Peter Attia MD Keypoints — Medicine, Science & Society

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Episodes in this pack: 34

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.

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.

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.

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.

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.

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.

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.'

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

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.

#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.

#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.

#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.

#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.

#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.

#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.

#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.

#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.

#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.

#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.

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.