Chapter 18  
Evolutionary Medicine

* Why are we susceptible to disease?
* Why hasn’t natural selection selected us to be immune to diseases?
* Why has natural selection left the body so vulnerable?

**Biological causation: proximate and ultimate**

* Much of biology is focused on the physical and biochemical mechanisms underlying the immediate causes traits or processes
* e.g. How is the sex of an individual determined? How does the adaptive immune system recognize foreign material?
* Physiology, genetics, biochemistry, development, and related fields concentrate on such **proximate causation**
* Evolutionary biology tends to focus, instead, on **ultimate causation:**
* How natural selection, evolutionary conflicts, historical contingencies, or chance events shaped the trait under consideration, on a time scale of many generations
* e.g. Why do most species have almost equal numbers of males and females? Why do vertebrates have adaptive immunity?
* All traits have **both** types of causes! A complete biological explanation requires analysis of both.
* It would be a strategic error to isolate the two types of causation from each other, or to focus always on one while excluding the other
* What is medicine?
  + Applied biology that focuses on the proximate causation of human disease

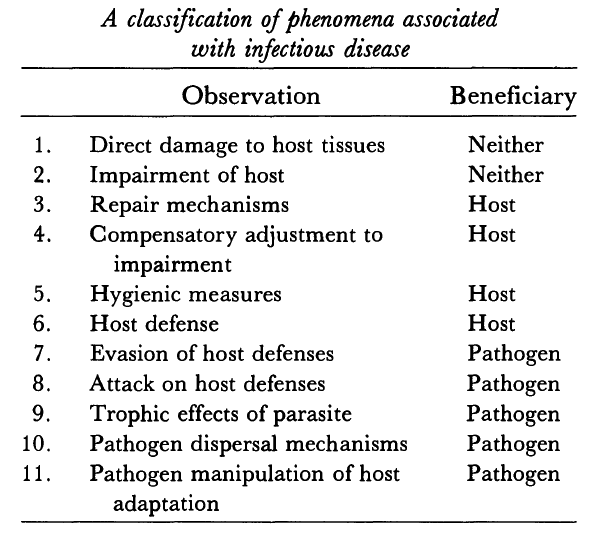
Darwinian medicine

* Evolution is the foundation for biology, and biology is the foundation for medicine, so it ought to pay to consider medical problems in an evolutionary context
* In a nutshell, that’s **Darwinian medicine** (a.k.a. evolutionary medicine)
* Darwinian medicine asks why the body is designed in a way that makes us vulnerable to infections, cancer, choking, depression, hypertension, ulcers, diarrhea, back pain, prenatal complications, you name it...
* It recognizes that the body is a bundle of compromises and is far from perfect
* Explanations for the body’s **flaws and vulnerabilities** fall into just a few categories, and discriminating between them can illuminate the study of medicine:
  + Defenses
    - e.g. symptoms such as cough or fever are not defects but in fact

are the body’s defenses in action

* + - Also **pain**, nausea, vomiting, diarrhea, anxiety, fatigue, sneezing, inflammation, anaemia, **morning sickness**
    - Do we do a disservice by blocking these defenses?
  + Conflicts
    - Who benefits?
      * e.g. human beings are in constant battle with other organisms that have been finely-tuned by evolution
    - Virulence
    - Antibiotic resistance
  + Novel environments
    - e.g. the human body has only recently adaopted its current environment, filled with former rarities, such as high-fat foods
    - new environments bring new health threats
      * common threats to health before modern times
        + accidents, starvation, predation, infectious disease
      * common threats to health today in technologically advanced cultures
        + heart attacks and other complications of artherosclerosis, cancer, non-insulin dependent diabetes, obesity, new infectious diseases
  + Trade offs
    - e.g. overdesign of any one system, such as a pair of unbreakable arms, would upset the entire organism’s functioning
    - Sickle cell anemia
    - Aging
    - Gout?
    - Immune responses take a toll
  + Constraints
    - e.g. the design of the human eye leads to a blind spot and allows for detached retinas. The squid eye is free of such problems.

A Darwinian approach to signs, symptoms and treatment of infectious disease

* As we know by this point in the course, infectious agents maximize their ability to survive and reproduce despite elaborate host defenses
* Parasites interact with hosts in complex ways and it’s helpful to break down phenomena associated with infectious disease:
* What’s the symptom/observation and who benefits?
* 
* Direct damage
  + Direct damage caused by the infectious agent
    - e.g. Gonococcal bacteria eroding joint tissues
* Impairment
  + Impairment of host function resulting from damage
    - e.g. Decreased mobility is an impairment from damage to joint tissues
* Repair
  + Repair mechanisms used by the host to rectify damage
  + Mechanisms for the restraint of maladaptive growth confine regeneration to the tissues where they are most needed
    - e.g. Skin regenerates quickly, CNS system have feeble repair ability
* Compensatory adjustments
  + Made by the host to mitigate impairment
    - e.g. when damaged lungs cannot adequately oxygenate the blood, there is a secondary increase in hemoglobin concentration
* Hygenic measures
  + Used by a potential host to avoid infection. Such defenses start long before infection begins
    - e.g. revulsion toward odors associated with bacterial decomposition helps prevent ingestion of pathogens
    - e.g. avoiding intimate contact with obviously ill individuals
* Host defenses
  + Expel, destroy, or sequester the pathogen
    - e.g. cough, sneeze, runny nose, vomiting, and diarrhea expel pathogens
    - e.g. fever and inflammation expel and destroy foreign matter
    - e.g. immune system recognizes and destroys
    - e.g. some pathogens are sequestered
* Evasion
  + Evasion of hosts defenses
* Attack on host defenses
* Trophic mechanisms
  + Processes whereby the parasite provides for its own growth and reproduction
    - e.g.consumption of host tissues
    - Diptheria and iron
* Dispersal mechanisms
  + Ways that pathogens reach new hosts. Special adaptations for getting infectious stages out of one hosts and into another
    - e.g.encystment, sporulation
    - Malaria and malaise?
* Manipulation
  + Pathogens often manipulate host adaptations for their own purposes
    - e.g.intensification of coughing and sneezing
    - e.g.cholera toxin interferes with reabsorbtion of liquid from the bowel
    - e.g.rabies virus alters aggression
    - e.g.lancet flukes in ants and sheep

Case study: the role of fever in disease

* An evolutionary perspective suggests different possible interpretations of fever:

1. Fever may represent manipulation of the host by the pathogen. Perhaps viruses or bacteria release chemicals that cause the host to elevate its temperature to increase the pathogen’s reproductive rate
2. Fever may be an adaptive defense against the pathogen. Pathogen reproduction may be impeded or immune response enhanced

* Are there any other possible interpretations?
* What predictions could you make from the previous interpretations?
* What tests could you carry out?
* Behavioral fever in the desert iguana
* Desert iguanas are ectotherms and regulate their temperature by moving to warmer or cooler locations
* In a study by Matthew Kluger and colleagues, when injected with dead bacteria they chose body temperatures 2 degrees C higher than normal
* So is fever an adaptive response by the host, or a manipulation by the parasite?
* In another study, lizards were infected with live bacteria, then prevented from thermoregulating
* Most lizards kept at temperatures mimicking behavioral fever survived
* Most kept at lower temperatures died
* Suggests that fever is in fact adaptive for the iguanas
* It would probably be a bad idea to give your lizard aspirin…
* Sodium salicylate reduces behavioral fever in iguanas just as it reduces physiological fever in mammals
* In a study on its effects, all control lizards infected with bacteria developed behavioral fever and survived, but several given the medication failed to develop fever and died
* Lots of examples of behavioral fever in reptiles, amphibians, fishes, invertebrates broadly support the idea that fever is an adaptive response to infection
* It’s unclear how the results in iguanas might apply to humans, and there’s been less work on this than you might expect…
* Case study: fever and chickenpox
  + Timothy Doran and colleagues studied 68 children with chickenpox
  + Experimental group took acetaminophen, control took placebo, double blind
  + By most measures of the duration and severity of illness there was no difference between the groups
  + Where the results hint at a difference, the placebo group recovered faster
  + The simple interpretation is that antifever medication has little or no effect on outcome and that fever is therefore not an adaptive defense in this case
  + The problem is that only slightly more than half of the children developed fever and the fraction with fever was the same in both groups!
  + Did the study test the hypothesis that fever is adaptive?
* Case study: fever and the common cold
  + Neil Graham and colleagues intentionally infected 56 adults with rhinovirus type 2, then treated some with over-the-counter medications
  + Placebo group suffered less stuffiness and made more antibodies to the virus
  + This time, the simple interpretation is that the antifever meds interfered with the immune response and therefore that fever is an adaptive response to the common cold
  + The problem here is that few of the study subjects ran a fever, and the fraction was not significantly higher in the placebo group
  + Few people with rhinovirus run a fever, so the hypothesis was not tested!
* Case study: fever and neurosyphilis
  + Julius Wagner-Jauregg noted that some syphilis patients improved after getting malaria and that syphilis was rare in areas where malaria was common
  + intentionally infected thousands of syphilis patients with malaria
  + remission rates for syphilis increased from less than 1 percent to 30 percent
  + Won the 1927 Nobel Prize for medicine or physiology, but isn’t talked about much these days…
* The case for fever as adaptation
  + The results of Wagner-Jauregg remain the most compelling evidence that fever may be adaptive against human infectious disease
  + Infection, trauma, and injury result in stereotypical responses including fever
  + Fever is a highly regulated response triggered by the release of “endogenous pyrogens”
  + There is clear evidence of its adaptive value in ectotherms
  + For thousands of years fevers were considered a protective response and were even induced by physicians
  + The opposing view may just be a momentary blip in history with the advent of antipyretic drugs
* Bottom line:
  + Despite the unclear results with humans, fever is very likely a very old adaptation
  + Nevertheless, it would be crazy to suggest it is always a bad idea to suppress fever
  + Fever may adaptive against some pathogens and not others (some may do *better*  at higher temperatures)
  + Fever carries costs even when beneficial (sometimes taking the aspirin and feeling better outweighs cost of diminished immune response)
  + Very high fever is bad, fever after stroke is bad
* Case study: the role of iron-withholding
  + iron is a crucial and scarce nutrient for bacteria so several mechanisms have developed to protect the host from bacteria trying to get iron
  + high concentrations of iron in the diet (and blood) is correlated with *increased* risk of infection
  + egg yolks are rich in iron, egg whites are rich in **conalbumin (12%)**, a protein that binds iron and withholds it from invading bacteria
  + egg whites used to be used to treat infection (prior to antibiotics)
  + contributes to longevity of fresh eggs
  + Zulus have high-iron diets, Masai do not
    - Zulus often get amoebic liver infection, Masai do not (less than 10 percent)
    - Masai with iron supplements got amoebic infections (88 percent) (similar effects in Somali nomads 38 vs 8 %)
  + **humans have iron-binding proteins that seem to protect against infection**
    - lactoferrin in milk (20 percent of milk’s protein)
    - cow's milk has only 2 percent lactoferrin
    - breast fed babies more resistant to infection
    - tears and saliva and wound sites
    - researchers predicted conalbumin-like protein should exists within body
    - **transferrin** in the blood acts like conalbumin
    - protein-starved people have low levels of transferin and can be killed by iron supplements, as seen after famines
    - **in the presence of infection, the body releases leukocyte endogenous mediator**
      * raises temperature
      * decreases availability of iron in blood
      * decreased absorption of iron by gut
      * change in diet away from iron-rich foods (ham and eggs seems unappealing)
* Why has natural selection left the body so vulnerable?
  + Old answer
    - Natural selection is just too weak to make body better
  + New answer
    - There are 6 reason why natural selection left the body vulnerable to disease:
      * Selection is slow
        + mismatch
        + competition
      * Selection is constrained
        + every trait is a trade off
        + constraints on natural selection
      * We misunderstand
        + organisms are shaped for reproduction
        + defenses and suffering
    - Mismatch
      * The body is in a novel environment
        + Explains most chronic diseases
      * Breast cancer
        + Much more common today
        + 400+cycles now vs about 110 then
        + Exposure to light at night (light pollution)
      * Cholesterol
        + Modern American 200-250
        + Pre-industrial 131
        + Hunter-gathers 123
        + Rural Chinese 127
    - Competition with fast evolving organisms
      * we evolve much slower than our pathogens
    - every trait is a trade off
      * Most genes are trade-offs
      * Gout: uric acid vs maximum life span
      * ▲ bilirubin = ▼heart attack
      * Lack of exposure to pathogens deprives immune system of inhibitory components
        + Type 1 diabetes (due to TH1 response)
        + Crohn’s
        + asthma
    - Constraints on natural selection
      * Blind Spot
      * Dangerous childbirth pathway
    - Organisms shaped for reproduction
      * Health is NOT selection’s goal
      * More males die early
    - Defenses and suffering
    - Defects:
      * Seizures, jaundice, cancer, paralysis, injury
    - Defense:
      * Fever, cough, pain, fatigue, anxiety
* Why is there aging?
  + Some genes that cause aging have to do with selective cost in the wild
  + Others offer advantages early in life when selections are stronger
  + Implication: Disrupting aging associated genes is likely to cause problems
* The body is NOT a machine
  + No design
  + No blueprints-just genes with variation
  + No normal genome
  + Selection left the body full of mal-adaptations as well as adaptations
* You could design a better body in one afternoon!
  + Eliminate the appendix
  + Take out the wisdom teeth
  + Turn the eye inside out
  + Make bones stronger
  + Improve immune system
  + Install a zipper so babies can exit more easily
* Current View
  + Imperfections are present for reasons
  + Natural selection shapes traits for genes
  + Pathogens evolve to maximize replication
  + Natural selection shapes the body to maximize reproductive success
  + Common genetic disease results mainly from quirks interacting with novel environments
  + Aging results because of pleiotrophy
  + Natural selection continues after reproduction