Darwinian Medicine
Basic theory with Practical Uses for Public Health
150 Years after *The Origin*

- Evolution just now being applied in many areas of medicine
- A historical transition in how we understand disease
In the animal self-help section
A Recent Flowering
Recent and Upcoming Meetings

- Humboldt University, Berlin
- York Hull Medical School
- University of Copenhagen
- NESCENT meeting at Duke
- American Institute for Biological Sciences
- American Physiological Society
- University of Arizona
- Wissenschaftskolleg zu Berlin
- American Clinical Epidemiology Society
- National Academy Sackler Symposium
Origins of Darwinian Medicine

"The purport of the following pages is an endeavor to reduce the facts belonging to animal life into classes, orders, genre and species; and by comparing them with each other to unravel the theory of diseases".  

*Darwin, 1794*

Erasmus Darwin  
Opening paragraph of *Zoonomia*,
E Conchis Omnia (Everything From Shells!)
Erasmus Darwin 1731-1802
Origins of evolution in medicine

- Erasmus Darwin—Physician
- Robert Darwin—Physician
- Charles Darwin—Medical school dropout
  - *Because he hated geology!*
What is Darwinian Medicine?
Darwinian (Evolutionary) Medicine

- The enterprise of using the basic science of evolutionary biology in the services of medicine and public health
Darwinian Medicine—NOT!

- Not radical in any way
- Not about improving the species
- Not opposed to ordinary medicine
- Not a method of practice
- Not a source of quick cures
- Not just about modern diseases
- Not just about the value of defenses

Evolution is a basic medical science with many untapped applications
Don’t Doctors Know Evolution?

- No, not even the basics
Evolutionary Biology Faculty in Medical Schools

Std. Dev = 1.76
Mean = 1
N = 33.00
Selection is everywhere

Explanations based on history

- Your penny jar
- What grocers stock
- What is on TV
- Who becomes an academic
- Who is here today!
Natural Selection

When heritable variations in a trait influence reproductive success, the trait will inevitably change over the generations.
Dogs from Wolves in a Blink

All modern domestic dogs are descendants of the Gray Wolf
Natural Selection

When heritable variations in a trait influence reproductive success, the trait will inevitably change over the generations.
Darwin: On the various contrivances by which British and foreign orchids are fertilised by insects. London, John Murray, 1862.

Angraecum sesquipedale The Star Orchid of Madagascar

Why would an orchid have a spur 30 cm. long?

Xanthopan morganii praedicta

Angraecum sesquipedale The Star Orchid of Madagascar
1. Infection and fast evolution
   - Still being developed

2. Constructing phylogenies
   - Established, new applications

3. Evolutionary genetics
   - Some old, much that is new

4. Why selection left our bodies vulnerable
   - New questions just being asked
1. Studies of Fast Evolution

- Pathogen evolution
- Immune system
- Cancer clones
Penicillin Resistance with *Streptococcus pneumoniae* in the United States

![Graph showing penicillin resistance from 1979-87 to 1999-00](image-url)
Last Week’s JAMA—Fatal Threats

- MRSA (Klevans, et al., JAMA)
  - 9% resistant
  - 10% mortality rate in hospital
  - 18,650 deaths/year vs AIDS 12,500

- Strep. Pneum. Untreatable (Pichichero, JAMA)
  - Because of vaccine?
  - Emergence of these non-PCV7 strains appears to have occurred as a consequence of replacement of PCV7 strains
Avoiding the e-word

Antonovics, PLOS Biology, 2007
A better way to prevent antibiotic resistance

Three different antibiotics:

Start:

3 months later:

6 months later:

9 months later:

12 months later:

15 months later:

18 months later:
2. Constructing Phylogenies

- Levels of selection
- Pleiotropy
- Quirks that Interact with environments
- Variation
Phylogenetic relationships of 21 pathogenic E Coli. Lacher, et al., in press
PREDICTING the Evolution of INFLUENZA Bush, et al. 1999
Cancer

Illustration from Merlo, 2006
3. Evolutionary Genetics

- Levels of selection
- Pleiotropy
- Quirks that Interact with environments
- Variation
Antagonistic Pleiotropy
Blasco, 2005

Figure 3 | Telomerase and telomere length in tumorigenesis. a | Changes in telomere length over time
Pleiotropy  Telomere length
Cawthon et al., Lancet, 2003
Crespi- Sig. Sel for Schiz genes

- Human-macaque
- Human-chimpanzee

Exon structure
Schizophrenia-associated haplotype
Protein interaction domains

- MAP1A-binding domain
- MIP3-binding domain
- NUDEL-binding domain
- ATF5-binding domain

- Microtubule dynamics and intracellular neuronal cargo transport
- Centrosome function and neuronal retrograde transport
Quirks

- Not disease genes, just variations that interact with environments to cause disease
- Myopia
- Apo E 4
Genes for Type I Diabetes to protect against freezing in the ice-age?

As published in

*The New York Times!*
Myopia
4. Asking why the body isn’t better
Gertrude Stein on Her Deathbed

“The answer, the answer, what is the answer? The answer, the answer, what is the answer?...
No, no that’s not it.

What is the question?”
Why has natural selection left the body so vulnerable?

Parts of the body are exquisite

Others are botched

Why?
The Old Answer: Natural selection is just too weak to make the body better.
The New Answer

- There are **six reasons** why natural selection leaves the body vulnerable to disease
Six Reasons Why Diseases Exist

Selection is slow
1. Mismatch: body in a novel environment
2. Competition with fast evolving organisms

Selection is constrained
3. Every trait is a trade-off
4. Constraints on natural selection

We misunderstand
5. Organisms shaped for R/S, not health
6. Defenses and suffering
1. Mismatch

- Breast Cancer
  - MUCH more common now
  - Hormone exposure
    - 400+ cycles now, about 110 then
  - Night light exposure
Atheroma
Cholesterol levels

- Modern American  200
- 20 pre-industrial  131
- 5 hunter-gatherer  123
- Rural Chinese     127

• Eaton, et al.
Myopia
Figure 1  (A) Percentage of patients achieving remission or response at week 12 or 24 after initiating ova therapy. (B) Mean change in Crohn’s disease activity index (CDAI, mean (SD)) for respondents to ova therapy. CDAI <150 is remission. $p<0.0001$, week 12 or week 24 compared with baseline (time 0).

2. Competition with other organisms

Mostly covered already—Fast Selection
Eco-Evo approach to pathogens
3. Every trait is a trade-off

Most genes are trade-offs

Gout

Uric Acid Concentration/SMR vs. MLSP

Y = -0.05 + 2X

Every trait is a trade-off.

Most genes are trade-offs.
Why does the body make bilirubin?

Heme

- heme oxygenase
- NADPH + O₂ → CO + Fe³⁺ + NADP⁺

Biliverdin

- biliverdin reductase
- NADPH → NADP⁺

Bilirubin
Why Bilirubin?
Sedlak and Snyder, Pediatrics, 2004
More Bili → Fewer Heart Attacks

Effect (observed OR vs. study mean OR)

y = -0.313Ln(x) + 1.7679

R² = 0.3446

serum bilirubin (μmol/L, logarithmic scale)
Bili and Antioxidant in Neonates
Hammerman et al., 1998

\[ y = 0.1334x + 0.3 \]

\[ R^2 = 0.13 \]
Why is there Aging?

- Some genes that cause ageing have no selective cost in the wild.
- Others offer advantages early in life when selection is stronger.

Implication: Disrupting aging associated genes is likely to cause problems.
If mortality stayed at early adulthood rates throughout life.


Additional reproductive years if senescence were eliminated.
4. Constraints

- Path dependence
  - Blind spot
  - Dangerous childbirth pathway
- Mutations
  - Huntington’s disease
  - Muscular dystrophy
5. Health is not selection’s goal

The vulnerable sex

- Sex mortality ratio
  \[
  \frac{\% \text{ males who die in a year}}{\% \text{ females who die in a year}}
  \]

- M.R. > 1.0 means that proportionately more males than females are dying
2000 U.S. Mortality from All Causes and the Male:Female Mortality Ratio (M:F MR)

[Graph showing mortality rates across different age groups for males and females, with an emphasis on the ratio of male to female mortality rates (M:F MR).]

- **Y-axis**: Mortality Rate (per 100,000)
- **X-axis**: Age categories
  - < 1
  - 1 - 4
  - 5 - 9
  - 10 - 14
  - 15 - 19
  - 20 - 24
  - 25 - 29
  - 30 - 34
  - 35 - 39
  - 40 - 44
  - 45 - 49
  - 50 - 54
  - 55 - 59
  - 60 - 64
  - 65 - 69
  - 70 - 74
  - 75 - 79

- **Legend**:
  - Male
  - Female
  - M:F MR

The graph illustrates the mortality rate for all causes across different age groups, highlighting the male to female mortality ratio (M:F MR) for each age category.
Composition of Excess Male Life Years Lost by Cause

Kruger and Nesse, 2006
M:F MR East Germany/M:F MR West Germany Before and After Unification

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<td>1980-1984</td>
<td>0.85</td>
<td>0.9</td>
<td>0.95</td>
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<td>1985-1989</td>
<td>0.9</td>
<td>1.05</td>
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<td>1990-1994</td>
<td>0.95</td>
<td>1</td>
<td>1.1</td>
<td>1.15</td>
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<tr>
<td>1995-1999</td>
<td>1</td>
<td>1.1</td>
<td>1.15</td>
<td>1.2</td>
</tr>
</tbody>
</table>
6. Defenses and suffering

- Defects
  - Seizures
  - Cancer
  - Paralysis
  - Jaundice
  - Injury

- Defenses
  - Fever
  - Cough
  - Pain
  - Fatigue
  - Anxiety
Defenses and Suffering

- Why are defenses aversive?
- Why so much unnecessary pain and suffering?
If the immediate and direct purpose of our life is not suffering, then our existence is the most ill-adapted to its purpose in the world.

Schopenhauer, 1851
Smoke Detector Principle  Nesse, 2005

- Express response whenever
  - $\text{CR} < \text{CH} \times p(H)$
- Many false alarms expected from the normal system
The Smoke Detector Principle

- False alarms are Normal
- This is why we can block pain, cough and nausea safely
  (Except for 1 time out of 1000!)
- Implication: It should be safe to block much suffering, but we must THINK
Six Reasons Why Diseases Exist

Selection is slow
1. Mismatch: body in a novel environment
2. Competition with fast evolving organisms

Selection is constrained
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We misunderstand
5. Organisms shaped for R/S, not health
6. Defenses and suffering
What Evolution Offers Public Health

- Established methods
- New research methods
- New research questions
- A feeling for the organism
  - There is no normal genome
  - The body is not a machine
The Body is NOT a Machine

- No design
- No blueprints
- No normal genome
- Selection left the body full of maladaptations as well as adaptations
Medicine Needs Evolution

THE CITATION OF “EVOLUTION IN ACTION” AS SCIENCE’S 2005 BREAKTHROUGH OF THE YEAR confirms that evolution is the vibrant foundation for all biology. Its contributions to understanding infectious disease and genetics are widely recognized, but its full potential for use in medicine has yet to be realized. Some insights have immediate clinical applications, but most are fundamental, as is the case in other basic sciences. Simply put, training in evolutionary thinking can help both biomedical researchers and clinicians ask useful questions that they might not otherwise pose.

Although anatomy, physiology, biochemistry, and embryology are recognized as basic sciences for medicine, evolutionary biology is not. Future clinicians are generally not taught evolutionary explanations for why our bodies are vulnerable to certain kinds of failure. The narrowness of the birth canal, the existence of wisdom teeth, and the persistence of genes that cause bipolar disease and senescence all have their origins in our evolutionary history. In a whole array of clinical and basic science challenges, evolutionary biology is turning out to be crucial. For example, the evolution of antibiotic resistance is widely recognized, but few appreciate how competition among bacteria has shaped chemical weapons and resistance factors in an arms race that has been going on for hundreds of millions of years. The incorrect idea that selection reliably shapes a happy coexistence of hosts and pathogens persists, despite evidence for the evolution of increased virulence when disease transmission occurs through vectors such as insects, needles, or clinicians’ hands. There is growing recognition that cough, fever, and diarrhea are useful responses shaped by natural selection, but knowing when it is safe to block them will require studies grounded in an understanding of how selection shaped the systems that regulate such defenses and the compromises that had to be struck.

Evolution is also the origin of apparent anatomical anomalies such as the vulnerabilities of the lower back. Biochemistry courses cover bilirubin metabolism, but an evolutionary explanation for why bilirubin is synthesized at all is new: It is an efficient free-radical scavenger. Pharmacology emphasizes individual variation in genes encoding cytochrome P450, but their evolutionary origins in processing dietary toxins are just being fully appreciated. In physiology, fetal nutritional stress appears to flip an evolved switch that sets the body into a state that protects against starvation. When these individuals encounter modern diets, they respond with the...
So Many Missing Studies

- Wise to block symptoms of influenza?
- Vaccine influences on virulence
- Rhinorrhea a defense, or for virus?
- Wisdom teeth, why?
- Fast sperm $\rightarrow$ short life?
- Lights for babies?
- Risks of central heating?
Next Steps for Evolution and Public Health

- Fast growth but dispersed community
- A textbook and a journal
- A web resource
- Training programs
- Research Funding
New Resources in New Media

Evolution and Medicine

Just completed!
A complete course
38 talks with slides
Mount on a server
Leading authorities
Up to the minute
INTERESTING!

A Henry Stewart Talks Series in Biomedicine and the Life Sciences

Evolution and Medicine: How New Applications Advance Research and Practice

38 seminar style presentations by many of the world’s leading authorities

For all those wishing to be briefed on the latest developments in the study and understanding of evolutionary medicine including students of undergraduate and graduate courses in biology, medical and nursing courses and health care dinicains. This is a complete course that covers the breadth of this new field in depth.

Topics covered
Fundamentals of evolution and medicine — Evolutionary genetics — Infectious diseases, co-evolution and arms races — Environmental factors — Constraints and trade-offs — Sexual selection and reproduction — Cancer — Mental disorders — Practical applications

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Look and feel of face-to-face seminars that preserve each speaker’s personality and approach

For research scientists, graduate students and advanced undergraduates

Available online and CD-ROM with licensing options to meet everyone’s needs

Series Editor:
Professor Randolph Nesse — University of Michigan, USA
Public Health

- A practical field, and a good thing too
- How can we improve health now?
- But little evolutionary basic science
Bimodality Bias

- Evaluations are usually bimodal
- We judge things, people, and groups as GOOD or BAD
- For evolutionary reasons that go back to bacteria going towards or away
- FIGHT Bimodality Bias!
- Don’t judge whole fields
- Assess one hypothesis at a time
Signals of Recent Selection

- Prevalent mutations with high linkage disequilibrium
  - ADH—Ken Kidd
  - Lactase—in herders
  - DRD4-7Rpt--Moyzis
  - G6PD/ CD4OL—Lander-Malaria
  - Apo E? —Sapolsky and Finch
  - BDNF??—Sen/Nesse Depression
A Biological View of the Body

- Medicine is still fleeing vitalism
- The metaphor of body as machine rose with Descartes and peaked with Schrödinger’s “What Is Life?”
- But it is seriously misleading
  - No blueprint, just genes with variation
  - Not optimal, not one aspect
  - Not for health, but reproduction
Politics

- Right—Creationists who fear evolution will undermine morality
- Left—vivid memories of eugenics and fears that explanations for bad behavior will be used to justify it
Dangers and Opportunities

- Media
- Politics
- Medicine
- Funding agencies
- Bimodality bias
Media

- Controversy
- Cures
- Bizarre ideas make good memes
- Fast, New, News Now!
Dangers and Opportunities

- Evolutionary biologists deeply involved
  - Although wary of applied science
- Medical researchers
  - Who love the power of evolutionary theory
- Doctors and Nurses
  - Who value “a feeling for the organism”
- Curious people everywhere who want to understand why diseases exist
Main Points

- Evolutionary Medicine is not one thing
  - It is a basic science for medicine
  - Suggests new studies, not new cures
  - Many applications, not just one
- Examples from four main areas
- It kills the false analogy of body as machine
- We can help it grow up healthy
Outline

- Origins and current flowering
- Four main lines of work
- Killer the analogy of body as machine
- Opportunities and dangers
- What we can do to foster hybrid vigor
The Long Eclipse

- In Flexner’s time (1910) evolution was dismissed.
- The Synthesis brought us pop genetics.
- Previous applications mostly fast evolution and physiology/anatomy.
- New studies of adaptation finally brought more evolution to medicine.
Disease and evolution

- Disease is **not** shaped by natural selection
- But **vulnerability** to disease has been.
- Natural selection can help explain maladaptation as well as adaptation
Two Complementary Explanations

1. **Proximate** explanations are about how a trait works.
2. **Evolutionary** explanations are about how a trait increases fitness.
Phyloproteonomics  Abu-Asab, 2006

A New Approach to MS Proteomic Analysis

- Ovarian Ca.
- Prostate Ca.
- Pancreatic Ca.
- Ovarian Ca.
- Prostate Ca.
- Pancreatic Ca.
- Ca. Transitional Clades
- Healthy (? Transitional Clades
- Healthy

Cancer
Levels of selection

- Haig
  - Parent Offspring Conflict
  - Complications of pregnancy
Modern environments and disease

- See Mismatch section below…
Constructive Engagement

- Understanding a proposal in depth
- Inhibiting global approval or criticism
- Saying what is right and what is wrong in detail, with suggestions for data that would settle the question
- This goes against human nature!
Fig. 1. Possible cross-species transmission events giving rise to SIVcpz as a recombinant of different monkey-derived SIVs

Immune System Development and the Hygiene Hypothesis

Birth: $\text{TH}_2$

Older siblings: Many infections [TH$_1$ stimuli]

Allergen Exposure

Only child: Few infections

$\text{TH}_1$

No allergies

Still $\text{TH}_2$

Allergies

Mean Negative Affect Scores vs. BDNF Genotype
(Sen, Nesse, Weder, Burmeister’s 2004)

![Graph showing mean negative affect scores vs. BDNF genotype.](image)

- **Val/Val**: N = 205, Mean Neuroticism $\pm$ 1 SEM $= 95$
- **Val/Met**: N = 161, Mean Neuroticism $\pm$ 1 SEM $= 85$
- **Met/Met**: N = 255, Mean Neuroticism $\pm$ 1 SEM $= 75$

Significance: $p = 0.0057$
Table 2. Human genes identified that influence HIV infection and disease. **Gene products Allele(s) Effect**

<table>
<thead>
<tr>
<th>Barriers to retroviral infection</th>
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<tbody>
<tr>
<td>TRIM5 SPRY species specific Infection resistance, capsid specific ABOBEC3G Polymorphisms</td>
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<tr>
<td>Infection resistance, hypermutation <strong>Influence on HIV-1 infection</strong></td>
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<tr>
<td>Coreceptor/ligand CCR5 32 homozygous Infection CCL2, CCL-7, CCL11 Infection (MCP1, MCP3, eotaxin), H7 Cytokine IL-10 5'A dominant Infection <strong>Influence on development of AIDS</strong></td>
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<tr>
<td>Coreceptor/ligand CCR5 32 heterozygous Disease progression CCR2 164 dominant Disease progression</td>
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<tr>
<td>CCL5 (RANTES) In1.1c dominant Disease progression</td>
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<td>CCL3L1 (MIP1) Copy number Disease progression</td>
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<td>DC-SIGN Promoter variant Parenteral infection Cytokine IL-10 5'A dominant</td>
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<td>Disease progression IFN-179T dominant Disease progression</td>
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<td>Innate KIR3DS1 (with HLA-Bw4) 3DS1 epistatic Disease progression</td>
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<td>Adaptive HLA-A, HLA-B, HLA-C Homozygous Disease progression <strong>HLA-B<em>5802, HLA-B</em>18 Codominant Disease progression</strong></td>
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<td>HLA-B*35-Px Codominant Disease progression</td>
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<td>HLA-B*27 Codominant Disease progression</td>
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<td>HLA-B<em>57, HLA-B</em>5801 Codominant Disease progression</td>
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<td>ABO/BE C3G Polymorphisms</td>
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<tr>
<td><strong>Coreceptor/ligand</strong></td>
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<td>CCR5</td>
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<td>CCL2, CCL-7, CCL11</td>
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<td>(MCP1, MCP3, eotaxin), H7</td>
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<td><strong>Cytokine</strong></td>
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<td><strong>Coreceptor/ligand</strong></td>
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<td><strong>Adaptive</strong></td>
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<td>KIR2DS1 (with HLA-Bw4)</td>
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Rats exposed to a cat for 10 minutes...
Darwinian Medicine Future

www.EvolutionAndMedicine.org
Olin Hall, Carleton College, 1967
Sophomore invertebrate biology
Why is there aging?

- Highly heritable
- Big differences in life-span in closely related species
- So, why isn’t life longer?
  - Maybe to ensure a turnover of individuals so the species can evolve?
Not a theory but a principle

- **IF** individuals vary on a trait that influences the number of offspring
- And that variation is passed on
- **THEN** the group will change over time

- **ADAPTATION**: Individuals get better
- **SPECIES**: New species split off from old
Breeding

All modern domestic dogs are descendants of the Gray Wolf
Natural Selection

Honeycreepers

- *Taenioptila cantans*
  - *Cremospiza hawaiiensis*
    - *Hamignathus virans*
      - *H. paru*
        - *Leucops caumeleasts*
          - *L. coelicanus*

- *Uaeka*
  - *U. coerulae*
    - *Palmaria dole*

- *Himatanoe sanguinea*
  - *Paroaria montana*
    - *Loysan Finch*
      - *Adakiki*
        - *Hawaii Amakihi*
          - *Aiala*

- *Nectar feeder and generalist*
  - *Nectar feeder and generalist*
  - *Nectar feeder and generalist*
  - *Nectar feeder and generalist*
Two Kinds of Explanation

“No biological problem is solved until both the proximate and the evolutionary causation has been elucidated. Furthermore, the study of evolutionary causes is as legitimate a part of biology as is the study of the usually physico-chemical proximate causes.”

E. Mayr, 1982

The Growth of Biological Thought
Two Complementary Explanations

1. **Proximate** explanations are about **how a trait works**.
2. **Evolutionary** explanations are about **how a trait increases fitness**.
Disease and evolution

- Disease is **not** shaped by natural selection
- But **vulnerability** to disease has been.
- Natural selection can help explain maladaptation as well as adaptation
Darwinian Medicine

- Not radical in any way
- Not opposed to allopathic medicine
- Not a method of practice
- Just a basic medical science
  whose power is just being recognized
Why We Get Sick
The New Science of Darwinian Medicine

RANDOLPH M. NESSE, M.D., AND GEORGE C. WILLIAMS, PH.D.
Medical school

- Why is there aging?
  - Things wear out, obviously!
  - And, natural selection isn’t that great
  - Stop asking questions and memorize more!
Hanging out with evolutionary biologists

- Why do organisms do what they do?
- Why is there sex at all?
- Why are some species social?
- FINE QUESTIONS!!
I ask a biologist:
“Why is there aging?”

Colleague Bobbi Low replies:

“WHAT?!?
You have never read Williams 1957?!!!”
What about my lovely model?

“Don’t you even know the problem with group selection?”
Some General Principles

- Imperfections cannot be eliminated because natural selection is too weak and random.
- Selection shapes traits to benefit the species.
- Pathogens evolve to co-exist with hosts.
- Natural selection shapes health and longevity.
- Genetic disease results from mutations that natural selection can’t eliminate.
- Aging results because body parts wear out.
- Natural selection cannot influence anything after reproduction ends.
Current Views

- Imperfections are present for 6 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 pleiotropy
- Natural selection continues after reproduction
Pain

- EXPERIENCE means something is wrong
- CAPACITY is useful
- Congenital absence VERY rare
  - 35 in USA
- Why? Lack of pain causes early death
Fixed defenses

- Skin
- Innate immune responses
- Stomach acid
- Ear wax
- Cells shed steadily
Inducible Defenses
(Tollrian, Harvell, Clark, Dill, Lima, Pulliam, et al.)

- Latent traits expressed only in response to a cue associated with a danger
  - Developmental changes—size, shape
  - Sustained—tanning, callus formation
  - Temporary—Physiological defenses
  - Emotions—Adjust body to situations with adaptive challenges
Daphnia
Different morphology induced by exposure to chemical cues from predator

The Ecology and Evolution of Inducible Defenses by Ralph Tollrian
Stress

- Too much cortisol is bad
- Too little is fatal
  - Addison’s disease
If stress is so useful, why not express it all the time?

- Many of us DO! However...
- It consumes energy
- It decreases ability to do other things
- It damages tissues!

Why? Because it is precisely those changes that damage tissues that must be packaged away in an emergency kit, to be opened only when the costs are worth it.
Fever

- A Defense that fights infection
- Evidence
  - Blocking fever can slow recovery
  - Does increasing fever help?

Diarrhea

- Clears pathogens and toxins
- Blocking diarrhea causes complications in Shigellosis infection

Anxiety

- Really useful to escape and avoid danger!
- People complain about too much anxiety
- What about hypophobics?
Fear of Heights at 18 vs. Severe Falls in Childhood
Poulan, et al., 1998

Fear of Heights

Fall with severe injury (hypophobia?) n=60
No fall with severe injury (fearful?) n=789
The Clinical Illusion
(that Defenses are Defects)

- Clinicians are prone to think that defenses are the problem because:
  - Defenses are expressed when there is a problem
  - They are painful
  - Blocking them is often safe
Love joins hate; aggression, fear; expansiveness, withdrawal, and so on; in blends designed not to promote the happiness of the individual, but to favor the maximum transmission of the controlling genes.

E. O. Wilson, 1975
Pain or suffering of any kind, if long continued, causes depression and lessens the power of action; yet it is well adapted to make a creature guard itself against any great or sudden evil.

Charles Darwin, 1887, pp. 51-52
The First Noble Truth

- Life Is Suffering
DESPAIR

It’s Always Darkest just Before it goes Pitch Black.
The Mystery about Defenses

- Natural selection should shape near-optimal defense regulation mechanisms
- But we are plagued by excess anxiety, pain and sadness, & other defenses
- And we know, from general medicine, that they often can be blocked safely
- Why are defenses expressed excessively?
How Should Defense Regulation Have Been Shaped by Natural Selection?

- Monitor cues associated with danger
- If the cost of the defense < harm reduction, express defense.
- Express all-or-none defense iff:

\[
C(D) < C(H_{NoD}) - C(H_{wD})
\]
What if the Cue is Unreliable?

- Signal detection analysis needed:
  - Cost of false alarm
  - Cost of missed alarm
  - Cost of Harm if Defense (correct response)
  - Probability that Harm is present (S/N ratio)

- Express defense whenever

\[ C(D) < pH \left( (C(H_{\text{NoD}}) - C(H_{\text{wD}})) \right) \]
At what $p(\text{Harm})$ is Defense Expression Worthwhile?

<table>
<thead>
<tr>
<th>Ratio of Cost of Harm to Cost of Defense</th>
<th>P Harm at which Defense Expression is Worthwhile</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:1</td>
<td>100%</td>
</tr>
<tr>
<td>5:1</td>
<td>50%</td>
</tr>
<tr>
<td>20:1</td>
<td>10%</td>
</tr>
</tbody>
</table>
Should you flee from a noise?

- Is it a monkey? … or a tiger?!!
- Cost of fleeing = 200 calories
- Cost of not fleeing if a tiger = 200,000 calories
- Ratio is 1000:1
- Optimum: Flee whenever p (tiger) > 1/1000

999 /1000 panic attacks will be unnecessary, but perfectly normal.
“Few failures are as unforgiving as failure to avoid a predator. Being killed greatly decreases future fitness”

Lima and Dill, 1989, p. 619
### Signal Detection Theory

**Green and Swets, 1966**

```markdown
<table>
<thead>
<tr>
<th>Decision:</th>
<th>Signal:</th>
<th>Decision:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respond</strong></td>
<td><strong>Present</strong></td>
<td><strong>False Alarm</strong></td>
</tr>
<tr>
<td><strong>Missed Resp.</strong></td>
<td><strong>Correct detection</strong></td>
<td><strong>Correct Rejection</strong></td>
</tr>
<tr>
<td><strong>Do not Respond</strong></td>
<td><strong>Absent</strong></td>
<td></td>
</tr>
</tbody>
</table>

- **Hit**: (Correct detection)
- **False Alarm**: (False Positive, Type I error)
- **Missed Resp.**: (False negative, Type II error)
- **Correct Rejection**
```
Signal comes from real danger

Signal comes from noise
By convention, the mean of the noise distribution is set to zero. In this example, $d' = 2$.

The likelihood ratio is the height of the signal distribution divided by the height of the noise distribution at the criterion value (1.3 in this example).

Distribution of cues from noise only

Distribution of cues from noise & signal

Increasing intensity of decision variable
Signal Detection Theory: To get high detection you have to accept many false alarms
Optimal Response Threshold

\[
\frac{p(x|s)}{p(x|n)} > \frac{p(n)}{p(s)} \times \frac{v(\text{rej.}) + v(\text{f.a.})}{v(\text{hit}) + v(\text{miss})}
\]
If the Defense is Graded?

- Optimal Defense depends on how Harm declines with increasing Defense
- Find point of minimal cost
At cost minimum
$C(D) = C(H)$

$CD = LD^{0.05}, \ CH = 1/(LD+0.1)$. 
At optimum, $C(D)$ is greater than $C(H)$.

B) $CD = 1 + LD^{0.05}$, $CH = 1/(LD + 0.1)$
Regulation of Defenses: The Perils of Positive Feedback

- When danger is likely, threshold should decrease, expressing the defense more readily.
- Positive feedback system, prone to runaway escalation.
Panic and Agoraphobia

- Panic is a false alarm fight-flight response.
- The experience of panic seems to down-regulate the panic threshold.
- Any hint of danger releases a panic response.
- When you have recently been the object of a predator attack, agoraphobia is useful indeed!
Immune responses

- One exposure induces an response
- Second exposure arouses faster stronger response
- Pathological extreme: Anaphylaxis
Nausea and Vomiting

- One exposure to novel taste/odor and toxin conditions nausea
- SDP explains generalization to related odors
- Repeated exposure increases sensitivity
- Example: Conditioned nausea and vomiting in chemotherapy
Depression

- First episode 80% precipitated by life event
- By the fourth episode, precipitants are no more common in depressives than controls
- Kindling is a neurological metaphor
- But this may represent positive feedback, with decreased motivation arising ever more quickly in response to unpropitious situations
Implications

- A theoretical foundation for general medicine
  - But most of the research has yet to be done
- Essential foundation for pharmacology
  - Pharmacological utopia possible?
Pharmacological Utopia?

- Most Suffering is normal but unnecessary
  - Many false alarms
  - Repeated arousal changes threshold
  - Modern environment relatively safe
- So we should be able to safely block most defenses and suffering
- Except for the one time in a hundred, when the defense will essential!
Medicine uses some evolution

- Antibiotic resistance
- Evolutionary genetics
- Human phylogeny
But much is missing

- Co-evolution and arms races
- Subtle evolutionary genetics
- Evolution and behavior
- Evolution and development
- Asking why natural selection has left the body so vulnerable
Percent of schools that include topic in medical curriculum (n=55)
Nesse & Schiffman, 2000

- Antibiotic resistance
- Virulence evolution
- Population genetics
- Sel. for disease genes
- Mutation sel. bal.
- Levels of selection
- Host-patho. arms races
- Mismatch of body-envir.
- Design trade-offs
- Comparative anatomy
- Defense regulation
- Life history traits
- Path dependence
- Human phylogeny
- Kin selection
- Proximate ultimate distinct
The Future

Medicine Needs Evolution

The citation of "Evolution in Action" as Science's 2005 Breakthrough of the Year confirms that evolution is the vibrant foundation for all biology. Its contributions to understanding infectious disease and genetics are widely recognized, but its full potential for use in medicine has yet to be realized. Some insights have immediate clinical applications, but most are fundamental, as is the case in other basic sciences. Simply put, training in evolutionary thinking can help both biomedical researchers and clinicians ask useful questions that they might not otherwise pose.

Although anatomy, physiology, biochemistry, and embryology are recognized as basic sciences for medicine, evolutionary biology is not. Future clinician are generally not taught evolutionary explanations for why our bodies are vulnerable to certain kinds of failure. The narrowness of the birth canal, the existence of wisdom teeth, and the persistence of genes that cause bipolar disease and senescence all have their origins in our evolutionary history. In a whole array of clinical and basic science challenges, evolutionary biology is turning out to be crucial. For example, the evolution of antibiotic resistance is widely recognized, but few appreciate how competition among bacteria has shaped chemical weapons and resistance factors in an arms race that has been going on for hundreds of millions of years. The incorrect idea that selection reliably shapes a happy coexistence of hosts and pathogens persists, despite evidence for the evolution of increased virulence when disease transmission occurs through vectors such as insects, needles, or clinicians' hands. There is growing recognition that cough, fever, and diarrhea are useful responses shaped by natural selection, but knowing when it is safe to block them will require studies grounded in an understanding of how selection shaped the systems that regulate such defenses and the compromises that had to be struck.

Evolution is also the origin of apparent anatomical anomalies such as the vulnerabilities of the lower back. Biochemistry courses cover bilirubin metabolism, but an evolutionary explanation for why bilirubin is synthesized at all is new: It is an efficient free-radical scavenger. Pharmacology emphasizes individual variation in genes encoding cytochrome P450, but their evolutionary origins in processing dietary toxins are just being fully appreciated. In physiology, fetal nutritional stress appears to flip an evolved switch that sets the body into a state that protects against starvation. When these individuals encounter modern diets, they respond with the
“What actions would bring the full power of evolutionary biology to bear on human disease?

1. Include questions about evolution in medical licensing examinations

2. Ensure evolutionary expertise in agencies that fund biomedical research.

3. Incorporate evolution into every relevant high school, undergraduate, and graduate course.

In the animal self-help section
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 responses
- Make blood clot a bit more slowly
- Install a zipper so babies can exit more easily!
An Example—The Eye

An organ of extreme perfection?
Or, a design so poor that no one would want credit?
First half of medical school: An organ of perfection

1. Upper eyelid
2. Lower eyelid
3. Lateral angle
4. Medial angle
5. Lacrimal caruncle
6. Limbus
7. Iris
8. Pupil
9. Lacrimal papilla
10. Sclera
In the Clinic: A botched design

- Glaucoma
- Cataracts
- Myopia
- Presbyopia
- Iritis
- Corneal clouding
- Retinal detachment
THE QUARTERLY REVIEW OF BIOLOGY

THE DAWN OF DARWINIAN MEDICINE

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Ann Arbor, Michigan 48109-0840 USA
1. Mismatch

- Our bodies were never designed to cope with this novel environment
- Selection is slow
- The mismatch explains most chronic disease
- Our fulfilled desires are killing us
5. Health is not selection’s goal

Selection maximizes reproductive success, NOT health, longevity, & happiness

- Ageing
- The feeble sex
“The human mind treats a new idea the way the body treats a strange protein; it rejects it.”

Peter Medawar
Origins of Control Theory

- Erwin Shrödinger’s classic “What is Life?” how organisms avoid entropy by using energy to create and maintain order (1944).
- Weiner expanded the basic principle of feedback control into cybernetics (1948).
- Shannon and Weaver codified information theory (1949).
- Grand syntheses—General systems theory (Bertalanffy, 1969) and biology (Miller, 1978).
- Perceptual control theory (Powers, 1973).
- Computer modeling (Holland, 1992).
Medicine Needs Evolution

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Fragmented knowledge

- A top flight medical education ignores core evolutionary principles
  - Group selection
  - Kin selection
  - Co-evolution
  - Trade-offs
  - Life history theory
  - Proximate vs. evolutionary explanations
Evolutionary Q. about disease

- Why has natural selection left us vulnerable to disease?

- Not just why some people get sick, but why natural selection has left us all with bodies that are vulnerable to disease

- Six possible reasons
Six Reasons Why Diseases Exist

Selection is slow

1. Mismatch: body in a novel environment
2. Competition with fast evolving organisms

Selection is constrained

3. Every trait is a trade-off
4. Constraints on natural selection

We misunderstand

5. Organisms shaped for R/S, not health

Nesse, QRB, March 2005
Genetic “Quirks”

- Harmless in a natural environment
- Cause disease in novel environment.
  - Atherosclerosis
  - Myopia
  - Drug abuse
Hygiene Hypothesis

- Lack of exposure to pathogens deprives immune system of inhibitory components
- Rapidly increasing immune diseases (Rook)
  - Type I diabetes
  - Crohn’s disease
  - Asthma
- Acute lymphoblastic leukaemia (Greaves)
Streptococcal infection

- Strep antigens mimic our proteins
- Rheumatic fever, scarlet fever, OCD
A better way to prevent antibiotic resistance

Three different antibiotics:

Start:

3 months later:

6 months later:

9 months later:

12 months later:

15 months later:

18 months later:
The percentage gene frequencies (numbers on map) of α-thalassaemia in Melanesia parallels the intensity of malaria transmission (endemicity). The malaria transmission intensity goes from most intense (holoendemic) to least intense (hyperendemic). A, Australia; PNG, Papua New Guinea; SI, Solomon Islands; NC, New Caledonia; V, Vanuatu; ES, Espiritu Santo — an island in Vanuatu where the study by Williams et al. was performed. Figure adapted from the data in Flint et al.3.
4. Constraints

- Path dependence
  - Just like our computer keyboards
- Happenstance
  - Mutations
A significant moment in the history of terrestrial whales

Let's take a load off our feet, and go for a swim.
\[ I = \frac{\text{IRY}_h - \text{IRY}_a}{\text{IRY}_h} \]
In the animal self-help section

Baby bear: “Do it by instinct.”

Goat: “How to avoid natural selection.”

Dare to be nocturnal.

Goat: “Become one of the herd.”
Defenses & suffering in AA today!
Shivering-Unpleasant but useful
How much shivering is best?

Just right?

Too little

Too much
Selection is everywhere

- Whenever variation influences prevalence
  - Coins in a jar
  - Programs on TV
  - Products in the grocery store
  - What politicians say
- Genes in organisms? Special kind:
  - NATURAL selection
Darwin: On the various contrivances by which British and foreign orchids are fertilised by insects. London. John Murray. 1862.

Angraecum sesquipedale The Star Orchid of Madagascar

Why would an orchid have a spur 30 cm. long?

Xanthopan morgani praedicta

Ang. sesquipidale

Angraecum sesquipedale The Star Orchid of Madagascar
Awe at the body’s perfection

- The eye
- The heart
- The nephron
- Regulation of clotting
Horror at the body’s flaws: You could do better in one afternoon!

- Eliminate the appendix
- Take out the wisdom teeth
- Turn the eye inside out
- Make bones stronger
- Improve immune responses
- Make blood clot a bit more slowly
- Let the heart get blood from its chambers
- Install a zipper so babies can exit easily!
Why has natural selection left the body so vulnerable?

Parts of the body are exquisite

Others are botched

Why?
Penicillin Resistance with *Streptococcus pneumoniae* in the United States
Depression is simple

- Life situation
- How you think about the situation
- How the brain is working
Disease and evolution

- Disease is not shaped by natural selection.
- But vulnerability to disease has been.
- Natural selection can help explain maladaptation as well as adaptation.
New Questions About Disease

- Not why one person gets sick
- But why we all share vulnerabilities
- Why didn’t natural selection do better?
  - Just because it is too weak?
- Yes, but also five other kinds of explanations
Pain, fever, cough, nausea, anxiety, etc. often seems excessive.

We can usually block them safely.

Did selection make a mistake?
BP, Genes, Latitude and Environmental change
Young, et al., PLOS 2006

GNB3 825T Frequency

(\(\beta_{GL} = -0.54\))

Absolute Latitude

(\(\beta_{SL,G} = 0.95\))

Systolic Blood Pressure

(\(\beta_{SG,L} = 0.49\))
Two Kinds of Explanation Needed

“No biological problem is solved until both the proximate and the evolutionary causation has been elucidated. Furthermore, the study of evolutionary causes is as legitimate a part of biology as is the study of the usually physico-chemical proximate causes.”

E. Mayr, 1982

The Growth of Biological Thought
Tinbergen’s 4 Questions Organized

<table>
<thead>
<tr>
<th>Transition over time</th>
<th>Proximate</th>
<th>Evolutionary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross section</td>
<td>Ontogeny</td>
<td>Phylogeny</td>
</tr>
<tr>
<td></td>
<td>Mechanism</td>
<td>Antidote to Reductionism</td>
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