cardiac MRI, even in patients in their 30s. BNP or NT-proBNP can flag strain on the heart.

- **Lower apoB aggressively**

  Since Lp(a) itself is hard to change, Attia controls everything else: apoB with statins and PCSK9 inhibitors, plus other drivers such as blood pressure and insulin.

#08 – Tom Bilyeu: nutrition, fasting, meditation, mindset, immortality, and fulfillment

Guest: Tom Bilyeu
Date: 2019-12-22 · Duration: 1:38:22
URL: https://www.youtube.com/watch?v=82jm5CA9PyQ

KEYPOINTS

• A 2013 meeting with Peter and Dom D'Agostino ended Bilyeu's fat phobia

Bilyeu, co-founder of Quest Nutrition, admits that even while running a nutrition company he believed 'fat makes you fat.' After Peter and D'Agostino visited, with Ron (one of his Quest co-founders) taking the first meeting, the mention of possible anti-cancer properties pushed him to try therapeutic ketosis. Since then he has eaten some version of high-fat, low-carb or fully ketogenic. He credits his habit of seeking disconfirming evidence: 'I want to know how I'm wrong.'

• His first ketosis attempt was miserable but fixed 15 years of wrist pain

He followed a 4:1 ketogenic ratio, with blood ketones above 3 and glucose in the low 60s, for about five days without knowing how to supplement. He calls it the worst experience of his life. But wrists he had iced up to twice a day for 15 years, leaving small burn patches, suddenly felt 'perfect.' He concluded fat mattered for cell membranes and inflammation, offered as his own interpretation.

• Before that, he lost 60 pounds on 'rabbit starvation'

For about two years he ate more than 80% of calories as protein, mostly steamed chicken breast with salt, at 1,200–1,500 calories a day. He went from 230 to about 170 pounds and was 'shredded,' but lost much of his strength. He describes moving from obsessing over size, to obsessing over aesthetics, to now focusing on performance.

• Bilyeu wants immortality; Peter tests whether that survives losing everyone

Bilyeu quotes Woody Allen on wanting to live forever 'by not dying.' Peter's thought experiment: would he accept immortality knowing his wife and friends will die? Bilyeu says yes without hesitation, and that he moved faster, not slower, once money removed any need to work. He and his wife chose not to have kids, and he rejects the 'deathbed regret' argument because your perspective changes with every phase of life.

• A fixed mindset nearly broke him; a growth mindset built Quest

With 990 SATs, he talked his way into film school, then botched his senior thesis film so badly that he stole the master copy. Classmates cut it into joke reels. Believing talent was innate, he was crushed until he began asking why he couldn't learn to tell stories better. A tech job meant to fund filmmaking for 18 months stretched on for years.

• He walked away from paper millions, and that is how Quest began

Bilyeu held 10% of a security software company worth about $22 million at its peak and was miserable. He told his partners they could sell it for a billion and he would take nothing. Instead they asked him to stay and build something meaningful, which led to Quest in 2010. He describes Quest as a food company aiming to 'end metabolic disease,' not a bar company.

• Money didn't change how he felt the next day

Bilyeu says he expected wealth to bring the reverence he once felt toward rich people and to wash out his insecurities. Instead it was like losing his virginity: great, but he was the same person. In his view money is 'inert' but enormously powerful when aimed at a clear problem, especially to direct capable people. He names Elon Musk as a role model.

• His formula for fulfillment is becoming someone you're proud of through hard skills used for others

Fulfillment ebbs and flows; it isn't a permanent state. Serving soup feels good, he says, but fulfillment is the Toyota engineer who used hard-won skills to multiply a soup kitchen's output. He defines power as the ability to manifest the world you imagine and cites Mother Teresa. Peter adds that it's hard to feel fulfilled without serving someone else.

EXAMPLES

• The magic genie question, across 1,500+ interviews

Bilyeu personally interviewed everyone Quest hired, from executive VP to janitor, more than 1,500 people. He asked what they'd wish for, with no curing cancer and no extra wishes. After nudging past 'a job' to 'money,' he says every single person named the same figure, one million dollars, which wouldn't even buy a house in LA.

• Quest University and the birth of Impact Theory

About 1,000 of Quest's roughly 1,400 employees grew up poor, like Rashon Jackson, a student Bilyeu remembered from college. Quest tried to treat 'making protein bars as your tuition' and helped one worker move into tech and later found a company. An internal show, Inside Quest, felt like a brand mismatch, so he spun the studio out as Impact Theory.

• Why he'd rather keep you four years than 20

Bilyeu says a happy employee for three or four years beats a resentful one for 20, and calls his motive frankly selfish. As a child he pretended not to see Easter eggs so his sister could win, saying he's 'wired' to enjoy others winning.

• Peter's sleep study example

Peter cites a University of Chicago study in which four hours of sleep a night for 14 days cut glucose disposal on a clamp by about 50%, making participants roughly twice as insulin resistant. He calls it 'one study' among several and now suspects sleep loss, not only diet, explains his metabolic decline during residency.

OTHER RELEVANT

• Bilyeu's routine

He eats high-fat, low-carb rotations of beef, chicken, lamb and pork, and cheats about twice a year. He alternates ketogenic weeks, when 16-hour fasts feel easy, with higher-protein weeks because extended ketosis 'softens' his muscles. His normal overnight gap is 14 hours, and he does one five-day water-only fast a year. He reaches ketones in the 3s but feels about 20% less energetic by day four, losing three or four pounds if lean versus ten pounds carb-fed, much of it water.

- **Protect sleep as a performance tool**
  For about 16 years he has been in bed by 9 p.m. on weekdays and woken without an alarm. His logic is that sleep makes waking hours more efficient.
- **Use breath meditation and abort bad lifts**
  Navy SEAL Mark Divine talked him into meditating. Diaphragmatic breathing before going on stage gets him to 'absolute zero' stress. In the gym he warms up to 315 pounds on the deadlift and aborts about one in five sessions if his sacroiliac joint or lower back feels off, a rule he also applies to squats.

#02 – Rhonda Patrick, Ph.D.: paradox of IGF-1, ketogenic diets and genetics, benefits of sauna, NAD+

Guest: Rhonda Patrick
Date: 2019-12-17 · Duration: 1:49:49
URL: https://www.youtube.com/watch?v=oXQ9yvGVJDE

KEYPOINTS

• IGF-1 sits in a paradox between growth and longevity.
Higher IGF-1 tracks with more cancer in human polymorphism data, while very low IGF-1 risks frailty and loss of lean mass. Peter describes a right-skewed U-shaped all-cause mortality curve that nadirs around the 70th percentile of IGF-1; above that, the uptick is mostly cancer, while cardiovascular and neurodegenerative risk largely flatline. Peter jokes that living forever at the absolute bottom of IGF is not the clinical goal the U-curve suggests.

• Cycling high and low IGF may beat living permanently suppressed.
Valter Longo's work and short water fasts (including clinical 48-hour protocols around cancer care) sit in this frame: periods of growth alternating with periods of lower IGF, rather than chronic caloric restriction alone. Rhonda notes rodent fasting results are hard to translate because mice lose ~20% body weight in a 48-hour water fast.

• A meaningful minority of keto patients are lipid hyper-responders.
Peter estimates roughly 10–20% of people he has seen on a standard ketogenic pattern—often "e40% of calories from saturated fat, ~40–45% mono—see LDL particle number explode even as triglycerides fall. One relatively young patient who loved keto came back with LDL-P above 3,500 nmol/L. He stresses he has personally seen dozens of patients on keto over his career, so the hyper-responder fraction is not a one-off anecdote.

• Genetics around PPAR pathways may help explain who thrives on keto.
Rhonda discusses PPAR-related fat-metabolism genetics and free vs comprehensive genetic reports as a way to match phenotype to genotype. Both want larger cohorts of hyper-responders genotyped rather than blog debates about whether sky-high LDL-P 'doesn't matter on keto.'

• Exogenous ketone esters can spike blood ketones dramatically.
Rhonda reported going from about 0.1 mM to 6 mM within an hour on a BHB ester—far above the ~0.5–1 mM she sees from overnight fasting or her usual feeding pattern while nursing (often an 11–12 hour eating window). Dom D'Agostino's ketone work comes up as context for how unnatural that spike is compared with fasting physiology.

• VO2 max falls about 1% per year with age—and is trainable.
That ~10% per decade decline roughly parallels age-related muscle loss. A study she cites found 24 sessions of HIIT (about 45 minutes with warm-up/cool-down and hard intervals) raised VO2 max by roughly 12%, enough to offset years of drift.

• Finnish dry-sauna data is dose-dependent and hot.
Observational work (Jari Laukkanen and colleagues) on men using traditional saunas around 175–179°F for ~20 minutes: 2–3 times per week associated with ~20% lower cardiovascular mortality vs once weekly; 4–7 times per week associated with ~40% lower all-cause mortality in the comparison Rhonda recounts. Dementia risk also looked ~20% lower at 2–3 sessions. She contrasts that with infrared cabins that top out near 140°F and cannot reproduce the same thermal load.

• Infrared saunas at ~140°F are not the same stimulus.
She argues you need the high heat and roughly 20 minutes (11 minutes showed smaller effects) to match the Finnish protocols. Sweat-based detox claims get less weight than the cardiovascular and mortality associations.

• Cold after heat is an additive recovery and mood tool.
Her stack is ~20 minutes of sauna then a cold shower or immersion. She has swam in Colorado River water around 42°F when air was hot enough to make it tolerable, and notes 50°F ocean swims of a few hours for a milder version of the same vasoconstriction/afterglow effect. Peter recounts that 42°F swim only worked because air temperature was near 90°F; the same water on a cloudy day would have been untenable.

• Exercise remains hard to beat for brain health.
Despite coming from a deep molecular-biology background, Rhonda says the minimum-effective-dose question for aerobic work plus HIIT keeps winning against supplement stacks when the outcome is brain and healthspan.

EXAMPLES

• LDL-P >3,500 on keto
Peter's young patient case: triglycerides and insulin sensitivity markers looked better, yet particle number and some inflammatory signals worsened—prompting genotype/phenotype curiosity rather than dismissal. Peter refuses the internet claim that particle number is irrelevant whenever someone is in ketosis.

• BHB ester: 0.1 !’ 6 mM in one hour
Rhonda's n=1 ester trial the day before recording, contrasted with ~0.7–0.9 mM from diet-plus-activity and ~1 mM after ~15 hours of fasting when she can manage that window.

• 24 HIIT sessions !’ +12% VO2 max
Roughly 45-minute sessions with five-minute warm-up and cool-down; she uses the result as a practical lever against the ~1%/year age decline. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Sauna dose ladder
2–3×/week ~20% lower CVD mortality; 4–7×/week ~40% lower all-cause mortality in the Finnish men comparisons she cites, with dementia associations in the same literature.

• Lemur caloric-restriction Nature study
Discussed early: CR raised median and maximum lifespan in the lemur model (on the order of an extra year against a ~11–

12 year maximum), as part of reframing growth vs restriction.

OTHER RELEVANT

- **If lipids explode on keto, measure particles—don't hand-wave.**
  Track LDL-P or apoB, inflammation, and consider genetic context. Loving the diet is not the same as a clean risk profile. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prefer Finnish-style heat over lukewarm infrared claims.**
  Aim near 175°F+ for ~20 minutes, several nights a week if tolerated, rather than assuming a 140°F IR cabin matches the epidemiology. Eleven minutes helped in the Finnish data, but twenty minutes carried the stronger association she wants people to copy.
- **Pair heat with cold and protect sleep with a temperature drop.**
  Sauna then cold shower, then a cool bed, uses a steep temperature gradient to fall asleep faster—an effect both endorse from experience.
- **Think in IGF cycles, not permanent suppression.**
  Training, protein, and occasional fasting create ups and downs; living forever at the bottom of the IGF curve is not the goal their data sketch.

#05 - Dom D’Agostino, Ph.D.: ketosis, n=1, exogenous ketones, HBOT, seizures, and cancer

Guest: Dominic D'Agostino
Date: 2019-12-17 · Duration: 2:43:21
URL: https://www.youtube.com/watch?v=q7kOs6bS1Hg

KEYPOINTS

• D'Agostino came to ketones through diving physiology and a lab accident.
His PhD was on how brainstem neurons sense oxygen and CO2. His postdoc built a hyperbaric atomic force microscope, funded through the Department of Defense, to image living cells under pressure. Around 2008–09, while testing different fuels in cell culture, he noticed cancer cells grew more slowly in 1, 2 and 5 mM beta-hydroxybutyrate (BHB) at the same glucose level, and sped up again when the ketones were removed.

• Cancer cells sit on a knife-edge of oxidative stress.
He describes a U-shaped curve. Tumor cells use elevated reactive oxygen species to grow, spread and invade, but because their mitochondria are dysfunctional, pushing oxidative stress further with high-pressure oxygen or chemotherapy can exceed their antioxidant capacity and trigger cell death. He says he saw this directly under the hyperbaric microscope, which no one had used for that purpose before.

• Seizures from oxygen toxicity limit Navy rebreather divers.
A closed-circuit Dräger rebreather leaves no bubbles, which allows stealthy dives, but D'Agostino says about 10 minutes at 50 feet of seawater can trigger a seizure in some divers. He puts brain oxygen pressure at roughly 2,000 times normal. Susceptibility varies with genetics, sleep loss, diet and illness. He notes seizures are likely underreported, because SEALs are known for hiding health problems that could get them removed.

• In his research, ketone esters greatly increased resistance to oxygen-toxicity seizures.
He says a ketone ester increases resistance by roughly 600%, and that exogenous ketones added to standard high-carb rat chow also protected against chemically induced and absence seizures in animal models. He thinks pairing a ketone ester with hyperbaric oxygen (HBOT) could make HBOT safer and more effective, though this is still a hypothesis for people.

• HBOT has about 14–15 approved uses and a powerful effect on stem cells.
Approved uses include decompression sickness, carbon monoxide poisoning, radiation necrosis, noise-induced hearing loss and diabetic wounds. D'Agostino estimates diabetic wounds make up over 90% of hyperbaric facility revenue. He says HBOT mobilizes stem cells about as strongly as drugs like Neupogen. Traumatic brain injury is the most controversial use, and he would want to test low-pressure HBOT soon after injury combined with ketones.

• Ketones act as signaling molecules, not just fuel.
Beyond replacing glucose for the brain, D'Agostino describes BHB acting as an HDAC inhibitor with epigenetic effects and suppressing the NLRP3 inflammasome in ways unrelated to metabolism. He began with the classic 4:1 ketogenic diet, about 90% fat, from the Johns Hopkins protocols, but reached only about 2–2.5 mM. He later moved to a modified diet with more protein plus MCTs.

• MCTs, especially C8, raise ketones because they go straight to the liver.
Medium-chain fats bypass the chylomicron and lymphatic route and travel through the portal vein to the liver, where they are quickly oxidized. He says two to three tablespoons can raise BHB to about 0.5–1 mM even on a high-carb diet, and pure C8 raises it about 20–30% more than a C8/C10 mix. Attia notes that stomach upset often limits the dose before ketones get very high.

• Exogenous ketones reliably lower blood glucose, and why isn't settled.
In rats, the maximum tolerated ketone-ester dose dropped glucose from about 140–150 to around 40 mg/dL, and doses above that made glucose spike. Candidate explanations include ketone-triggered insulin release, better insulin sensitivity (Richard Veech's view) and a shift in the liver's redox balance. Attia says a talk with Stephen Phinney convinced him nobody fully knows the answer.

• Salts and esters differ in chemistry, and D'Agostino isn't worried about racemic forms.
Ketone salts bond BHB ionically to sodium, potassium, calcium or magnesium. He calls them 'ketone electrolyte formulations' and limits magnesium BHB to about 1–3 grams per dose for digestive tolerance. Esters bond covalently, for example to 1,3-butanediol, which was researched as a spaceflight fuel. He says the D-form is the better fuel, the L-form lingers longer, and both suppress the inflammasome. He has seen no data suggesting racemic products are harmful.

• His 'press-pulse' idea for managing cancer metabolically is presented as experimental, not as advice.
Attia frames the question as a thought experiment with a clear caveat: D'Agostino is a PhD researcher, not an oncologist, and is speaking about a loved one who is still receiving standard treatment and losing. The 'press' is continuous metabolic stress: a calorie-restricted ketogenic diet, eating within about six hours, possibly low-dose metformin, and exogenous ketones. The goal is a glucose-to-ketone ratio of 1–2, versus his guess of 25–50 for a typical person. The 'pulse' includes chemotherapy, radiation and HBOT, which he argues may work better in that changed metabolic state.

EXAMPLES

• A seizure in the chamber
In a video D'Agostino shows in talks, a diver breathing 100% oxygen at 2.7 atmospheres has a violent tonic-clonic seizure. It stops as soon as he switches to air at the same pressure.

• Scheck's glioblastoma mouse study
D'Agostino cites Adrienne Scheck's work at the Barrow Neurological Institute. In the GL261 glioblastoma mouse model, a ketogenic diet combined with radiation made the radiation far more effective and cured the tumors in that model, which helped launch clinical research.

• HBOT dosing in his research

For his press-pulse approach he describes 2.5 atmospheres for 60 minutes three times a week, with rest days to allow adaptation. For glioblastoma, where seizures are a risk, he would start around 1.5 atmospheres. Pressure dissolves oxygen into plasma so it can reach poorly perfused, hypoxic parts of a tumor.

- **The 'ketone tolerance test'**

  He came up with this during the conversation: take a known dose of ketones and measure BHB, glucose and insulin at 30, 60, 90 and 120 minutes. Fat-adapted athletes clear ketones quickly, while one commercial packet can push some sedentary people to 5–6 mM.

- **The 'jet fuel' diester**

  The acetoacetate diester raises BHB and acetoacetate roughly 1:1, which he links to anti-seizure effects. It tastes so bad that even in capsules you can taste it, so he sees it more as a medical food or IV therapy.

OTHER RELEVANT

- **Track your glucose-to-ketone ratio, not just ketones.**

  In D'Agostino's framework the ratio matters more than ketone level alone. It is meant for therapeutic settings with medical supervision.

- **Dose exogenous ketones carefully.**

  D'Agostino says he starts to feel 'a little bit weird' once exogenous ketones push him above about 3 mM, even though he uses ketones well. Responses vary widely: in data people have sent him, one commercial packet sent some to 5–6 mM. He also notes that well above the tolerated dose in rats, glucose rose rather than fell.

- **Treat HBOT for unapproved uses with skepticism.**

  Attia notes how much off-label use there is, such as for mercury toxicity. The approved uses are specific, and HBOT itself can cause oxygen-toxicity seizures.

#06 – D.A. Wallach: music, medicine, longevity, and disruptive technologies

Guest: D.A. Wallach
Date: 2019-12-17 · Duration: 2:20:04
URL: https://www.youtube.com/watch?v=nJM0nRS__vs

KEYPOINTS

• Explore an instrument freely first, then learn theory.

Wallach argues that theory should answer questions you have already run into while messing around on an instrument, so it never 'imprisons' you. His plan for teaching his future kids piano is a daily 30-minute sit at the piano with no rules. Anyone sitting there that long will start playing, and after tens of hours of exploration, theory feels like a gift because it explains what you've already found.

• Singing is musical speaking.

Wallach had never sung before college. He tried out for Chester French as the drummer, lost the spot to his friend Damien Chazelle, who later made Whiplash and La La Land, and became the singer as a 'consolation prize'. Once touring demanded an hour or two of singing every day, vocal coaches taught him that speech already has pitch and singing is just controlling it deliberately, which made singing much easier for him.

• Chester French broke through with recordings, not live shows.

The usual path of playing campus parties and then touring East Coast colleges failed for the band. After sophomore year they decided their real product was recorded music and spent about two and a half years in the studio making one complete album. They sent it out midway through senior year, it reached Kanye West, and they eventually signed with Pharrell and Jimmy Iovine's Interscope. Wallach thinks they were a musician's band whose fans were mostly people who played music themselves, and that the internet was just then disrupting how labels found artists.

• Wallach is skeptical of elite universities.

He studied African American Studies with a minor in Kikuyu, and calls Harvard essentially a 'vocational school' for investment banking and management consulting. He estimates 40–50% of his classmates went that way, and partly rebelled by committing to music. He argues these schools reproduce social hierarchy and turn unique high schoolers into 'boring high-achieving technocrats'.

• Spotify succeeded because the music industry had already been wrecked.

Wallach says piracy through Napster and CD burning shrank the record business to about a quarter of its former size. Sean Parker and Shawn Fanning had wanted to legalize Napster, but labels were too defensive. It took decades of decline before rights holders were desperate enough to license something like Spotify. To Wallach as a customer, $10 a month felt 'as if I bought everything ever', unlike Pandora's algorithmic radio, where you couldn't pick songs.

• Healthcare has barely been disrupted, and Wallach sees no obvious 'Spotify of healthcare'.

Most healthcare money goes to labor. Hospitals are not great businesses, and he cites Kaiser's roughly 3–4% margin. Insurers have legally capped margins. Drug companies earn large profits, but they are the ones taking the risk to invent new treatments. He expects many small efficiency gains from consultants, a shift toward technology plus highly skilled nurses and fewer scarce physicians, and the biggest gains from new medicines.

• New medicines are what give people more years of life.

Wallach turned from fixing the US care-delivery system, which is important but local, to biotech, because 'the biggest game changers in human health in the past 50 years have been pills.' He describes precision medicine as treating disease at the level of mechanism with little collateral damage, and says we are in 'inning one or two'. He says his personal motivation is reducing existing suffering more than extending lifespan.

• Wallach's 'singularity' is the ability to simulate biology digitally.

Today biology is learned one variable at a time in mice, dogs, monkeys and people. He calls clinical trials 'a brutal form of learning' whose participants are heroes. Systems biology, which turns mechanistic diagrams into formal code, is a waystation toward simulating biology and running experiments at zero marginal cost. He doesn't know whether that is 20 or 1,000 years away.

• Finding tumor DNA in blood is like finding 'a needle of hay in a haystack'.

Prenatal blood screening works because roughly 10% of the DNA in a pregnant woman's blood can come from the fetus, and half of it is foreign, coming from the father. Early tumor DNA may be under 0.5% or even 0.1% of the total, and it is the patient's own DNA with only a few mutations. Grail, spun out of Illumina, tries to find it by sequencing very deeply against known cancer genes.

• Attia suggests stacking screening tests like layers of Swiss cheese.

Each test has holes. Mammography sees calcified lesions, and diffusion-weighted MRI sees most of the rest. Attia would layer those with a liquid biopsy and a Bayesian layer of family history and mutations, so few cancers can slip through every layer. He thinks liquid biopsies should confirm findings rather than lead. Wallach pushes back that leading with them depends on their sensitivity and specificity, and both agree no test is perfect on both.

EXAMPLES

• A gig with about five to seven people in the audience

The band handed out flyers outside a Boston club for three nights and recruited friends from campus, a 10-minute trip away. Only about three came, and the Thursday show drew roughly five to seven people after two and a half hours of setup.

• OncoBlot's overcalling problem

Attia says this ENOX2-protein blood test correctly identified cancer type about 99.4% of the time in people known to have cancer. In his limited blood-bank analysis of people without a diagnosis, it overestimated cancer prevalence about fivefold. That means it was either useless or detecting cancers the immune system would clear on its own.

• Mammography math from Judea Pearl's The Book of Why

Wallach describes the example as an incidence of about 1 in 700 and a sensitivity of 73%, which still leaves a positive result with under a 1% chance of cancer for a random woman. For someone with a BRCA mutation and roughly a 50% lifetime risk, the same positive result means far more. He uses this to argue that screening only makes sense within risk groups.

- **Glympse Bio's synthetic biomarkers**

  Sangeeta Bhatia's MIT work notes that the human genome has about 550 endoproteases, and that cancers recruit specific ones to remodel tissue. Injected nanoparticles break apart when they meet those enzymes, and the fragments produce an amplified signal in the urine. Wallach is an investor in the company.

- **Peanut desensitization at Stanford**

  Attia credits Sean Parker's funding and Dr. Nadeau's work. He has seen patients once at risk from peanut dust become able to eat peanuts, and says he is far more optimistic than four years earlier. Wallach is getting allergy shots himself and has had no anaphylactic reactions.

OTHER RELEVANT

- **Judge a screening result against your own baseline risk.**

  A positive test means very different things for a low-risk person and someone with a known mutation or strong family history. Ask what your starting probability is before acting on a result.

- **Learn frameworks rather than collecting facts.**

  Attia says medical school taught about 12,000 new words but not how to think, even though many facts have a short half-life. Wallach focuses on the 'skeleton' of a subject, the theoretical structure underneath it, and says he is poor at dates and names.

- **Watch inflammation as a cardiovascular target.**

  Attia points to the anti-IL-1 trial and a methotrexate trial he believed was stopped early, both of which tested improving outcomes without changing lipoproteins. He sees endothelial resilience as the next frontier, and adds that this was his expectation at the time.

#01 – Tim Ferriss: depression, psychedelics, and emotional resilience

Guest: Tim Ferriss
Date: 2019-12-16 · Duration: 2:36:36
URL: https://www.youtube.com/watch?v=MgJTzkRg3cA

KEYPOINTS

• Tim opened Peter's podcast by shifting focus from startups to mental health science.
At the time he was already known for five #1 bestsellers and a podcast with hundreds of millions of downloads. He told Peter he planned to put at least a million dollars over the next few years into psilocybin and MDMA research, compounds that had been shelved for decades more for politics than for evidence.

• His own depression history includes a close call with suicide that became a TED Talk.
He describes himself as someone who was never 'wired to be happy,' recalling childhood mornings when happiness felt incompatible with getting up at 4:30 to train. College friends who later killed themselves left him with a visceral sense of how sudden those outcomes can look from the outside. He frames the TED Talk as an attempt to make that private near-miss useful to strangers who might be in the same tunnel.

• A girlfriend's ayahuasca report became the sales pitch that finally moved him.
She returned from Peru saying two nights felt like fifteen years of therapy. For someone who measures interventions by leverage, that comparison stuck. When he finally went, he took an 'absurdly high' dose—starting around 7.5 and boosting toward 9—because he did not know how to dose what he had taken before.

• About six weeks after those two nights, roughly 90% of a decades-old rage toward his father was gone.
He could watch himself as a 13-year-old in the old scenes without being trapped inside the washing machine of the emotion. He expected the shift to last—forty years out he still believed he would feel the same way about that person. The shift was not a personality transplant so much as a change in vantage: storm outside the window instead of inside the washing machine.

• Heroic-dose psilocybin had been an earlier, private 'reboot' tool.
Drawing on Terence McKenna's framing, five dry grams is a dose meant to flatten even a resistant ego. Tim says looking back he was almost certainly at or above that level during deep depressive episodes, using the experience to interrupt spirals he could not think his way out of.

• MAPS-era MDMA-assisted psychotherapy numbers were the public case for urgency.
As Tim recalled them (with some hedging on exact scales): psychotherapy alone moved roughly 20–27% of PTSD patients below the clinical cutoff, while combining psychotherapy with MDMA reached something like 70%. The FDA had granted MDMA breakthrough therapy designation for PTSD, which he read as regulators becoming collaborators rather than mere gatekeepers.

• Meditation is non-reactivity rehearsal, not a personality transplant.
Friends including Rick Rubin and Chase Jarvis pushed him for more than a year before he started. He frames consistent short sessions as practice sitting with discomfort so that a later psychedelic experience is not your first time on a surfboard in a hurricane. Paul Conti's point about self-treatment also made meditation feel less like self-help and more like relational hygiene.

• Beginner formats he trusts are concrete and short.
Headspace's ten-and-ten program (ten minutes a day for ten days) and Jeff Warren's guidance on Dan Harris's 10% Happier app both get named. Paid apps had a sunk-cost upside for him: having paid made him more likely to show up for lunch-break sits.

• The Catherine McCormick / Gregory Pincus story is his model for philanthropic leverage.
A relatively unknown dinner-table conversation helped bend the arc toward the birth-control pill. Tim treats psychedelic science funding the same way: small, well-aimed capital can move history more than diffuse goodwill.

• His standing advice to a younger self starts before email.
Meditate 10–20 minutes first thing in the morning, before checking messages. Expect to fail about half the time and return anyway. A foldable floor chair lowers friction. The consistent imperfect practice beats the perfect program you quit.

EXAMPLES

• Fifteen years of therapy vs two nights
The girlfriend's Peru report—and Tim's recognition that that ratio is an almost unfair sales pitch to his own optimization brain—is the hinge that turned years of curiosity into action.

• Anger toward his father
He had long given up on that pattern changing. Six weeks after ayahuasca, roughly nine-tenths of it was gone, replaced by the ability to sit with the younger self without fusion.

• PTSD response rates (as Tim recalled them)
Psychotherapy alone ~20–27% crossing below the diagnostic threshold versus ~70% when MDMA was added—numbers he presented with caveats but as 'not subtle' on a graph.

• Opiate deaths among Long Island peers
Friends and family who overdosed, including fentanyl, made the mental-health and addiction case personal rather than abstract, and fed his urgency around understudied compounds. Accident had been the leading cause of death up to about age 40; opiate overdose had overtaken it in the cohorts he watched.

• Morning meditation stack
Ten to twenty minutes of non-reactivity training before inbox; Headspace 10×10 or a two-syllable mantra if that is all that fits; return after lapses instead of restarting from guilt.

OTHER RELEVANT

• Treat yourself as you would treat someone you love.
A line from mutual friend Paul Conti stuck: the way you treat yourself is how you will treat the people you love most. If you

would not wish your inner climate on them, do not accept it as permanent programming. That reframe turned mental-health work from optional optimization into something closer to an ethical obligation to the people around him.

- **Build meditation mileage before high-dose work.**
  Tim's metaphor is ~50 boogie-board sessions before hurricane surf. Concentration practice with eyes closed, then open, reduces the chance that a powerful experience is pure overwhelm.
- **Fund the science, don't DIY the uncontrolled version as policy.**
  He is explicit that Schedule I status looks scientifically unjustified to him, while still pointing listeners toward rigorous MAPS-style work rather than romanticizing unguided heroic doses.
- **Shrink the practice until it is unmissable.**
  If twenty minutes fails, do one two-syllable mantra once and count it. Consistency outruns perfection when the goal is a durable coping mesh, not a streak.

AMA #3: supplements, women’s health, patient care, and more (EP.26) | The Peter Attia Drive

Guest: None
Date: 2018-10-29 · Duration: 2:16:57
URL: https://www.youtube.com/watch?v=kzs7GgxR_FQ

KEYPOINTS

• Lab reference ranges describe the average, not what's optimal

Ranges are built from population distributions and drift as the population changes, so 'normal' increasingly means 'typical' in a country where most people are overweight. Attia argues it's backwards to aim for average on atherosclerosis, the most common cause of death, which is why he wants 'some alpha' on metrics like LDL particle number.

• Attia's stricter lipid and liver targets

Instead of the standard triglyceride cutoff of under 150 mg/dL, he prefers under 100, ideally lower than HDL cholesterol (both in mg/dL). He wants LDL particle number below 1,000 nmol/L, about the 20th percentile. Although his lab's upper limits for the liver enzymes ALT and AST are around 40–44, he likes to see both below 20.

• He prefers an oral glucose tolerance test to HbA1c

Attia calls HbA1c not particularly helpful. His targets: fasting glucose under 90 mg/dL and fasting insulin under 6. One hour after a 75-gram glucose drink, a reasonably muscular man should be under 120 (at most 130) with insulin under 20–30. At two hours, glucose should be back under 100 and insulin ideally under 20. He allows slightly higher values for smaller people, including many women.

• Thyroid testing needs more than TSH

TSH only reflects what the pituitary senses. Attia finds it hard to call someone hypothyroid if TSH is about 0.5–2.0, free T3 above 3.0 and reverse T3 below 12, while acknowledging that symptoms matter alongside the numbers. Sex-hormone panels involve about nine markers, from DHEA, FSH and LH through to DHT.

• The menstrual cycle is the poorly understood variable in women's health

Women's hormones swing sharply across a 28–31-day cycle. Attia describes drawing it out for a patient whose main complaint was PMS mood swings: progesterone drops around days 22–28, and in some women that withdrawal in the brain causes emotional instability. His message to her was 'you're not crazy', comparing it to depression caused by low serotonin.

• Women may respond differently to fasting and ketosis

Attia expects to anger 'the keto herd'. His evolutionary argument is that high ketone levels signalled separation from food, a bad time to reproduce, so the reproductive system should be sensitive to them. He cites David Mangelsdorf's FGF21 data showing different male and female brain responses, with the pituitary among the few tissues involved. His takeaway is that women may need more caution with prolonged fasting or ketosis.

• Oral NR and NMN probably don't raise NAD where it matters

Citing a Cell Metabolism paper by his medical-school classmate Josh Rabinowitz, Attia says tracer studies showed that oral NR and NMN were taken up and turned into NAD essentially only by the liver, 'not exactly the place you want it'. He considers IV NAD infusion clinics quackery, since cells can't take up NAD itself. Because NAD seems to be made in the cytoplasm and imported into mitochondria, he was 'completely unconvinced' the supplements do more than enrich their makers. He flagged it as a view David Sinclair would challenge.

• Low-dose aspirin is now a closer call

Attia used to prescribe baby aspirin when a urine test showed high platelet activity plus one other risk factor, such as high Lp(a), Lp-PLA2 or strong family history. He takes it himself for that reason. A new trial in low-risk people found small risks but also very small benefits, roughly a wash. He says he'll be a little less inclined to prescribe it for otherwise low-risk patients.

EXAMPLES

• A year on 600 mg of lithium

Groundwater lithium levels correlate with better mental health. Attia calls that better-than-usual epidemiology, since nobody chooses their water, though other explanations remain possible. With close blood monitoring and advice from psychiatrist Paul Conti, he took 600 mg a day for about a year. After time-zone confusion accidentally pushed him to about 900 mg and caused nausea, he dropped to roughly 10–20 mg, the range the groundwater data imply. He explicitly warns listeners not to copy the high dose.

• Lipitor 10 mg three times a week plus Zetia

Attia's personal regimen is atorvastatin 10 mg three times a week, about 30 mg a week, which he calls almost a placebo dose next to the 80 mg daily maximum, plus 10 mg ezetimibe because his plant-sterol levels were high. This minimum effective dose put him in roughly the 10th–15th percentile for LDL. His goal is to delay atherosclerosis as much as possible, and he notes the regimen changes over time.

• Berberine as a weak PCSK9 inhibitor

Attia would rather use metformin than berberine for blood sugar, because a regulated drug is consistent from batch to batch. He still uses berberine for LDL because it weakly inhibits PCSK9 and seems to work in people who overproduce that enzyme. Rather than testing for that, he simply tries it and rechecks lipids.

• Tracking glucose and sleep

Attia says a continuous glucose monitor (a Dexcom G6) and the Oura ring are the only wearables he can't stop using. He uses real-time glucose to control his own eating, admitting the iron willpower he had before 2015 is gone. For heart-rate variability, he explains that beats at a steady 60 bpm still vary by tens of milliseconds, which RMSSD captures.

OTHER RELEVANT

• Always ask for absolute risk and time frame

Attia criticises the Women's Health Initiative coverage, which reported a 24% relative rise in breast cancer when the absolute increase was about 0.1%. Whenever you see a relative risk, look for the absolute risk and the length of the study relative to the natural course of the disease.

• Judge diets by your own biomarkers

Attia dismisses headline studies based on food questionnaires, saying he couldn't recall his own meals from two days earlier. He doesn't believe saturated fat is harmless for everyone, so watch how lipoprotein and inflammation markers respond in you.

• Protect sleep first

Asked for one habit, Attia points to sleep as the thing we're least able to go without: people can survive weeks without food and years of poor eating, but only days without sleep before going badly off the rails.