EVOLUTIONARY MEDICINE

Joe Alcock MD
Blair Wolf PhD
Christopher Eppig

Evolutionary Medicine

- Intersection of evolutionary biology and medical science
- Has medicine ignored evolutionary biology?
- Human vulnerabilities to diseases
- Research + Clinical Applications

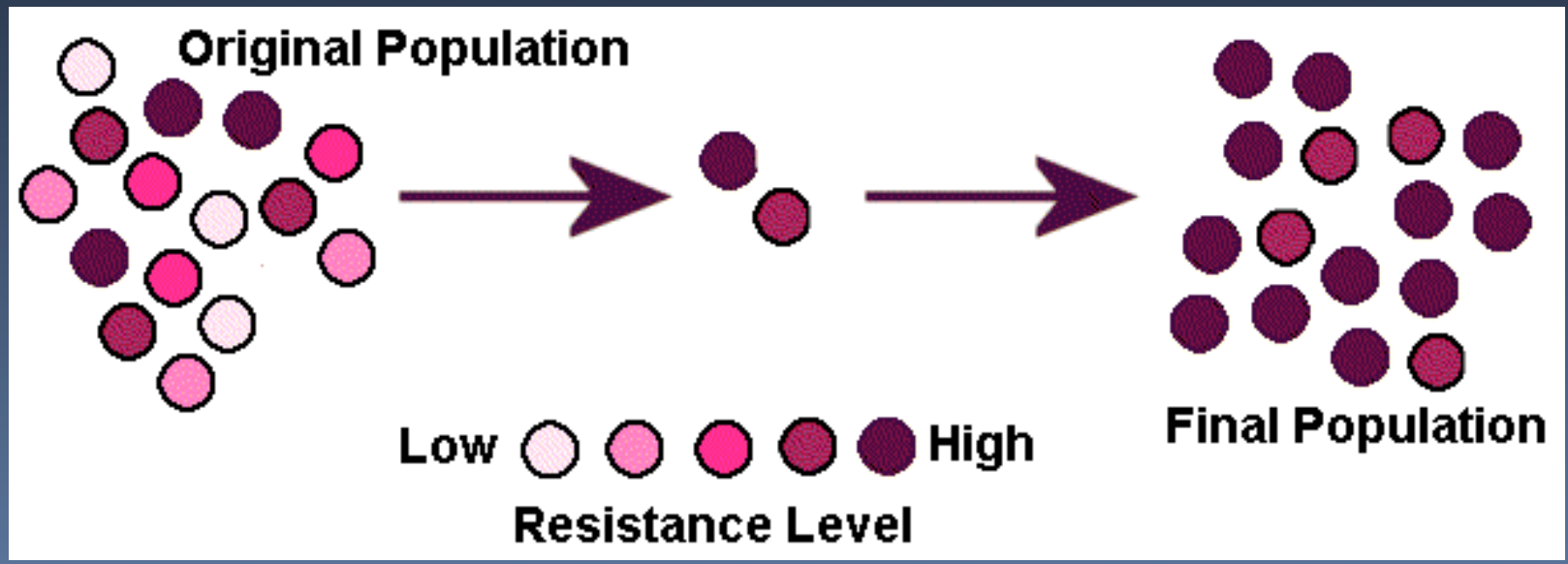
Medicine

- Older than the field of evolutionary biology.
- Medical "practice" may date to earliest social humans
- Medical education - tradition-bound
- Resistant to innovation
- Not quick to embrace evolutionary biology

Example

- Pathogens develop antibiotic resistance
- Multidrug resistant TB, Methacillin resistant Staph Aureus (MRSA). HIV
- Language of medicine: we don't talk about the **evolution** of resistance, we talk about bacteria **developing** resistance.
- In fact we are seeing evolution on action! How do bacteria become resistant?

Bacterial population



Natural Selection

- Natural selection is the engine of evolution
- Natural selection was the insight of Darwin and Wallace back in the 1850s.
- When antibiotics are given to a human population natural selection favors resistant strains
- How?

VIST

- Variation
- Inheritance
- Selection
- Time

Change in gene frequencies

- Heritable variation + Selective pressure +Time
- Without antibiotics, mutant bacteria might die out or remain a tiny minority of the population.
- Add antibiotics & mutant bacteria will reproduce much faster than bacteria without the mutation.
- Difference in reproduction = natural selection
- Changes in genes in the population over time

Simple?

- Does this happen in people? You bet! It just happens a lot slower in people than bacteria
- Example: resistance to pathogens. Malaria infects 300 million yearly. 1 million die.
- RBC mutations are more prevalent in populations where malaria occurs.

Evolution by natural selection

- Changes in gene frequencies – changes in survival and reproduction.
- All you need is genetic variation and differences in reproduction

Key Questions

- Natural selection allows the healthiest and most disease-free individuals to survive and pass their genes. Wouldn't humans evolve towards health?
- Obviously this doesn't always happen
- Selection apparently maintains genetic "achilles heels" in generation after generation.
- Breast cancer genes, genes that cause Alzheimer's disease. Why?

Key Insights

- You are product of innumerable ancestors who survived until reproduction
- Natural selection should promote survival during childhood and early adulthood
- Selection rewards reproductive success not longevity

Levels of analysis

- Most medicine is concerned with what and how questions.
- Evolution concerns itself with historical why questions.

Levels of analysis

- Proximate answers - Physiology and Pathophysiology

- Ultimate answers: reproductive advantages & disadvantages of traits.

Levels of analysis

- During this semester we will ask ourselves lots of "why" questions about diseases.
- Why do illnesses exist?
- What makes certain diseases common?
- Why hasn't natural selection eliminated the genes that cause diseases?
- What are the implications of asking these questions?!

Example: Pain

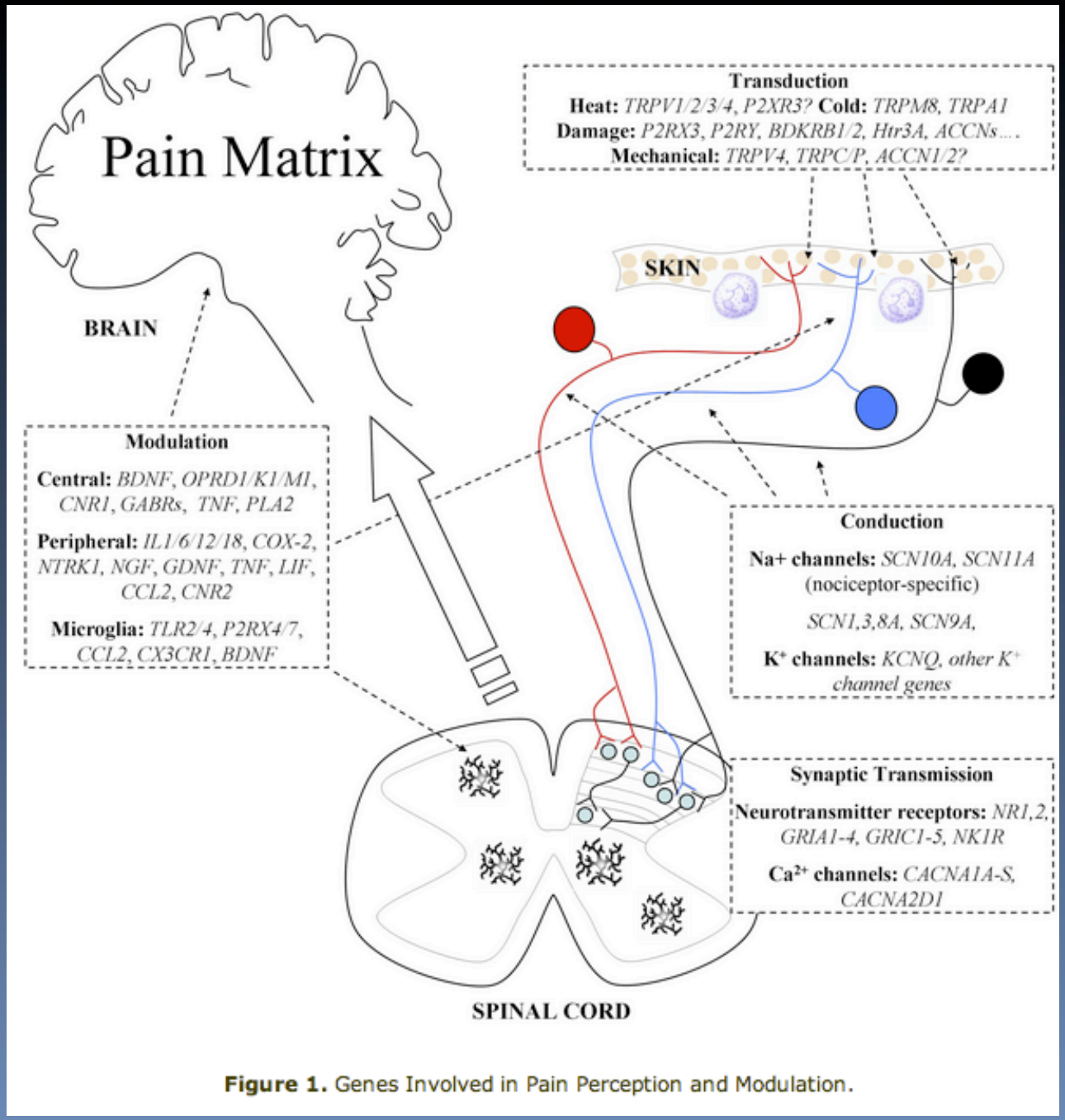


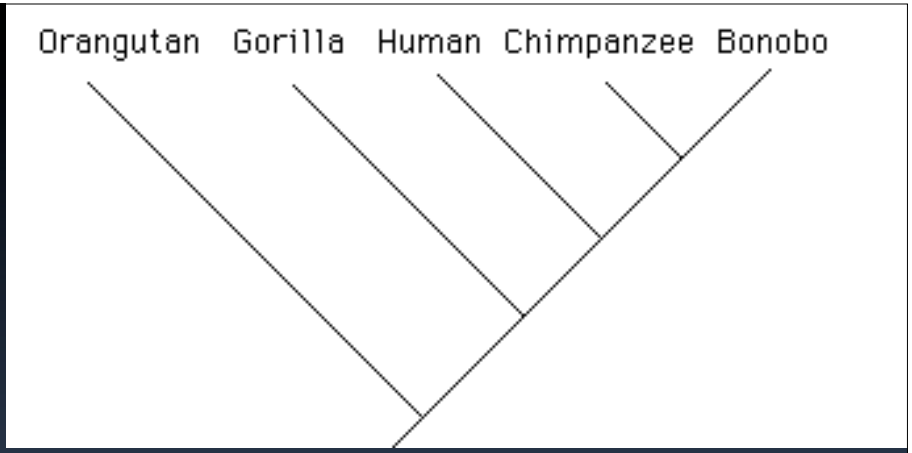
Figure 1. Genes Involved in Pain Perception and Modulation.

Examp
Pain

Evolutionary Explanations for Diseases

- Trade-offs and Constraints
- Evolved host defenses
- Evolution of virulence
- Gene-environment mismatch
- Host-pathogen arms race
- Genetic conflict in reproduction
- Antagonistic pleiotropy

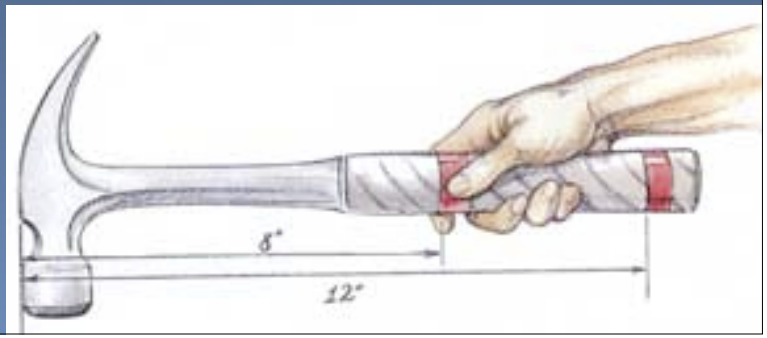
Evo Med Hypotheses



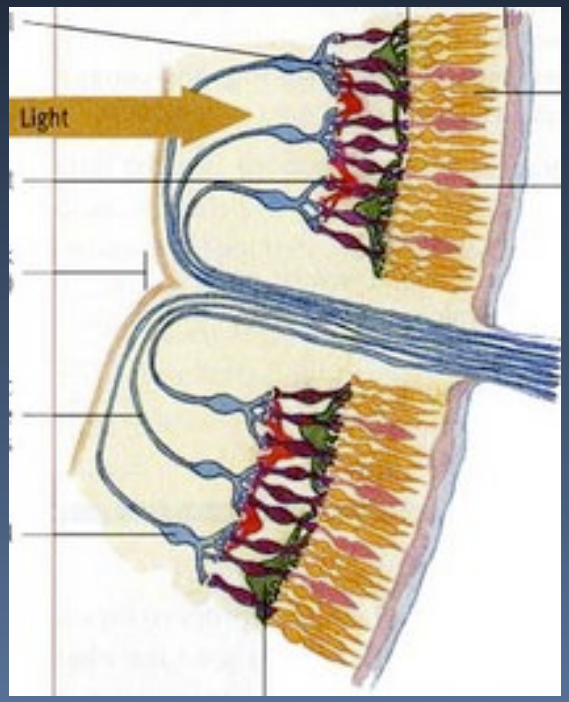
- Two main categories:
- Phylogeny (history)

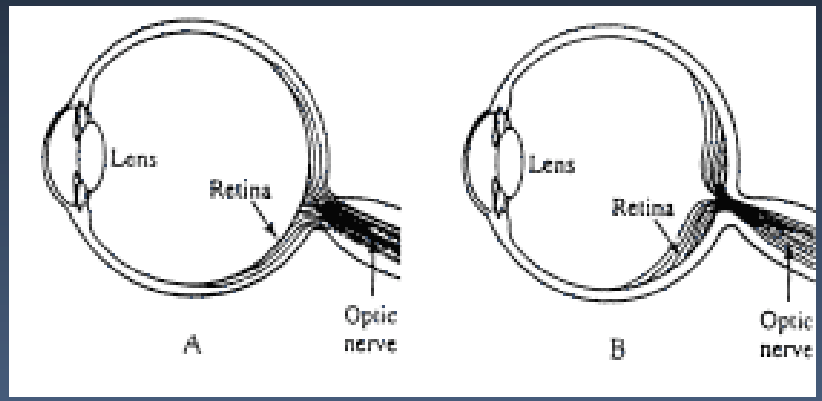
  what series of historical events led to predominance of a particular set of traits?
- Adaptation

  what (function) reproductive benefit does an inherited trait confer?



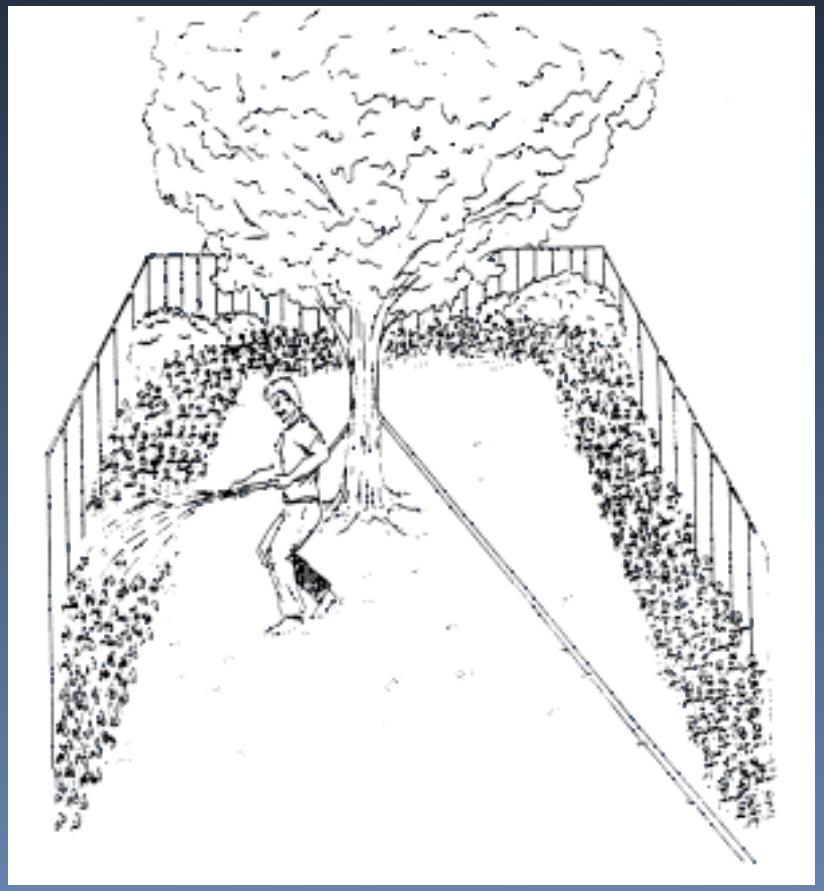
Phylogeny can explain puzzling phenomena – blind spot

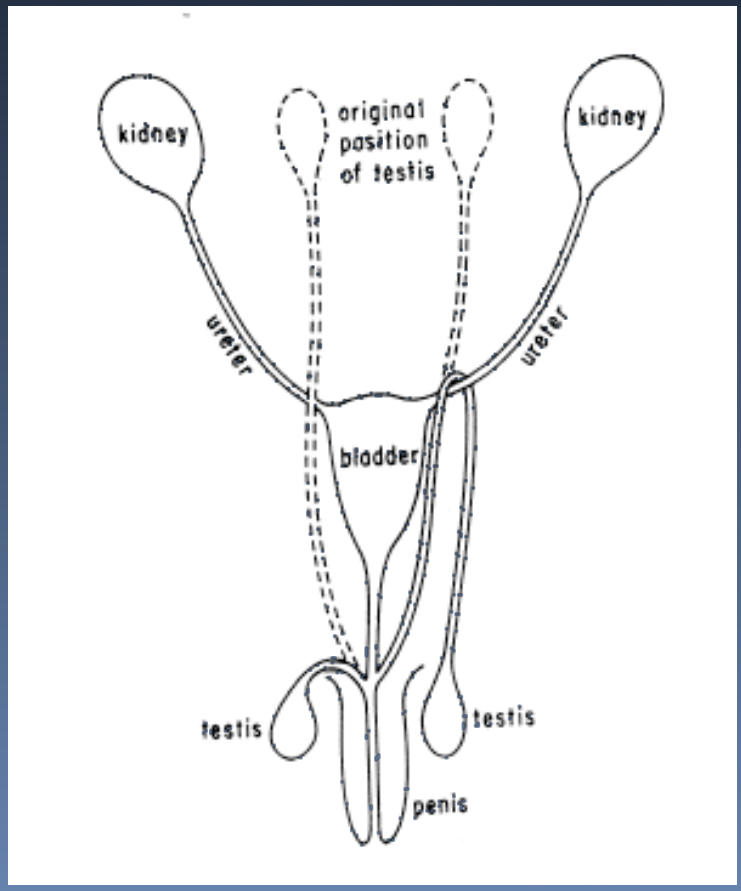




- Constraint of history
- Human Inverted Retina – optic nerve has to puncture the retina

Phylogeny can explain puzzling phenomena - hernias





(from G. C. Williams, Plan and purpose in nature, p. 144)

Tradeoffs and Constraints

- Large neonate head size vs limits of maternal pelvis – cause some childbirth injuries/deaths
- Why can't female pelvis accommodate a larger head size?

Constraints - Example

- Wisdom Teeth
- Why?

Why do we have them?

- How likely is it that they evolved just to mess up our orthodonture?
- Come up with a reason for their existence.
- Come up with a hypothesis for why wisdom teeth might cause problems.

Elephants live 69 years

- Elephants have 6 sets of teeth throughout their long lifespan.

Wisdom teeth have function?

- Unlikely that natural selection would retain structures that cause illness in everybody.

- Prediction:

  An evolutionary approach would suggest that prophylactic removal of asymptomatic wisdom teeth in adolescents would be a bad idea.

Lets test this prediction

- A review of the literature:
- Complications of extraction *far exceed* the consequences of leaving teeth in place.
- "At least 2/3 of these extractions, associated costs, and injuries are *unnecessary*… a silent epidemic of iatrogenic injury that afflicts tens of thousands of people with lifelong discomfort and disability"

The prophylactic extraction of third molars: a public health hazard.
Am J Public Health. 2007 Sep;97(9):1554-9. Epub 2007 Jul 31.

What other parts of our anatomy are routinely removed?

- <- Tonsils surgery becoming much rarer.

- Appendix –>

Surgery for Appendicitis: Is It Necessary? Surg Infect (Larchmt). 2008 Aug 7.

Concept: Cryptic Function - Benefit

- Some diseases might be explained by a hidden benefit
- Benefit does not have to be to the person suffering from the disease
- Might accrue to a pathogen
- Or to a sexual partner
- Or to a person in a different environment
- Or to individuals with a different combination of genes

Evolved Host Defenses

- Cough
- Fever
- Nausea
- Diarrhea

- Symptoms may give pathogens a reproductive advantage– or may help humans survive infections

Example: Itch

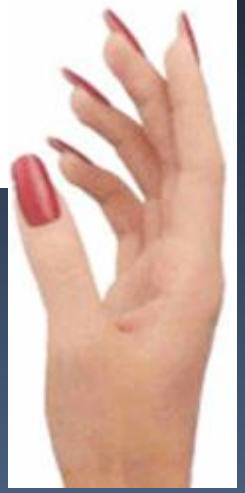
- Why does a mosquito bite itch?
- Does itch have a function?

Evolution of Virulence

PSEUDOMONAS OUTBREAK LINKED TO NURSES' FINGERNAILS.

Infectious Disease

AJN, American Journal of Nursing. 100(7):17, July 2000.



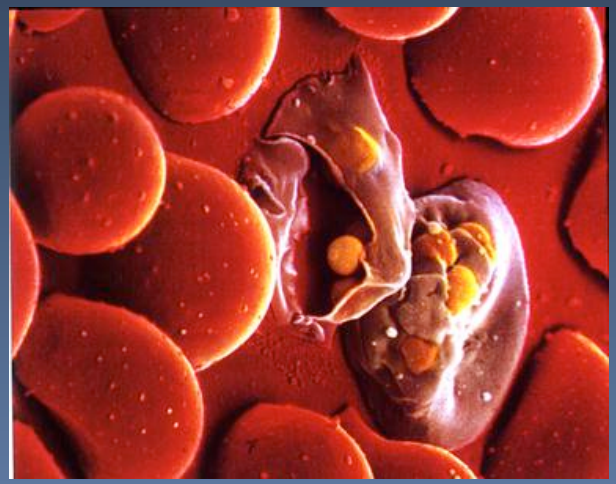
- Artificial nails and hospital setting benefit pathogens
- Easy transmission leads to more virulent bugs
- Community acquired and Hospital acquired pneumonia

Gene Environment Mismatch

- In Sickle cell, benefit accrues to heterozygotes in malarial areas
- Others suffer disease
- The stronger the mortality pressure – the higher the cost of defense

Host-Pathogen Arms Race

- Defense against pathogens becomes increasingly costly as bugs learn to evade defenses.



Genetic Conflicts in Pregnancy

- Gestational Diabetes
- Cryptic benefit accrues to paternal genes

Antagonistic Pleiotropy

- Evolution has BIGGER effects the YOUNGER you are.
- Gene that helps early survival might be favored even if it kills you in old age
- Infectious Diarrhea and Hypertension

Discoveries during my career…

- Pneumococcus resistance to azithromycin
- Gonococcus resistance to ciprofloxacin
- Sinusitis & otitis media can be managed expectantly

Rivers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet. Oct 21 2006;368(9545):1429-35*

In vivo emergence of high-level macrolide resistance in Streptococcus
J Clin Microbiol. 2007 Dec;45(12):4090-1. Epub 2007 Oct 17

Discoveries 2…

- Hormone replacement therapy increased mortality from both heart attacks and breast cancer

Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin
JAMA. 2008 Mar 5;299(9):1036-45

Discoveries 3…

- Chlamydia pneumonia in atherosclerosis
- Zetia – perhaps dietary fat and cholesterol not quite so bad

Chlamydia pneumoniae infection and coronary artery disease
Int J Cardiol. 2008 Aug 15

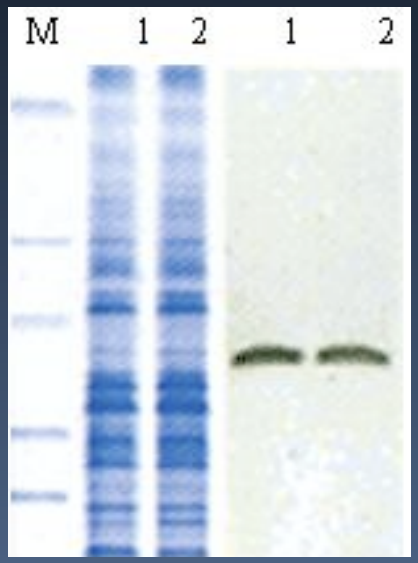
Does ENHANCE diminish confidence in lowering LDL or in ezetimibe?
N Engl J Med. 2008 Apr 3;358(14):1504-7. Epub 2008 Mar 30.

Discoveries 4…

- A vaccine that prevents cancer
- Widespread recognition that cervical cancer is a sexually transmitted disease

Evolutionary Viewpoint

- Research:
- Leads to new hypotheses
- Helps explain existing findings
- Can inform directions for future work

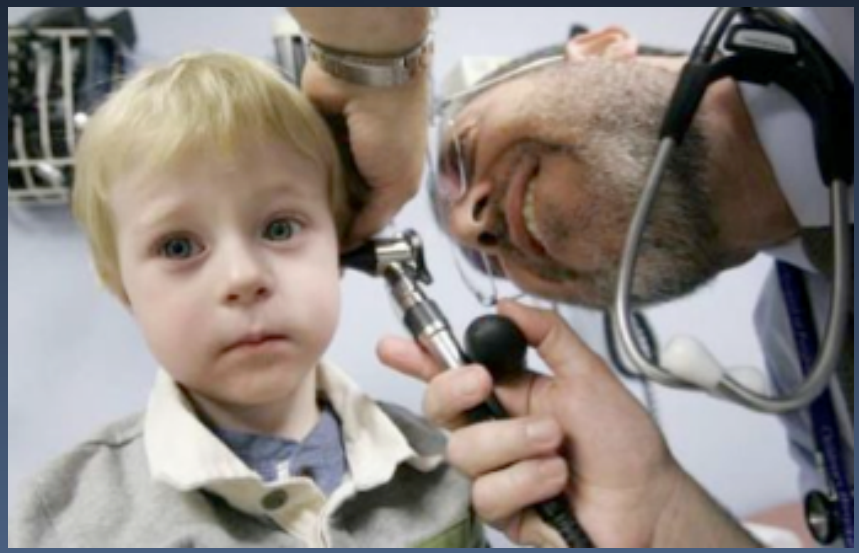


Evolutionary Viewpoint

- Education:
- Gives a framework for understanding normal and abnormal physiology
- Has potential to place lots of disparate facts in context

Evolutionary Viewpoint

- Clinical medicine
- Healthy skepticism
- Non-interventionist



- Helps define "disease" and "normal"
- Default: *most* "normal" physiology reflects selection for beneficial processes

Evolutionary Medicine Summary

- Incorporates noncontroversial basic principles of natural selection
- Asks "why" questions of disease
- Evolutionary explanations fall into discrete categories
- Can help guide clinical medicine, research and medical education