Why DO we get sick? Why hasn’t natural selection, over millions of years, prevented us from getting cancer, heart disease, and depression?

Our bodies seem at times to be faulty designs, prone to error and calamity. Diseases seem like mere accidents of evolution (like the appendix). Or perhaps natural selection just isn’t powerful enough to get rid of some diseases?

The science of evolutionary medicine says this thinking is totally, utterly wrong. Instead, our bodies have evolved over millions of years as a set of compromises, largely in pursuit of reproductive fitness. Frankly put, whatever gets you to survive and have kids is going to persist in the gene pool, even if it causes you lots of disease and pain in adult life.

Why We Get Sick is one of the most insightful and profound books on disease I’ve ever read (including all of my medical school training). After reading this summary, I don’t think you’ll look at disease - and humans in general - the same way again.

In this Why We Get Sick summary, you’ll learn:
• Why humans haven’t evolved to live for 200 years, and why we don’t regrow limbs
• The evolutionary purpose of depression
• Why females evolved to bear children, and why this has led to the classic male fear of commitment and all sorts of confusing sexual behaviors (it takes a few logical steps, but trust me)
• How the fact that we evolved in small tribes in the Stone Age, combined with today's mass media, may increase depression
• Why we’ve evolved to dislike the sound of baby crying

Full Title: Why We Get Sick: The New Science of Darwinian Medicine, by Randolph M. Nesse and George C. Williams

Main Points of Why We Get Sick

• If natural selection is so great, why do we humans even have disease in the first place?
  ◦ The standard arguments of “natural selection just isn’t powerful enough” or “this is just an accidental byproduct of evolution” are usually wrong.
  ◦ Instead, there are powerful principles of evolutionary medicine below.
• 1) Natural selection selects for reproductive fitness. Adaptations that net promote reproductive success are selected for, even if they cause disease after the organism reproduces.
  ◦ In other words, anything that kills or debilitates you after you already raise kids to independence is not strongly selected against. Further, genes that increase your lifetime reproduction will be selected for, even if they reduce your longevity or ‘happiness.’
  ◦ In an extreme example, Huntington’s Disease is an intimidating disease - patients die between ages 40-60, and it’s autosomal dominant. But because it causes no apparent harm before age 40, all their kids are born, so the disease faces little selection pressure.
  ◦ Genes that promote eating and fat storage may increase survival and thus reproductive fitness (especially in the Stone Age), even at the expense of later heart disease.
• 2) Adaptations that might have been helpful in the Stone Age are maladaptive in the modern environment.
  ◦ Genes leading to engorging on foods helped humans survive famine periods, but in today’s abundance leads to massive nutritional excess.
  ◦ Energy conservation and laziness helped us avoid wasteful activity, but today get us to binge Netflix on the couch an entire day.
  ◦ Susceptibility to alcohol addiction - not a problem until readily available, high concentration alcohol. This may also be associated with persistence to seek rewards despite obstacles.
  ◦ Myopia - this might not have been a problem in Stone Age - only when humans starting doing close work did it manifest.
• 3) Behaviors that seem entirely harmful may have unobvious benefits that improve fitness. Traits that give an overall fitness advantage, despite increasing vulnerability to some disease, can still be selected for.
- A clear example: physical pain is useful for indicating injury, withdrawing from the injuring agent, and causing painful memories to avoid the future behavior.
- Morning sickness in pregnancy protects the early fetus from toxins; then subsides in later term when the fetus is less susceptible.
- Depression prevents us from investing resources in impossible goals, forcing us to conserve energy and reflect.
- Bipolar disease/schizophrenia may be associated with creativity.
- Sickle cell allele protects against malaria.
- Gout is caused by uric acid, which is an antioxidant that helps extend longevity.
- Some genetic disorders may decrease miscarriage, thus providing a childbirth advantage.

- **4) Lack of features on our “body wishlist” often stem from tradeoffs we’re not aware of.**
  - The body needs to balance functions like reproduction, survival, damage recovery, defense, growth, energy usage, and disease.
  - Why don’t we regenerate limbs? This is a balance of utility vs. maintenance cost. In the Stone Age, losing an arm would likely mean death, while losing a finger wouldn’t be incapacitating. However, maintaining this system may increase the risk of cancer - there is substantial risk in allowing cells to be multipotent. Thus there wasn’t strong selective pressure for limb regeneration.

- **Why don’t we live for 200 years? Why do we age?**
  - Theoretically we would be able to reproduce for longer, a huge advantage. There must be a competitive equilibrium at play.
  - Animal experiments show that increasing lifespan causes lower and later reproduction. Somehow there is a tradeoff between longevity and vigor.
  - The competitive pressure is for earlier reproduction and shorter generations - these will breed much more within the same time.

- **Other interesting evolved behaviors that present modern problems from a**
  - The huge difference in size of sperm and egg are products of specialization - egg contains the nutrients and are metabolically expensive to produce, while sperm are quick and compete to penetrate the egg. This leads to a slew of follow-on effects, such as women bearing children; men’s fear of being cuckolded; jealousy; and mate selection preferences.

  **Much more interesting details in the Chapter 13: Sex and Reproduction.**
  - If foraging in the forest, consider the competitive equilibrium. Easily accessible foods need some kind of defense, thus are likely to be toxic. Foods that require a lot of effort (eg nuts with hard shells, deeply buried tubers) are less likely to be toxic.
  - The interaction between virulence and dispersal. Pathogens need to spread between hosts. If the pathogen has a method of transmission independent of host function (eg mosquitoes or doctors’ ties) the pathogen can afford to be more virulent and exploit the host resources. Removing the mechanism of dispersal may lower virulence.
  - We evolved in small bands of 25-50 and tribes of hundreds. Before agriculture, mortality balanced reproduction so human population was relatively fixed. This means we have no evolved sense of global altruism and in many senses still have tribal us vs them mentality. Further, many modern aspects of mass media, communication, and social structure are totally foreign.

- Considering evolutionary reasons for illness can help inform the cost-benefit of intervening with medicine.
- If something seems like a maladaptation of the body or an error in natural selection, we probably
have missed something. Instead, consider what utility it might have in reproductive success, today or earlier in human history, and what compromises are in play. It’s unlikely that “natural selection just isn’t powerful enough” is the best reason.

- Consider other aspects of modern society to which we may be poorly adapted: large stratified societies and employers (vs Stone Age small tribes of no more than hundreds); separation from extended family; lack of exposure to outdoors.

1. The Mystery of Disease

- Why do our bodies seem so flawed? Why hasn’t natural selection prevented heart attacks, nearsightedness, and Alzheimer’s disease?
- The common answer that “natural selection isn’t powerful enough” is usually wrong. Instead, the body is a bundle of careful compromises.
- Distinguish between **proximate causes** and **evolutionary causes**. Proximate = “what? How?”. Evolutionary = “why?”
  - For heart attacks, the proximate cause is atherosclerosis and its associated causes.
  - The evolutionary cause questions *why* natural selection hasn’t eliminated the genes that promote fat craving and cholesterol deposition.
- Evolutionary explanations in Darwinian medicine require more than just explaining the current function - it should explain 1) **how the adaptation gives an advantage**, 2) why lacking this adaptation causes a disadvantage, and 3) what was gradually shaped by natural selection to arrive at the current form.
- They’re useful in predicting what to expect in proximate mechanisms.
  - eg if low iron levels in infection are not caused by infection but a defense, then giving iron will worsen the infection
- Causes of diseases
  - Defenses
    - Eg cough, often confused with manifestation of disease
  - Infection
  - Novel environments
  - Genes
    - Damaged genes are selected against by natural selection. Thus defective genes with no compensating benefit are usually not a common cause of disease.
  - Design compromises
  - Evolutionary legacies
    - Evolution is incremental and path-dependent, meaning some setups are legacies from previous evolution (eg esophagus and trachea having the same input thus risking choking)
- Note: The authors of *Why We Get Sick* are not advocating that medicine should assist natural selection, or that biology should guide moral decisions.
2: Evolution by Natural Selection

- If a gene codes for characteristics that result in fewer viable offspring in future generations, that gene is gradually eliminated. The inverse is true.
- Do not think about natural selection as “survival of the fittest” - survival increases fitness insofar as it increases later reproduction.
- **Genes that increase lifetime reproduction will be selected for even if they reduce longevity.**
- It’s no surprise parents are so concerned about their kids’ reproduction.
- Fitness is not determined in isolation - it is in reference to a particular species in a particular environment. Change the environment, and the gene may no longer be fittest.
- Natural selection benefits genes, not groups.
  - Imagine that an individual lemming sacrifices himself for the group to allow group survival in limited resources. The selfish lemming stays back and reproduces as much as possible. The gene for sacrificing oneself gets eliminated.
- Kin selection promotes doing things that increase reproduction of close relatives.
  - Siblings share half of their genes; cousins 1/8th.
  - Selection favors extending help if the cost to oneself is less than the benefit to relative times degree of relationship.
- Reciprocal exchanges - being nice to each other gives mutual benefits without being kin.
- Chance influences natural selection, so that our current state is very path-dependent
  - Creation of a mutation
  - Whether bearer will live long enough to show effects
  - Chance events that influence individual’s reproductive success
  - Whether gene is by chance eliminated in the next generation
  - Unpredictable environmental changes that will occur
- **Thus, natural selection will not create every adaptation that would be valuable, and it does not always take the best path for the long-term welfare of a species.**
  - [Yet this also gives rise to the argument that “this exists merely because the adaptation for it has not arisen yet,” which the author of Why We Get Sick discounted earlier.]
- Natural selection does optimize for quantitative features well.
  - Eg bird wing length, long enough for lift but short enough for control. After hurricane, found dead birds had unusually long or short wings - intermediate ones survived.
- When we find something that seems like an error in natural selection, more likely we are missing some important function that compromises for the deficit.
- **Parable of compromise**
  - Henry Ford: “is there anything that never goes wrong with any of these cars?” Engineer: “Yes, the steering column never fails.” Ford: “redesign it. If it never breaks we must be spending too much on it.”
  - There is nothing in the body that never goes wrong. Traits that give an overall fitness advantage while increasing vulnerability to some disease can still be selected for.
- Good evolutionary hypotheses are testable and stand up to reason.
  - Eg “we die by age 100 to make room for new individuals” - but group selection is not supported
  - Eg “Crying is useful for exercising lungs” - yet lung health in adulthood does not require crying in infancy
Testing evolutionary hypotheses - the “adaptationist program”
- By understanding the functional significance of some aspect of biology, you should predict other unknown aspects, then investigate to confirm whether they are there or not.
- Eg a species of bird may each mating season lay between 3-5 eggs. One may naively think that this happens merely by chance. Instead consider that the individual bird lays a different # of eggs each season to maximize her individual reproductive success. Thus if you add an egg to birds who lay 3 eggs, they are more likely to die than birds who naturally lay 4 eggs.
- Eg sex ratio in humans. One might reason that this is because the X and Y chromosomes are randomly chosen with equal probability, but this is proximate. The evolutionary reason is that producing the gender that is scarce has the reproductive advantage, and that if parents collectively spend equal resources on rearing sons as on daughters, the sex ratio will be balanced.
- Can also use evidence for function in other species, and the match between traits’ characteristics and its functions

Traits can have multiple functions.
- Tongue used for both chewing and speech

3: Signs and Symptoms of Infectious Disease

- Conditions that seem like defects of infection are actually evolved defenses.
  - Maintaining these defenses all the time would be too costly.
  - Hypothesis: Removing these defenses should aggravate and lengthen infection.
  - Fever to increase effectiveness of immune system
    - Syphilis treated by infecting with malaria. 1927 Nobel Prize in Medicine (!)
    - Fever depletes nutrient reserves 20% faster and causes temporary male sterility, may cause tissue damage.
  - Iron depletion to limit bacterial reproduction.
    - Leukocyte endogenous mediator decreases blood iron availability. When sick, we even tend to dislike iron-rich foods like ham and eggs.
    - Transferrin in blood releases iron only to cells with recognition markers; bacteria can’t get iron.
    - Suggestive: Egg white protein is 12% conalbumin, which binds iron, and thus keeps eggs fresh. Human milk protein is 20% lactoferrin.
    - Giving iron supplements in famines can increase fatal infections, before body has chance to develop transferrin.
  - Pain to reduce use of damaged tissue that can compromise reconstruction and defensive mechanisms. Also pain in memory to avoid same situation in future.
    - People who can’t feel pain are nearly all dead by age 30.
  - Mucus traps pathogens, then cough dislodges to be swallowed so invaders killed and protein recycled.
  - Diarrhea to expel pathogens more quickly.
  - Partially: itch from mosquito bite to stop bites as they happen, and avoid situations that
promote bites

- Damage that occurs to host, beyond procuring more resources for pathogen or supporting its spreading/reproduction, is often incidental and costly to both host and pathogen.
  - It does no good for tapeworm to have host malnourished, or for hepatitis to destroy liver.
- Less accessible body areas have less regenerative capabilities.
  - If brain or heart are infected, they are usually fatal, so regenerative capabilities would have little normal benefit.
  - [This is somewhat circular - if these areas did have defense mechanisms, then infections might be less often fatal. So it must be that a defense mechanism sufficient to prevent death in these tissues in rare infections must not outweigh its maintenance costs.]

- Other adaptations
  - Taste receptors detect bitterness, which are more likely to be toxins.
    - Toxins pass by chemoreceptor trigger zone (only brain cells directly exposed to blood) which triggers nausea and vomiting. Hence why many drugs are nauseating, like chemotherapy.
  - Menstruation sheds uterine lining to defend against uterine infections, esp. Sperm-borne ones.
    - Suggestive: menstrual blood differs from circulating blood to destroy pathogens while minimizing loss of nutrients.
    - Species menstruate to the extent appropriate for vulnerability to sperm-borne pathogens. Species who restrict sexual behavior to widely separate fertile periods may menstruate less.
    - Counter: menstruation does not increase with infection, no consistent relationship between amount of sperm females exposed to and amount of menstrual flow. [Good idea of hypothesis testing]

- Defenses need not be adaptive, and may not be essential. Authors aren’t suggesting never relieving these defenses, but rather to be mindful of when it is and isn’t net positive.
  - Naturally, studies that show lack of effectiveness of remedies (like nasal sprays delaying recovery from cold) are unlikely to get funded by industry
- Some behaviors have dual purposes, benefiting both host and pathogen.
  - Sneezing and diarrhea may both be defensive mechanism but also help spread pathogen.
  - Ideally we titrate the mechanism to net benefit the human host.

- Misc notes
  - Antibodies to strep can cause rheumatic fever; and attack nerve cells on basal ganglia, leading to Sydenham’s chorea, possibly even OCD.
  - Rabies moves to brain and increases aggression, spreading by bite; paralyzes swallowing muscles, causing saliva to build up in mouth.

Infectious disease phenomena classification

<table>
<thead>
<tr>
<th>Observation</th>
<th>Examples</th>
<th>Beneficiary</th>
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<tbody>
<tr>
<td>Hygienic measure by host</td>
<td>Killing mosquitoes, avoiding sick neighbors, grooming, removal of parasites</td>
<td>Host</td>
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Host defenses
Fever, iron withholding, sneezing,
vomiting, immune response

Repair of damage by host
Regeneration of tissues

Compensation for damage by host
Chewing on other side to avoid
tooth pain

Damage to host tissues by
pathogen
Tooth decay, hepatitis liver
damage

Impairment of host by pathogen
Ineffective chewing, decreased
detoxification

Evasion of host defenses by
pathogen
Molecular mimicry (MHC
complex), change in antigens
(trypanosome changes surface
proteins in 9 days while host takes
10 days to make antibodies)

Attack on host defenses by
pathogen
Destruction of white blood cells;
secretion of factors that inhibit
inflammation

Uptake and use of nutrients by
pathogen
Growth and proliferation of
trypanosomes, rabies entering
Ach receptor, rhinovirus binding to
ICAM.

Dispersal of pathogen
Transfer of blood parasite to new
host by mosquito, sneezing

Manipulation of host by pathogen
Exaggerated sneezing, diarrhea,
behavioral changes (parasite
causes ant to climb to top of blade
of grass)

4: An Arms Race without End

- Predator and prey adapt to each other in continuous cycles, thus the Red Queen Principle: “It takes all the running you can do, just to keep in the same place.”
  - An arms race can escalate to the point where the organism is hard put to meet other basic needs, but the cost of losing the arms race is so great that enormous expenses must be maintained. [The same may be true of politics.]
  - Bacteria can have 300 generations in a week, viruses even more, and they have vast numbers. Humans have a huge handicap, and instead must have adaptable mechanisms like diverse antibody production to compensate.
- Bacterial resistance to antibiotics
  - MDR-TB has a 50% mortality rate.
  - Bacteria can share plasmids causing drug resistance.
  - Bacterial resistance arises not by gradual tolerance but by rare mutations.
  - If the antibiotic is removed, ancestral strains slowly replace the resistant forms [suggesting
maintaining resistance has a fitness disadvantage].
- Yet the disadvantage of resistant strains can itself be mutated away, such that resistance can persist even when no antibiotics are present for a long time.
- **Myth:** Parasites should help hosts live longer, so that parasites themselves can disperse more offspring to new hosts. Thus the most successful parasites should help the hosts in some way.
  - The authors of *Why We Get Sick* believe this is **grossly wrong** - instead, infections are in a stable equilibrium, where both pathogens and hosts make tradeoffs between values like growth rates, reproduction, and defense.
    - [Though the incorporation of bacteria into mitochondria and chloroplasts might be an extreme example of cooperation.]
  - Another error in thinking: parasites go through thousands of generations of evolution in a host’s lifetime, so it is likely in an equilibrium. It seems unlikely to slowly shift to cooperation, unless perturbed by an environmental change.
  - Another error: neglect of selection among different parasites within the host, and even within the same parasite species.
    - A liver fluke and *Shigella* are competing for the same resources in the host, and the one that most effectively exploits those resources will win.
    - If one parasite selects for cooperation and less virulence, other members of the species will overtake it in reproduction.
- A complete model of virulence would include all the factors:
  - Namely, balancing within-host selection and between-host selection.
    - Selection within a host promotes reproduction and resource usage so that it outcompetes pathogens in the host.
    - Between-host selection limits virulence to increase dispersal.
  - Including factors like rate of new infections, virulence of competing pathogens, origin of new strains by mutation in host (and variation of virulence), and dispersal.
- **Balancing virulence (severity of disease) and dispersal**
  - A pathogen that relies on host function for dispersal will be less virulent.
    - A common cold that spreads through coughs when host is mobile does not benefit by incapacitating host.
  - A pathogen that has an independent mechanism of dispersal can be more virulent (to outcompete other pathogens and promote replication).
    - Malaria pathogen benefits by making host bedridden, so mosquitoes can further feast without recourse. Further, malaria is mild in mosquitoes, since harming mosquito would hamper further dispersal.
- **Importantly, changing the mechanism and ease of dispersal may change virulence.**
  - For *Shigella*, purifying water shifted pathogen population from deadly dysentery strain (which was previously transmitted by water) to less virulent flexneri strain (transmitted directly)
  - Nosocomial infections can increase virulence of pathogens.
  - Theory: HIV could have become more virulent because of cultural factors promoting dispersal (eg prostitutes serving hundreds of men per year) making host survival less important.
- **Thus, epidemics may result when a novel environmental circumstance promotes virulence.** Like bubonic plague festering in Asia but becoming epidemic in Europe among concentrated populations with flea-infested rats.
- Related: polio in early childhood has only mild effects and wasn’t a problem until the early 20th century. Then sanitation prevented polio infection until later age, when it is much more severe.
  - [Hypothesis: therapy that stifles reproduction of pathogen will promote less virulent strains that bypass diagnosis and suppression.]
  - [Hypothesis: therapy that stifles protective symptoms without affecting pathogen reproduction (eg coughing) will lessen punishment of virulence; when this more virulent strain infects a host without treatment, it can be severe.]

- Arms race in deception
  - Some species visually mimic toxic models and dilute the efficacy of the toxic model’s appearance. This sets up an arms race where the toxic model deviates from the mimic.
  - The same likely applies to chemical and molecular mimicry.

**5: Injury**

- Pain (signal that tissue is damaged) and fear (signal of possible danger) are useful to avoid injury. Blocking them can make damage worse.
  - Some fear is innate (rabbit being afraid of foxes) since making a mistake once is very costly.
  - Others can be learned so as to be situationally useful and limit false positives (eg fawn seeing mother running from wolf) which is quickly extinguished when removing the cue.
  - Humans have the benefit of reasoning and memory, so we can learn that fire is dangerous and install smoke alarms without knowing anyone who died in a fire.

- **Avoidance can be conditioned more easily to some cues than others.**
  - Avoiding smells associated with GI illness is easier to learn than noise associated with the same.
  - Avoiding sounds associated with shocks is easier to learn than smell associated with shocks.
  - Hence smell and toxic food are more strongly linked, and sound and acute injury are more strongly linked.
  - Some phobias are learned more readily than others. Monkeys can learn fear of snakes by watching a video faster than fear of flower.

- As with infection, distinguish between impairment from injury vs adaptive responses.

- Repair of injury balances scarce resources vs time; use of part vs protection and healing; recovery of injured cells vs destruction.
  - Separating the functions of repair for different situations may hasten recovery. Eg the immune system may be triggered incidentally in sunburn, but one might suppress it to prevent impeding healing.
  - Yet second-order effects are worth considering. Inhibiting inflammation in sunburn might prevent damaged and precancerous cells from being destroyed.

- We haven’t yet evolved visceral responses to new environmental dangers
  - Fire has been used for 100,000 years, so we might be better adapted to dangers of fire than closely related species (eg being more sensitive to hot objects or faster healing of burns)
Liquid nitrogen and dry ice cause damage, but we do not yet have as instinctive reactions.

Light-skinned races vulnerable to sunburn aren’t adapted to sunny areas. They overexpose themselves, and pain from sunburn comes hours later, thus limiting associating to the event.

- Why don’t humans regenerate limbs or body parts?
  - The balance is between (improvement of fitness and frequency of occurrence) vs (maintenance costs).
  - Maintenance costs include not just energy in maintaining machinery, but increased rate of cancer. **It’s dangerous to let mature, specialized tissue have more than the minimum needed capacity to repair likely injuries.**
  - In the Stone Age, a human who lost an arm could bleed to death in minutes. If it happened rarely, maintaining this machinery in the population could be net negative. Also better to evolve other behaviors (like fear of cliffs).
  - Why not a finger? Loss of a finger is rare and need not hamper fitness.
  - This kind of Darwinian medicine thinking can help us predict what kinds of repair machinery we could expect upon loss of a finger - likely an optimal tradeoff between rapid and reliable repair, costs of needed machinery, and dangers of cancer.

6: Toxins: New, Old, and Everywhere

- In the wild, plants undergo natural selection to develop defenses from eating, like hard pods and toxins.
  - Example toxins: tannins, alkaloids, cyanide, glycosides (foxgloves), diazepam (potatoes), solanidine/tomatidine (nightshades, potatoes)
- If foraging for plants in the forest, **consider the natural competitive equilibrium that would result in the phenotype observed.**
  - Plants readily accessible with little seeming defense (tubers, mushrooms, leaves) must have selected other defense mechanisms, like potent toxins. In contrast, those that have clear defenses (hard shells around nuts, thorns on berries) are less likely to be toxic.
  - Seeds are likely to be toxic if destroyed, but fruits are meant to be eaten and disbursed. Further, immature fruits without ready seeds are wasted if eaten, so they’re likely to be toxic.
  - Same applies to easily accessible prey (caterpillars, insects). Eat the camouflaged frog, not the bright yellow one sitting idly on a branch.
  - Toxins are metabolically taxing for plants to produce, so rapidly growing plants and first leaves of spring are less likely to be toxic.
    - Some plants might adopt the strategy of fast growth with no toxins (eg bamboo).
    - Also a local area devoid of herbivorous predators would have plants less likely to be toxic.
- **We evolved a preference for variety of foods to avoid overconsumption of a single nutrient, which could be risky.**
  - One of many maladaptations for today’s resource plenty world.
- The reduction of toxins in our everyday environment might predispose us to being incapable of
handling large toxic insults.

- **Cooking neutralizes many toxins, giving rise to cultural traditions.**
  - Olmec people boiled corn with alkali which frees vitamin niacin and balances amino acid composition.
  - Porno Indians in California mixed acorn meal with red clay, which bound tannin.
  - [It’s unclear how this arose - whether wise elders noticed a pattern decreed this must be done, or whether the cultures who mutated this trait were selected above cultures who didn’t.]

- We haven’t evolved instinctual avoidance (or metabolic destruction) of new toxins like heavy metals, antifreeze, PCBs, radioactive isotopes.

- People vary in susceptibility to pathogens depending on growth stage and gender.
  - Actively metabolizing tissues are more vulnerable to toxins than dormant ones; dividing cells more than quiescent ones; undifferentiated cells more than differentiated ones.
  - **Morning sickness peaks in first trimester, then subsides over time.** Fetal vulnerability to toxins is also highest in first trimester.
    - It makes sense to be picky with foods (prefer bland foods, avoid strong spices and odors like lamb) since the early fetus is a minor nutritional burden.
    - Suggestive: women with no pregnancy nausea are more likely to miscarry and have birth defects.
    - [Possibly, choice of diet also changes morning sickness, causing some of the variability.]
    - **Consider that suppression of morning sickness may cause birth defects by encouraging harmful dietary choices.**
      - Similarly, children tend to hate bitter vegetables (and prefer sweets).

- Misc
  - GMOs to reduce pesticide use may produce more toxins.
  - Ability to taste phenylthiocarbamate (PTC) may have advantage in avoiding natural compounds that cause goiter. 70% of people in most populations can taste it, while 93% of people in Andes, where compound is prevalent, can.
  - Oxalate (in rhubarb leaves) binds metals and causes kidney stones. Yet eating less calcium causes more kidney stones - because consumed oxalates have nothing to bind to in gut and are absorbed.
  - Mercury fillings may increase gut bacteria resistant to common antibiotics.

### 7: Genes and Disease: Defects, Quirks, and Compromises

- Chance of any gene being altered is one in a million per generation. Thus given world population, 5% of us start life with a brand new mutation found in neither parent.
- Natural selection may not be able to completely eliminate disease genes due to insufficient adverse selection.
  - A harmful recessive gene that confers no disadvantage fo heterozygotes has low rate of adverse selection (even if the unfortunate homozygous recessive die without reproducing).
  - Mutation can create the defective gene as fast as natural selection eliminates it.
- Lethal recessive gene arising in 1/1 million pregnancies will stabilize in frequency at 1/1000 individuals.
- Genes giving rise to serious diseases may have some less obvious benefits that allow persistence.
  - Maintenance of homozygous lethal genes of 3-11% in population requires reproductive advantage of 6%.
  - Bipolar disease may promote risky feats leading to success, and sexual aggression, during manic periods.
  - Cystic fibrosis (deltaF508) may reduce death from diarrhea
  - Tay-Sachs disease may protect against tuberculosis.
  - DR3 (causing childhood-onset diabetes) decreases miscarriage - mating of Dd x DD suggests babies are half Dd, but the observed rate is 66%!
- Further, genetic diseases that occur after reproductive age are less selected against
  - Huntington’s Disease causes little harm before age 40.
- Genes may have benefits only in certain environments
  - In malaria-prevalent regions, G6PD deficiency (causes RBC to burst when parasite uses oxygen); sickle cell
- Benefits in an ancestral environment, costs only in modern environment
  - Tendency for weight gain
  - Susceptibility to alcohol addiction
- Heterozygote advantage
  - They persist despite punishment of homozygous recessives
  - Sickle-cell allele in malarial areas
- [Put crudely, genes that lower the punishment of homozygous recessives - eg fetal death, before substantial investment is made in the child - have less adverse selection. Those that cause death in reproductive years are most costly and selected against. Possibly why genetic diseases tend to cause most malady in either side of the age spectrum.]
- Outlaw genes promote themselves at the expense of the individual
  - T-locus gene in mice - two copies are lethal in males, but males with one copy transmit to over 90% of offspring
  - [Unclear what the mechanism is - does it bias meiosis toward its persistence, or promote spermatid survival]
  - Meiotic drive

- Consider the vastly different survival conditions of early humans.
  - Mortality balanced reproduction - an increase of 1% per century would have led to 1000x fold growth in 70k years, which did not happen.
  - Infectious diseases were probably most common cause of mortality, mainly vector-borne diseases.
  - Humans hunted and gathered. Less aggressive weapon raids, more scavenging from carcasses.
  - Food sources were highly variable subject to environment, promoting strife between groups.
  - Strong local, parochial kin selection and altruistic traits within a group (love, charity, honesty) promoted survival. But no selection for global altruism.
- Ancestral genes may have only recently become a liability in modern environments. They were either neutral in the past or conferred advantages.
Dietary Inadequacies
- Agriculture caused vitamin C deficit due to less foraging for berries and relatively abnormal diets (more wheat, corn)
- Artificial sweeteners may trigger a pathway that reduces glycolysis and blood sugar, in expectation for dietary absorption. If no real sugar is absorbed, body may go into hypoglycemia and crave more food.

Nutritional excess
- In a resource-scarce world, wanting more sugar, fat, protein, salt was a survival trait.
- Storing more weight in response to food was a survival trait in times of famine (“thrifty genotype” as in Pima)
- We have natural limits to overeating, stopping us from overburdening our GI systems. Modern overnourishment is a result of long-term overeating
- We adapted to pick the sweetest fruit - what happens if you surround yourself with eclairs and Snickers bars? Modern food shows supernormal stimuli
  - If you put an egg and a tennis ball near a goose nest, she will roll the tennis ball back into the nest. The ball is more egglike than an egg.
- Having evolved to handle famine, cutting calories may trigger reset of basal metabolism to conserve calories, making further weight loss difficult
- Modern sugar-rich diets cause cavities (were not a problem in skeletal remains)

Lack of movement
- In human history, it was adaptive to conserve energy by being lazy whenever possible.
- Clearly in today’s sedentary environment we move far less than hunter-gatherers.

Myopia
- If a huge 25% of the population is myopic, one wonders how they could have possibly survived in ancestral times? Instead consider that this might be a modern artifact.
- The eye may grow in response to visual blurriness fed to the brain. (If only one part of visual field is blurry, only that part of eye grows - leading to astigmatism). It is remarkably accurate - the leeway for focusing the lens on retina is 1% the length of the eyeball.
- For 25% of people, something about reading or other close work causes eye to keep growing inappropriately.
  - Could be blurred edges of letters, or focus on book with blurred surroundings.

Dyslexia was not a problem when humans didn’t read.

Alcoholism/addiction
- Only a modern problem with widespread availability of alcohol and distillation; and processing of opium into heroin, coca into cocaine.
- Wasn’t a problem with low ABV alcohols like fermented fruit, or when homes had to prepare their own alcohol, or from natural sources.
- The same genes promoting alcoholism may in fact have positive effects: ability to pursue rewards despite difficulties, or reinforcement in response to certain rewards.
Just like with myopia, all people may be exposed to the same stimulus, but a fraction are genetically predisposed to prodigious drinking and addiction

- Skin color
  - Light skinned people in sunny areas get skin cancer
  - Dark skinned people in shady areas get insufficient vitamin D
- Blood pressure might have overcompensated for increase in human size, causing hypertension?

- In some cases, it’s a mistake to ask what proportion of cause is genetic and what is environmental. Both in isolation is insufficient but necessary.
  - Genes interact with one another and the environment to determine the phenotype.
  - [Another counter to the fallacious “we’re 99% genetically alike”]
- Discovery of a genetic cause may actually be a blessing, if a specific feature of the environment causes the disease.
  - Phenylketonuria is minimized in diet free of phenylalanine.
  - Myopia may be prevented with lack of close activity.

8: Aging as the Fountain of Youth

- Over the past centuries, human average lifespan has increased, but maximal lifespan of effectively 115 years has not.
- What people really call aging is biologically termed senescence, the bodily deterioration accompanying age.
- Theoretically it would be a huge reproductive advantage to maintain health for more time - imagine humans who lived to be 300 and reproduced for 100 years. Why haven’t humans selected to live longer?
  - Early theories suggested senescence was necessary to make room for the young. But again, group selection doesn’t occur - the individual that reproduced en masse and lived longer would rapidly overtake the population.
  - Later theories suggested that there is no selection against senescence after reproductive age. Further, if most people are dying for reasons other than old age, there isn’t adverse selection against senescence [and in fact would select for genes that promote early survival but increase senescence].
  - Yet all strategies are relative - the gadfly is born, reproduces, and dies in the same day.
  - Again, per evolutionary medicine principles, there must be a competitive equilibrium at play - living longer must confer some compensatory fitness disadvantage, and the inverse is true.
  - The competitive balance is between faster, more aggressive mating (which may necessarily trade off with decreased longevity) vs longer lifespan and reproductive health (which may necessarily trade off with decreased fertility).
  - Example genes that confer early advantages but later disease
    - Hemochromatosis - excess absorption of iron avoids anemia in early life, causes disease later.
      - 10% prevalence of gene may be explained by heterozygote disadvantage.
• Or it may preferentially benefit females because of menstruation, but handicap men
  ▪ Pepsinogen I - more likely to get peptic ulcers, but may protect against infections
  ▪ Immune system is age biased - protects from infection, but damages tissues and promotes cancer.
  ▪ Alzheimer’s is absent in primates, and is abnormal in recently evolved regions of the brain.
  ▪ Thus genes causing it may confer some intelligence advantages?
    ○ Suggestive: mice on caloric restriction extend their lifespans, but they don’t reproduce, instead staying suspended in a prereproductive state waiting for adequate food supply.
      ▪ [Further, it seems the experiments show benefits when undergoing CR from birth, so it’s unclear if starting midway through life is as helpful.]
    ○ Suggestive: artificial breeding for earlier reproduction in beetles showed shorter lifespans and earlier senescence. The opposite was true of fruit flies bred for longer lifespans (less total reproduction).
    ○ Suggestive: species of opossums on an island without predators age more slowly, live longer, and reproduce later and with smaller litters.
    ○ Suggestive: Males that must compete for mates have shorter lives than females - physiology is devoted more to competition than to preservation of body.
      ▪ [If true, suggests those with more sexual aggression and strength may have shorter lifespans.]
    ○ [All this suggests that modern culture selecting for later age of reproduction (eg from 18 to 35) may unintentionally select for decreased senescence.]
• Menopause is a related mystery. Why stop reproducing at any age?
  ○ This might be explained by a mother stopping reproduction to allow more resources for her offspring.
    ▪ [This might suggest that people in historical areas of plenty (if such places existed) evolved to have menopause at later ages, or that menopause occurs at later ages today than millennia ago.]
  ○ Why don’t males undergo something like menopause? Part of this could be from the lack of ability of males to identify their own offspring, so they partake less in childcare. Their strategy is, to put it crudely, spray and pray throughout life; any male that ceased reproduction early would be at a large reproductive fitness disadvantage.
• Senescence is difficult to observe in the wild because the decrepit old, with just a slight disadvantage, are picked off by predators before the healthy young.
  ○ (Cue joke about just running faster away from lion than the slowest person)
• Some genes may do the opposite of the above, conferring advantages throughout adult life at some cost.
  ○ Gout is caused by urate, which is an antioxidant that scavenges radical oxygen species.
    Might be interesting to see decreased senescence with gout sufferers.
• Our organ systems remarkably seem to decay their reserve capacity at the same rate - heart, lungs, kidneys, neurons.
  ○ Any organ that prematurely fails before the others would be strongly selected against.
  ○ They grow frail enough that any insult to one may spell death. [Thus the fortunate 100-year olds may be those who by random chance suffer no extreme malady, like flipping 30 heads in a row.]
• [This suggests organ replacement may not really move the needle - The authors believe extending maximum lifespan is a fool’s errand, but delaying senescence and maintaining ability up until this maximum is more tractable.

9: Legacies of Evolutionary History

• Evolution is path dependent, making incremental changes on what came before. This can lead to some local maxima that are not global maxima.
  ◦ In all vertebrates, esophagus and trachea have the same input (the mouth), which can lead to choking. This resulted from an early wormlike ancestor that used the same tube for both respiration (mere passive gas exchange) and digestion.
    ▪ From this starting point, local optimization led to accessory openings for air breathing at nostrils at edge of snout, then shortening the intersection of nostrils into back of throat.
    ▪ Insects and mollusks have complete separation
  ◦ Our retina is inside-out, covered by a layer of blood vessels and nerves, an artifact of positioning in transparent animals.
    ▪ To overcome the blind spots of vessels, our eyes perform microsaccades in fractions of seconds to form a complete picture.
    ▪ Promotes detached retina, vs squid eyes that have retina anchored from below by nerve fibers.
  ◦ Appendix was used for digestion as caecum, but now mainly causes appendicitis.
    ▪ Interestingly, if the appendix gets too small, it is more prone to bursting, since swelling is more likely to burst a long thin appendix than a large one. Thus there is a counterforce to gradual reduction of appendix size.
    ▪ Other vestigial traits might be maintained because further diminishing them increases vulnerability to disease.
  ◦ Childbirth process has to deal with increased skull size, limited by constraint of fitting through pelvic ring of bone.
    ▪ Might otherwise design uterus to be below pelvis.
  ◦ Problems with becoming bipedal
    ▪ Lower back pain from compressive forces
    ▪ Knees, ankles, feet subject to different forces than quadrupeds
    ▪ Abdominal viscera designed to hang from upper wall of abdominal cavity
    ▪ The increased size of modern humans might cause blood pressure problems, as an overcorrection for
    ▪ We have two kidneys and one heart, like all vertebrates.
• In heart muscle is too weak to pump fully, congestion happens. We’d wish for body to excrete excess fluid, but historically low blood pressure was likely caused by bleeding or dehydration, during which retention of fluids is useful.
• Consider major aspects of modern society to which we may not be adapted.
  ◦ Working in large organizations of hundreds/thousands - surpassing Dunbar number by orders of magnitude
Stratified societies (early nomadic tribes were small)
Low degree of child mortality (in the past, infanticide may have been necessary to survive)
Readily available, soft, nontoxic foods (less preparation and chewing)
  - Could this affect our misaligned wisdom teeth and need for dental surgery?
Staying sedentary most of day (early humans squatted more)
Artificial lighting most of day, then periodic intense bouts of sun exposure
Nuclear family largely separate from other families
  - Even further, transient caretakers (nannies, day care)
Large exposure to diverse strangers
Jet lag
Lack of exposure to outdoors, natural light
Addictive, endless information customized to us
Lack of food resource scarcity

11: Allergy

- Allergies show such a strong reaction, are so inconvenient, and form a system of such complexity that, per evolutionary medicine principles, it seems unlikely they have no useful function to compensate, else they’d have been selected out.
- Briefly, allergies result when a foreign substance is consumed by macrophages, which present proteins to helper T cells, which present to B cells, which secrete IgE antibodies, which bind to basophils or mast cells, which release chemicals - histamine, defensive enzymes, platelet activators, smooth muscle stimulators
  - IgE makes up just 1/100000 of the total antibody in blood
  - In an allergy, 10% of IgE may be specific to the antigen (eg pollen)
- The function of allergy is unclear, with a few leading hypotheses:
  - Defense against internal parasites and bacteria
    - Worm parasites stimulate local IgE production, and IgE is protective against parasite infection
    - Yet the inverse may be true: worms may stimulate IgE for their benefit (eg increasing blood supply)
    - Some without low levels of IgE have recurrent infections of lungs and sinuses
  - Defense against ectoparasites
    - Inflammatory response may prevent ticks and lice from getting blood meal
    - Explains concentration of mast cells on surface and stimulation of itching
  - A defense against toxins (eg foxgloves, venom)
    - The responses of allergy seem useful to guard against toxins - shedding tears, mucous secretions, vomiting, diarrhea
    - This fits the rapidity and severity of allergies
    - This may help explain why people differ in sensitivity to different antigens - people are allergic to the corresponding toxins to which they are especially vulnerable.
    - Like a smoke alarm, the many false negatives compensate for the one real emergency
It would help to discover the toxins associated with common antigens (eg seafood, pollen, cat hair)

- Allergies are incidental responses to bystander molecules
  - When IgE got triggered in a person’s history (eg during infection), and the immune system developed sensitivity to antigens that happened to be around at the same time
  - An alarm that warns against toxins

- Some data suggest allergies may protect against cancer
- Why are allergies getting more common over the past century?
  - Sensitization to antigens in home environment
    - Lower allergy rates in households with mothers taught to clean of allergens, prevent mites
    - Or lack of exposure to parasites, thus system targets harmless antigens
    - Breastfeeding decreases allergies
    - Greater pollutant exposure in urban environments

12: Cancer

- Cancer arises from malfunctioning of normal mechanisms for cell growth and replication.
- The human body has 10 trillion cells, many of them replenishing and causing mutations in genes, and it’s really a wonder that we’re typically protected against cancers for decades at all
  - Our bodies of course did not evolve to keep us alive for 80 years, so the normal protective may senesce with age
  - We’re also exposed to certain carcinogens that didn’t previously exist (tobacco, meat cooking, plastics, ionizing radiation)
- The relationship between cancer and host operates in some ways like that between virus and host, in being a parasite that appropriates resources for its own gain at the expense of the host
  - Though the cancer is noncommunicable and thus dies with the host
- Cells have normal mechanisms of preventing cancers:
  - Repair of DNA mutations
  - Tumor suppressor genes that inhibit cell growth (eg destroy factor essential to replication)
  - Multiple checkpoints that need to be active for cell replication (like firing a nuclear missile)
  - Inducing apoptosis in cancerous cell (eg p53)
  - Extracellular recognition of cancer (from eg from antigen presentation) and triggering apoptosis or inhibiting growth secretion
- Studying cells in culture can be deceptive, since this environment selects for cells with increased division rates
- One clear linkage between modern environment and cancer: more menstrual cycles means more cancer of female organs (breast, ovaries, uterus)
  - Stone Age women experienced later menarche (eg 15) and earlier menopause (eg 47), in response to scarce resources and infections. Further, they had more children, and breastfeeding meant many fewer menstrual cycles.
Today’s early menarche, late menopause, lack of breastfeeding, and few pregnancies causes 2-3x the number of menstrual cycles. The underlying mechanism could be that the hormonal responses promoting reproduction cause increased vulnerability to some cancer. This suggests that long-term hormonal birth control suppressing menstrual cycles **should decrease rate of cancer**
- Though it’s currently unclear - increases breast cancer, decreases ovarian, endometrial cancers
- Optimistically, this also provides an angle of attack for finding a way to simulate Stone Age menstruation patterns to reduce cancer risk

13: Sex and Reproduction

**Sex and Mating**

- Why sexually reproduce in the first place?
  - Classically this promotes genetic diversity, which avoids overoptimization and promotes survival in changing environments and pathogens.
  - A parthenogenetic woman who can bud off offspring may win in the short-term but the entire breed may be wiped out in one calamity.
  - It may also prevent steady accumulation of deleterious mutations.
- Different animals have different reproductive strategies, varying the # of offspring, the mode of childbearing, the manner of selection of males by females, the split of childcare between female and males.
  - The egg and sperm specialization contrasts with hermaphrodites producing both sex cells. Hermaphrodites may be possible when the same adaptation can serve both functions (eg flowers and plants).
  - Specialization may be driven to the competitive limit when the sperm that carries less nutrients is fastest, thus pushing more of the nutrient storage to the eggs.
- The small size of sperm and large size of eggs make it easier to get sperm inside females, rather than the opposite. This has follow-on effects.
  - Thus embryo development happens in the female, which is a much larger commitment for females than males. **Females know for sure the child is theirs while males don’t.**
    - Thus males naturally have higher risk of commitment compared to female.
    - Future in vitro embryo incubation could lessen this effect for females.
  - Males expend little resources when creating a child and thus can theoretically have hundreds of offspring, while females can have only 5-6.
    - Females therefore tend to be choosier about having sex, leading to known stereotypes.
  - Males compete among each other to have the chance to inseminate the female (through strength, showmanship). Thus female has ability to be choosy among males.
  - Sperm from different males even compete within the female’s body.
    - Relative testis weight is higher for species in which females mate with multiple
males (chimp) and low in monogamous species (gorillas). Humans are somewhere in between.
- Some sperm are incapable of fertilizing egg, and possibly are meant to find and destroy sperm from other men.
- Volume of ejaculate also increases with time couple has been apart as well as time since last ejaculation - possibly to outcompete sperm from another man.
  ○ Orgasm speed
    - If female orgasms happened quickly, they may lose interest in sex before insemination occurs, thus decreasing reproductive success. Similarly with male who took too long to ejaculate.
    - Premature ejaculation is common in young men, perhaps to quickly inseminate before the tribal elders arrived. [Conjecture: ejaculation is also faster in less competitive men who have to sneak in and out and can’t compete in the open.]
- In humans, children require a long period of care to become self-sufficient because of the limitation of skull size able to be born in a female, and need for cultural teaching to operate within society.
- **This long period of childcare requires the participation of both males and females**, which has engendered the following mating-related behaviors:
  ○ Selection
    - Males want women of fertile age, attractive (suggesting good genes), nurturing, uncommitted to others (have no prior children, thus preference for chastity) and sexual loyalty (don’t want to be cuckolded and take care of another man’s child)
      - [Conjecture: babies have adapted cute features (eg big eyes) and parents were selected to prefer these features to increase childcare interest. In turn, female beauty might have the same mechanism - certain facial and body features are selected for to get males to stick around for longer, and males who prefer these features are also selected for]
    - Females want men capable of providing resources, are faithful to the family (thus participating in childcare for long term and not splitting resources with other women), and provide good competitive genes for offspring.
      - This can turn into maladaptive runaway selection, like huge antlers not marginally useful and peacock feathers.
      - [Conjecture: females prefer males larger than they are, because it allows a broadening of scope of survival. Mother wants a male who can fight off a larger lion than she can, thus derisking survival further.]
  ○ Sexual behavior
    - **Female humans conceal when they’re ovulating** (some primates change color).
      - This prevents mates from being absent most of the time and returning only to reproduce.
      - This prevents rival males from swooping in opportunistically and protects the female.
      - This prevents females from associating the pain of childbirth with sex and thus avoiding mate when fertile. [Unexplained why primates that do signal don’t fall prey to this.]
      - This prompts more frequent mating, which could in turn prompt more frequent menstruation cycles as defense against pathogens.
[Conjecture: women have sex with men more often to deplete him of sperm to limit insemination elsewhere. One would expect that the more trust there is in a relationship, the less sex the couple has.]

○ Testing relationship for loyalty
  - **Might provoking the prospective partner** - through arguments, instigating jealousy - be a test for commitment in spite of difficulties?
  - [If true, then relationships where the parties are unsure of each other’s capacity for commitment tend to be more volatile]

○ Jealousy
  - The father can’t guarantee the child is his (while the mother can) thus the man is fearful of being cuckolded.
  - **Jealousy is a response that discourages other mates and the mother from straying. (eg through threat of anger).**
  - This has been institutionalized in many cultures (Chinese foot binding, chastity belts, demonstration of virginity on wedding night, Muslim veils)
  - Imagine what the world would be like “if someone invented a pill that cured jealousy!”

○ [Note this argues against polyamorists’ view of “humans aren’t naturally monogamous”]
  - [Hence double standard of sexual activity. Females who sleep around are chastised by males for risking cuckold, and by women for possibly drawing away men. Males are admired for sexual prowess because of competitive traits.]
  - From the standpoint of efficiency, a single male could fertilize hundreds of females. The fact that humans are equally split in gender illustrates how group selection does not work, and that individual selection has pushed toward

[Not in book, but interesting question: Why is there a range of male:female size in animals? Angler females are much bigger than males, who just attach to the female and wither away. While human males are 60%? bigger than human females]

The competing effects are:

- How many offspring are born and what % of them survive
  - The more that are born, the less males contribute to care and in the extreme just provide the seed, pushing male size down. Also the less selective the female needs to be with mate, since by chance some of the survivors will be quite fit.
- Resources devoted to offspring
  - If females need to lay lots of eggs (eg fish), this pushes female size up. Just carrying one child (eg mammals) may push female size down.
- How much offspring require care before reaching full potential
  - The more this is, the more selective the mother needs to be because of sunk cost in carrying to term and the care afterward. This creates further pressure for males to compete between each other and against her, increasing size.
- How many spare resources are in the environment
  - The less there are, the more resources should go to the female for young (males smaller, anglerfish)
- How much males need to fight each other for dominance to mate
Both of the above if stronger stimulate bigger size for both

- How much females need to fight off males to only mate with strong ones
  - Why don’t females grow larger than males to compete them away?
  - 1) The job of filtering is already done by male competition, so no extra selection need be done by the female.
  - 2) There must be a tradeoff to increased size (higher energy needs, shorter lifespan).
  - So there’s less benefit for females to be larger than males.

- How much males need to survive the environment to reproduce
  - The more hostile the environment, the bigger the male

- How much males need to secure the female from environment vs female securing herself and young
  - The more males participate in the care for the female, the smaller the female needs to be

- How long males and females live
  - The longer they live, teh more capable they have to be to keep survivng

There are some positive feedback loops

- Males that need to compete with each other get bigger
- When males get bigger, females need to get bigger to defeat weaker males she doesn’t want to mate with. This happens until reaching some capacity constraint in resources or survival advantage (eg huge fetus makes mom slow and get eaten)
- This in turn causes both prey and predator species to get bigger (or more agile or stealthy) to avoid being eaten and stirs a feedback loop within that species.

Pregnancy and Childcare

- Pregnancy is a conflict between mother and fetus, according to evolutionary medicine
  - The fetus carries only half the mother’s genes, so their interests are not identical. The fetus will manipulate the mother to provide more nutrition and the mother will resist this.
  - Some argue this is zero sum because the fetus would later need to suffer the same fate as a mother. But of course the fetus has only 50% chance of being a female, and not all its offspring will receive the gene. Thus the gene in the fetus can be greedy with only partial risk of suffering the same fate later.
  - Example: human placental lactogen, which is anti-insulin and raises blood glucose. Mother counteracts by secreting more insulin, which can lead to gestational diabetes.
  - Example: preeclampsia increase blood pressure to provide more nutrients to placenta. Placenta makes substances that constrict arteries in mother’s body.
    - Higher BP mothers have larger babies, and increases in maternal BP show lower fetal mortality.
    - These both incur risks to the mother (and possible death of fetus) but on average the fetus wins and is playing the odds.
    - Further, genetic imprinting may prevent random gambling, expressing greedy genes when coming from the male but preventing it from the female.

- Childbirth
  - More successful (lower C-section rate, lower use of forceps) with a supportive woman around. May be because human are born in odd position.
Oxytocin is secreted during birth with pressure on vaginal walls. Oxytocin makes mother bond to child.

- What are effects of administering oxytocin to minimize bleeding?
- Babies may get jaundice from fetal hemoglobin breakdown, or Rh incompatibility.
  - But bilirubin scavenges free radicals, useful when baby starts breathing for first time.
  - Light treatment is useful to avoid brain damage but should consider side effects (like color vision impairment).

- Crying, Feeding
  - Babies naturally cry to get attention, and this sound is naturally aversive to parents so they try to make it stop.
  - Crying could increase fitness by promoting bonding with mother through contact, and encouraging feeding and lactation, which prevents competing pregnancies.
  - Babies who cry more for no apparent reason are often diagnosed with colic, but colicky babies don’t cry more or at special times, just longer. Maybe this results from modern infrequent feedings and less contact
    - Some native tribes carry babies around constantly and feed multiple times per hour.
  - Spitting up, and “regression” (baby acts younger than it really is) may be manipulation of mother to produce more milk and thus limit future pregnancy

- SIDS
  - May result from immaturity of infant’s nervous system
  - May be higher nowadays because babies and mothers sleep apart. In past, sleeping together led to coordination of sleep cycles and intermittent arousals that sustain SIDS-vulnerable babies

14: Are Mental Disorders Diseases

- Psychiatry has tried to codify the profession through sharp definitions of symptoms and use of effective medications to change emotion. However, the authors of Why We Get Sick argue that ignoring the underlying function of emotions is like ignoring physiology in medicine.
  - This was a shift from understanding mental disorders as maladaptive psychological processes, rooted in experiences and environment.
  - As an analogy to today’s approach to psychiatry, imagine if we investigated “cough disorder,” creating objective criteria for diagnosis and subtyping (like coughing more than twice per hour), then discovering a cough center in the brain and musing what dysfunctions lead to coughing, then investigate genetic causes for people prone to coughing.
    - This is clearly silly, but only because we know cough is a defense and look not for the causes of cough in the nerves and muscles but rather upstream in the stimuli that provoke a cough.
  - Understanding the normal function of emotions should give insight into when it goes wrong.
As with everything else discussed in Darwinian medicine, our emotions are adaptations shaped by natural selection and have powerful uses.

- Emotions adjust cognition, physiology, subjective experience, and behavior to respond effectively in a situation.
- Aversive emotions protect us from bad situations, and positive emotions help us seek opportunity.
- Even if we’re not conscious of the cause of our emotion, it likely exists.

Anxiety

- The fight or flight response is clearly useful in escaping danger - rapid heartbeat, breathing, sweating, increase in blood glucose.
- Justifiable modern day triggers include hearing a gunshot, having a paper due.
- But the system may be overly sensitive, per the smoke alarm principle, since a false positive is not costly but a false negative can be fatal.
- If it’s protective, why not be anxious at all times? It uses extra calories, makes us unable to perform many everyday activities, and damages tissues. But why does stress damage tissues? It makes sense for “expensive” defense mechanisms to push the body past normal operating limits and be released only in case of emergency.
- Passions (somewhat irrational ones) can push past anxiety and be productive in the long run, like quitting job to find more meaningful work.

Sadness and Depression

- Sadness often stems from a loss that can harm reproduction - resources, a mate, reputation, friends.
- The evolutionary function of sadness is to stop current losses and prevent future ones. In particular,
  - It immediately stops you from continuing what you were doing, so as not to repeat losses.
  - It dampens your overconfidence and optimism so that you can reassess your capabilities and goals realistically.
  - It prevents you from wasting energy on impossible goals. Sit tight, save energy, then redirect later.
  - It causes emotional pain in memory to punish whatever behavior led to the loss.
- Some depressions go away after a person gives us a long-sought goal and turns energies in another direction.
- Other functions of depression
  - It suppresses action in people whose abilities threaten superiors (who may then attack)
  - It results when a person cannot win a hierarchy battle yet refuses to yield - depression is an involuntary signal of submissiveness.
  - If researchers removes the alpha male from a primate group and gives antidepressants to another randomly chosen male, that male regularly becomes the new alpha male.
  - Serotonin may thus function in mediating status hierarchies.
- Bipolar disease is so common (1 of 200 people) that it should have some compensatory function. Might it be the benefit of manic periods in chasing opportunity, or creativity?
- **Possible modern causes of depression**
  - **Mass communications make us all one competitive group. No longer do we compare ourselves within a tribe of 100, but rather to 6 billion people.**
    - In the Stone Age, you were likely good at something and valued for what you did, also giving rise to purpose.
    - Now it can feel daunting to be merely average in nearly all respects, and to view all your kin and friends as similarly inadequate.
- **Disintegration of communities**
  - We have a primal need for a secure place in a supportive group.
  - People often live in competitive communities with no blood relatives.
  - Extended families have disintegrated.
  - Religion, social groups, and therapy have substituted for kin.
  - [I suspect a lack of purpose in giant corporations may also trigger a feeling of helplessness]
- **Attachment**
  - Monkeys raised in isolation with no bonding to mothers never recover behaviorally - they don’t get along, have trouble mating, and treated offspring poorly.
  - Those growing up with absent or indifferent mothers may have trouble trusting people, feel prone to rejection, and are eager to please to protect themselves from abandonment.
  - This might manifest in clinging and withdrawal behaviors [or maybe self-sabotage to avoid others hurting them].
- **Child Abuse**
  - Lack of genetic relation between parent and child strongly increases the risk of fatal child abuse.
    - The adaptive strategy for males who take over a group is to kill unrelated children. This prompts the mothers to mate and concentrates resources.
    - In mice, the smell of a strange male can induce miscarriage, possibly to avoid bringing to term a baby that will likely be killed anyway.
  - Non-fatal child abuse may be an extension of this.
- **Schizophrenia**
  - The authors believe schizophrenia (paranoia, bizarre beliefs, hearing voices) is not normal functioning.
  - Yet with 1% prevalence, it should confer an advantage - perhaps in increasing creativity or sharpening intuition about others’ thoughts?
    - Relatives of schizophrenics seem highly accomplished
- **Sleep Disorders**
  - Is sleep shaped by natural selection? Seems so because it’s so widespread among animals, and universally sleep deprivation causes poor performance.
  - How did sleep arise?
    - The Earth naturally has dark-light cycles. Assuming there is greater danger at night (eg from not seeing predators) and more opportunity during day, then an individual that rested at night was more likely to survive than one that was active the entire day.
    - Once you’re inactive at night, then bodily processes (eg memory formation, cell
division, neurotransmitter synthesis, bodily repair) might take advantage of inactivity. This kicks off a positive feedback loop wherein we become more dependent on sleep, and thus more processes become confined to sleep.

- Dreaming may function to purge unnecessary memories.
  - Deprivation of dreaming sleep in cats shortens lives and disrupts behaviors.
  - Note that during dreaming, we have strong visual sensations and perform actions, but little sound, smell, or tactile sensation. This may be defensive - sight is blocked by closed eyes and movement is inhibited by motor paralysis; but we need sound, smell, and touch to detect danger.

- The authors of *Why We Get Sick* understand that many mental disorder cases are pathological and should be intervened in. Mental problems result from genes, early life events, drugs, relationships, life situations, and more, and they can be maladaptive.

- One should wonder - what will happen when we try to neutralize all negative emotions? Further, are there disorders resulting from too little emotion?

### 15: The Evolution of Medicine

- The human body has been shaped over millions of years as a well-functioning bundle of compromises. What looks like mistakes in evolution are more likely the result of:
  - Behavior that seems harmful likely have unappreciated benefits that outweigh costs.
  - Natural selection doesn’t punish genes that cause damage late enough in life.
  - Novel environments make some evolved genes maladaptive today.
  - Design compromises (like upright posture and back problems)
  - Historical legacies.

- The authors of *Why We Get Sick* wish for discussions of disease to include these questions:
  - Which aspects of the syndrome are direct manifestations of disease, and which are defenses?
  - If the disease has a genetic component, why does it persist? What possible benefits might arise?
  - Do novel environmental factors contribute to the disease?
  - If the disease is related to infection, which aspects benefit host, which pathogen, and which neither?
  - What design compromises or historical legacies account for our susceptibility to this disease?

- The authors call for more funding of research for evolutionary medicine.
- There have been barriers to adopting evolutionary medicine
  - Antipathy to ideas of adaptation and natural selection
  - Indoctrination in the randomized-controlled-trial method of scientific inquiry (despite geology being a credible science with its own methods)
  - Allergy to concepts resembling previous mistakes, like vitalism
  - Medical education being too expansive and overwhelming

- Treating patients with evolutionary explanations of disease may transform the way patients see disease, possibly making them easier to address.
For instance, some patients understand heart disease as proximately caused by high cholesterol, high blood pressure, and diet; and see doctors as admonishing them for avoiding foods they like.

But understanding why their dietary preferences evolved in a certain way that is maladaptive in today’s world, and how food manufacturers have co-opted this to produce deceptively tasty food, may give them more ammunition in their behavioral battle.

- Understanding evolutionary bases of disease give satisfying reasons for why disease exists, preventing the feeling of helplessness and meaninglessness to disease.

Open questions

- Evolution can only make incremental changes. Could our species’ next step function in evolution occur with a massive gene rewrite and reinstatement to today’s environment?

- Having dynamic, meta genes would help evolve faster than generational periods and random mutation.
  - Eg for the moth wing color, instead of the gene coding directly for darkness and adapting that gene over generations, you have an upstream gene that changes expression of the color gene in response to current population distribution or outside environment.
  - Then selection will be based on this meta gene’s performance
  - A historical limitation has been inability to receive enough data to inform gene behavior. Genetic engineering hinging on environmental sensors could make this possible (eg if gender ratio is off, push gametes toward less common gender)
  - A strong skill is adaptive learning

- If group selection isn’t real, how do you explain things like soldiers dying to protect one another/a country?
  - Could get so close to fellow soldiers that they feel like brethren, and so close to country that citizens feel like kin
  - Could be unusually high degree of bravery that is maladaptive from a Darwinian point of view

- How do social customs promoting health arise (like raising children and punishing lack of hygiene/incest)? Is it consciously set by people (eg smoking) or does it get selected through natural selection (cultures vary in customs, and the ones that are better for long term success enhance fitness and growth)

- Stupid idea: engineer a harmless virus that constantly infects cells and limits new viruses from competing. Like the Hulk, the secret is that the cells are always infected. Side effect - weight loss.

- What is the mechanism for behavior change by which parasites control ants to climb to the top of grass and hang on?
  - Is it simple hijacking of height-seeking and another that causes muscle lock?

- How controllable is your behavior once you realize biology has pushed you to this behavior?
  - The fear of death is biologically evolved - people who didn’t fear death generally were selected out before reproduction. In practice nowadays death is often very rapid - a car crash or bullet, like losing consciousness when sleeping. You don’t perceive it.
  - Thus one might train away a fear of death by realizing this.
  - Yet I can’t prevent myself from thinking a burger is delicious. Or can I?

- Culture now provides new selective pressures for reproduction
  - Promoting mating with people who are fitter, even if genes promoting weight gain doesn’t
harm natural reproductive ability
- Through inability to support children through resource constraints
- Reproduction pushed to later age (from 18 to 30s) selects against senescence, for longevity.
- Decreased physical competition for reproduction between males (?) may weaken selection for early virility and later senescence.

- Caloric restriction - extends lifespan in rodents.
  - But is this required from birth? Can you induce this halfway through life and extend lifespan?
  - This seems to cause lack of reproduction - are there other penalties?
- Interesting how people can enjoy things without understanding why they like it. Eg the first person to refine sugar or make chocolate clearly knew it was delicious without needing to know why he evolved to enjoy it
- Much of sexual inequalities are biological differences in child rearing. Can we only achieve true gender equality by neutralizing these inequalities - eg with in vitro pregnancy removing the requirement for women to bear children?

Ideas:

- Use body’s natural mechanisms to wire behavior. Like shock collar upon eating food or playing games. Don’t rewire the body.
  - Note that some associations are stronger than others (smell and GI illness more than sound)
- AR glasses that detect food and estimate calorie count
- Weight loss
  - Limit diversity of foods
- Genetic/physiological engineering to promote certain good biological behaviors as crutches
  - Impotence for anyone other than your wife
  - Nausea when looking at any food to avoid, or when stomach is distended, or when contents are off macro balance