From Darwin to Genomes
The Emergence of Evolutionary Medicine

Massachusetts Medical Society Webinar

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19 September 2016
Evolutionary Biology in Clinical Medicine
September 19, 2016

Summary of Disclosure Information

The Department of Continuing Education and Certification (DCEC) of the Massachusetts Medical Society has determined that none of the individuals in a position to control the content of this CME activity, and/or their spouse/partner have any relevant financial relationships with commercial interests to disclose.
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“Nothing in medicine makes sense except in the light of evolution”

1973
Evolution and Medicine

• Evolutionary considerations answer many of the “why” questions in Medicine

• Explaining the deep underlying principles that have shaped us and thus result in health or sickness
  – Illustrates the importance of “biological history”

• As genetics increasingly permeates medicine we routinely use evolutionary principles
General Education & Evolution

• I would characterize my educational background in evolutionary biology as:
  – No formal exposure dedicated to evolution beyond occasional mention in biology classes
  – Modest (e.g. having taken a class that focused primarily on evolutionary biology)
  – Extensive (e.g. having taken several classes that focus on evolutionary biology)
Evolution and Medical School

• For those of you who went to Medical School, was evolution mentioned in your curriculum?
  – Yes
  – No
The interpretation of genetic data hinges on evolutionary evidence. As sequencing is applied more generally, "completely conserved in mouse, rat, rabbit, dog, horse, armadillo, elephant, opossum, lizard and puffer fish."
The Theory of Evolution by Natural Selection

• Proposed in 1859 by Charles Darwin and Alfred Russel Wallace to explain the diversity and exquisite adaptations exhibited by life on earth
  – Existence of inter-individual variation within any population
  – Selection by the environment for fittest organisms which then differentially reproduce
  – Heritability of variations

• Posits common descent with natural selection as a driving force in speciation

"How stupid of me not to have thought of that."
- T.H. Huxley
The Explanatory Power of Darwin’s Theory

Key pieces of evidence included:

- Homologous structures in different organisms
- Similarities in embryos
- Artificial selection (e.g. pigeons and dogs)
- Geographical distribution of species
Predictions

- Discovery of intermediate fossil forms
  - Archyopteryx
  - Tiktaalik roseae
- The age of the earth
- Modern Genetics
  - The mechanism underlying heredity had to be compatible with particulate inheritance & subject to selective pressures
  - Genetics represents a grand fulfillment of predictions inherent in evolutionary theory

“I think the most significant aspect of DNA is the support it gives to evolution by natural selection”
- Francis Crick
Genetic Similarity Reveals Common Descent

- Identical Twin – 100%
- Un-related individual – 99.9%
- Chimpanzee – 98%
- Broccoli – 37%
Numerous prosaic examples of evolutionary processes relevant to medicine

- The (micro) evolution of bacterial antibiotic resistance
  - Clear implications for antibiotic use in
    - Clinical practice
    - Farming

- The evolution of resistance to anti-HIV agents within an individual

- Human cancer as a microcosm in each tumor of selection and evolutionary change
There exist important contemporary medical implications for all phases of evolution.
Phase 1: Structural Evolution

• Our bodies evolved structurally in ways that are not necessarily optimal to health.
• Such “design flaws” exist because of the necessary constraints of evolution’s mechanism:
  – Evolution works on a pre-existing substrate.
  – Does not see the big picture.
  – Does not plan for the future.
  – New adaptations are rarely “optimal”, they must only be better.
What Would You Do Next?

1) Get another length of hose?
2) Go back around the tree?

*Evolution chose option 1*

Adapted from Alan R. Rogers
Evolution Explains Human Anatomy

• During evolution testes moved from abdomen to scrotum
• Went down “wrong” side of ureter

Adapted from Alan R. Rogers
Medical Implications of Evolution’s 1st Phase

The Structural Level

• You engage in a life-threatening event several times each minute
  – Swallowing is hazardous due to the risk of aspiration
  – 5-10% of community acquired pneumonia results from aspiration
  – Our lungfish ancestor developed an air opening at the top of the snout, leading to a common opening with the food passageway
  – Respiratory and food passages remain shared at their proximal extent

• Aspiration pneumonia is a 400 my old legacy of our evolutionary past

• Another such example is shared / near-shared orifices for reproductive and excretory purposes
Some Medical Implications of Evolution’s 1st Phase

• Low back pain
  – 80% of US population will experience at least one prolonged episode of severe low back pain
  – A direct result of our evolutionary history
  – It was advantageous for us to walk upright
    • Freeing the forelimbs
    • Range of vision
    • Communication cues?
  – However the resultant mechanical stresses result in a high rate of injury and pain
Medical Implications of Evolution’s 1st Phase

• The appendix, a lethal evolutionary remnant
  – Each year in the US 250,000 people require appendectomy
  – Appendicitis was a uniformly fatal disease prior to the modern era
  – Evolutionary considerations explain its presence…and its persistence
Medical Implications of Evolution’s 1st Phase

The Molecular and Cellular Level

• Cancer and Aging as “Rival Demons”\(^1\)
  – Our defenses against cancer and our susceptibility aging represent an evolutionary tradeoff

• The evolution of metazoans with renewable cells required mechanisms to strictly regulate cell growth
  – These mechanisms protect against developmental problems and cancer
  – But their legacy is one component of senescence and aging
    • Mouse line\(^2\) with increased p53 activity demonstrating lower tumor rates but an \(~30\%\) shorter lifespan\(^2\)

\(^1\)Judith Campisi; Nature Reviews 3:339; 2003
\(^2\)Tyner; Nature 415:45; 2002
Medical Implications of Evolution’s 1st Phase

- Childbirth was a very risky endeavor prior to the modern era.
- An evolutionary trade-off between the maximal size of the birth canal (& thus head size) vs. the mechanics / dangers of the birth process.
- The result was a stunning rate of maternal/infant mortality in the era before modern obstetrics counterbalanced by the selective advantages of a large brain.
- But for the intervention of modern medicine we have likely reached the limit of head size.
Evolution’s 2\textsuperscript{nd} Phase

The Emergence of Cognition and Emotion

• The emergence of sophisticated cognition allowed
  – Nimble response to the environment
    • Forgoing the need for rote programs & enhanced flexibility
  – Ability to alter the environment
    • Through tool use
    • The eventual development of technology
    • Now on a global – and dangerous - scale
The evolution of emotion was a corollary of cognition:
- Emotions are potent evolutionary mechanisms that evolved by their ability to enhance reproductively successful behavior.
- And drove our evolution as a social species:
  - Anxiety
  - Lust
  - Fear
  - Love for mate and offspring.
Dopamine Pathways Represent the Principal “Pleasure” System of the Brain

Comings (1987) pointed out that the limbic system has been characterized as controlling the 4 F's--fight, flight, feeding, and sexual activity.

Natural Rewards Elevate Dopamine Levels ~100%

Adapted from Donald R. Vereen, M.D., M.P.H., NIDA
Medical Implications of Evolution’s 2nd Phase

• Many psychiatric illnesses have clear evolutionary roots, stemming from the development of higher cognition and emotions.

• Clear selective pressures which lead to heightened anxiety, “neuroses”, obsessive compulsive disorders, phobias, etc.

• Corollaries in other mammals illustrate the continuity between humans and other animals:
  – Pharmacologic effects of mood altering agents in dogs with anxiety disorders illustrate common neurochemical pathways.
Medical Implications of Evolution’s 2\textsuperscript{nd} Phase

• Reward pathways, being biochemical, are susceptible to manipulation by
  – Naturally occurring substances
  – Synthetic substances
Synergism Between Evolution of Cognitive & Emotional Capacities

• The rise of cognitive prowess eventually led to technologies capable of artificially & directly triggering our evolved emotional reward pathways
  – EtOH (9,000 BCE)
  – Heroin (1860’s)
  – Crack cocaine (1980’s)

![Graph showing % of basal release of DA in Accumbens over time after administration of amphetamine and cocaine](diagram.png)

Source: Di Chiara and Imperato
Costs of this Evolutionary Synergy

- Diabetes costs society $131.7 billion annually
- Cancer costs society $171.6 billion annually

Substance Abuse Costs the US More than $484 Billion per Year
Medical & Societal Burden of Our Ability to Manipulate Evolved Reward Pathways

– Direct causation of disease
  • Cigarettes
  • Ethanol
  • Other substances

– Indirect causation
  • Trauma
  • Role in crime
  • Domestic Violence

– Addiction
  • To substances
  • To activities (e.g. gambling)

The combination of our highly evolved cognitive abilities along with the existence of evolved chemical emotional reward pathways result in a modern public health burden of immense proportion.
Evolution’s Second Phase Influences our Definition of Disease

- Natural selection is not concerned with your happiness or health
- A single, very narrow priority to enhance reproductive fitness
  - No necessary match between the optimal evolutionary strategy our ancestors unwittingly pursued and their (or our own) happiness
- Unhappiness, suffering and pain (physical or emotional) are transparent to the sieve of natural selection unless they affect reproductive success
- Morning sickness in pregnancy
We Commonly Work Against Evolution

...and that’s okay

• Heightened anxiety, worry, discomfort were all likely adaptive in our evolutionary past
• As physicians we sometimes “work against” evolution in order to minimize suffering and enhance quality of life even at the expense of an individual’s evolutionary fitness
  – As we may well when do each time we prescribe anti-anxiety agents
  – And birth control
Evolution’s 3rd Phase
The Emergence of Culture

• The rise of cognition and emotion stimulated sociality and the emergence of culture in the last 100,000 years
  – Complex group activities that vary geographically and are transmitted non-biologically (now mostly symbolically)
    • Including technology, art, decoration, science, moral systems, religion and characteristic behaviors and habits

• Cultural evolution is far faster than biological evolution
  – And more powerful
Evolution’s 3rd Phase
The Emergence of Culture

- Human health is now highly dependent upon culture and in some sense, we are freed from proximal biological & evolutionary constraints
  - Myopia was a severe detriment to fitness prior to the rise of glass grinding technology
  - Childhood infectious diseases are now of little significance
    - If you happen to live in a culture with access to vaccines
- Leading to the oft-heard but nonsensical claim that human evolution is “dead”
- Evolution is faster & less predictable now due to the complex interplay between culture and biology
Medical Implications of Evolution’s 3rd Phase

Diabetes, Obesity and Culture

• Neel’s “Thrifty Gene Hypothesis”
  – Certain human alleles emerged to maximize metabolic efficiency & food searching behavior
    • We evolved to lust after fat and to binge eat

• In times of abundance these alleles predispose their carriers to diseases caused by excess nutritional intake, such as obesity & DM

• Populations with a history of food scarcity may harbor more such thrifty alleles than other populations

Worldwide Prevalence of Diabetes 2000 and 2010

A thrifty variant in CREB5 strongly influences body mass index in Samoans

Ron L. Minster1,2, Nicola I. Hawley3,4, Chi-Ting Su1,2,13, Guanyun Sun1,2,13, Erin E. Kershaw4, Hong Cheng1, Olivia D. Buhole5,6, Jerome Liu1, Muangrat Ja Sefuiva Reupena6, Satupaitea Viali7, John Tuttle6, Take Naseri6, Zoolt Urban9,10, Ranjan Deka8,11, Daniel E. Weeks1,2,13 & Stephen T. McGarvey1,10,11,12,13

VOLUME 48 | NUMBER 9 | SEPTEMBER 2016
Calories are Cheap

- The average citizen of NC earns $30,553/yr
- The price of a Hardee’s Monster Thickburger© is $5.59
- It takes 21 minutes to earn one
  - It supplies almost a day’s worth of calories
  - It is engineered to appeal to our evolutionarily derived compulsion to seek concentrated fat, salt, carbohydrates and protein
  - And we don’t even have to leave our car to get it
  - Never in the history of our species have calories been so cheap

Disease as a clash between our evolutionary past and our cultural present
A Similar Clash Can Be Observed in Other Disorders

- Lactose tolerance/intolerance
- Hypertension
- Coronary Artery Disease
- Breast Cancer
- HIV & emerging infectious diseases
- ADHD
  - Prevalence reaches 18% in populations world-wide
  - Very strong genetic component
  - Predisposing genetic variants are frequent and fixed in some populations
  - Attributes which may have been driven evolutionarily but are now not adaptive to our cultural milieu
    - Hyperactivity vs. hypoactivity
    - Multi focus (“attention”) vs. mono-focus
Evolution and Precision Medicine

The central role of individual variation

- Darwin overturned “essentialist” thought in biology
  - Fixed species modeled on an archetypical ideal
- He pointed to the importance of variation
- This insight is now highly relevant to modern medicine
  - Individual differences (the raw material of evolutionary change) can now be elucidated
    - Accounting for differential disease susceptibility, drug response, etc.

*Precision Medicine seeks to harness such variation for better health*
Variation in Action
Pharmacogenomics and Abacavir

- Abacavir is a nucleoside analog inhibitor of HIV RTase effective for treatment of HIV infection
- 4.3% of patients develop severe hypersensitivity reaction
- Strong association found between the presence of HLA B*5701 allele & risk for abacavir hypersensitivity
- In clinical trial, screening for HLA B*5701 completely eliminated immunologically confirmed cases of hypersensitivity, with NNP = 100% & PPV = 48%
- It is now standard of care to screen candidates for RTase Rx for this allele & use alternative Rx if positive
Evolution Reveals our Collective Family History

- Modern genetics illustrates the importance of a patient’s family history to guide
  - Diagnosis
  - Risk of disease
  - Therapy

- Human evolution represents the deep “family history” of our species

- As such it contains important insights for medicine
We shall not cease from exploration, and the end of all our exploring will be to arrive where we started and know the place for the first time.

TS Eliot, 1942
Little Gidding
Thank You!
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