Summer School 2018

Introduction to the field of evolutionary medicine

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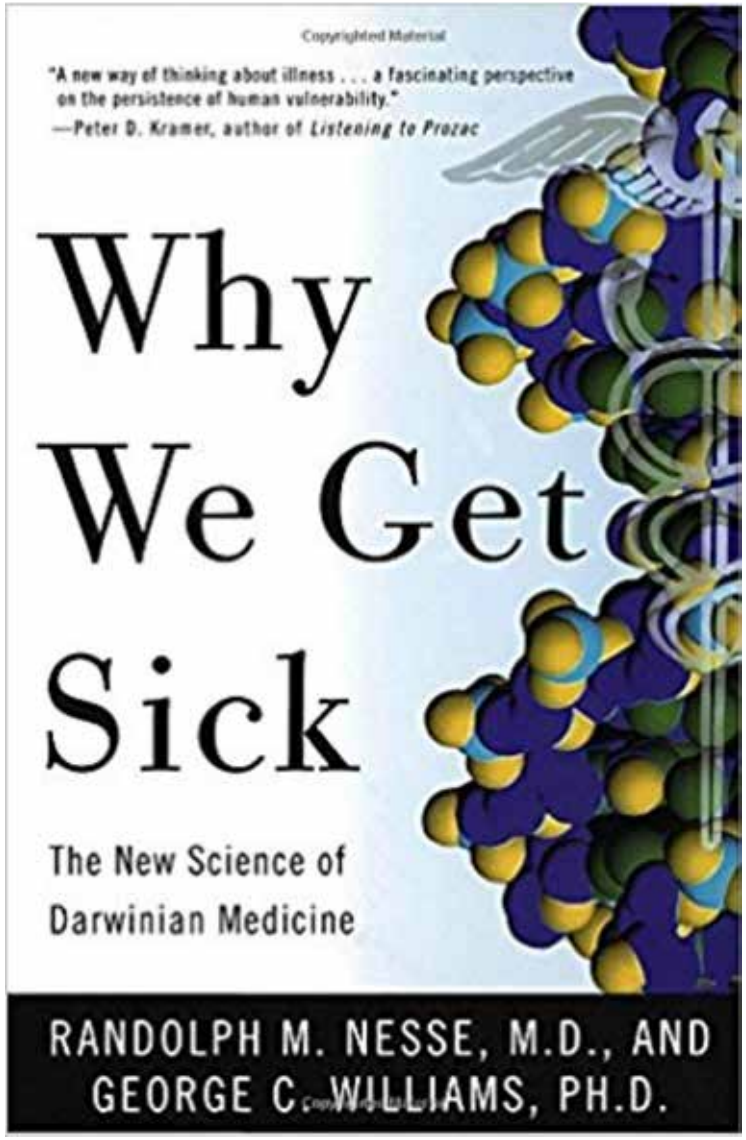
The field of evolutionary medicine



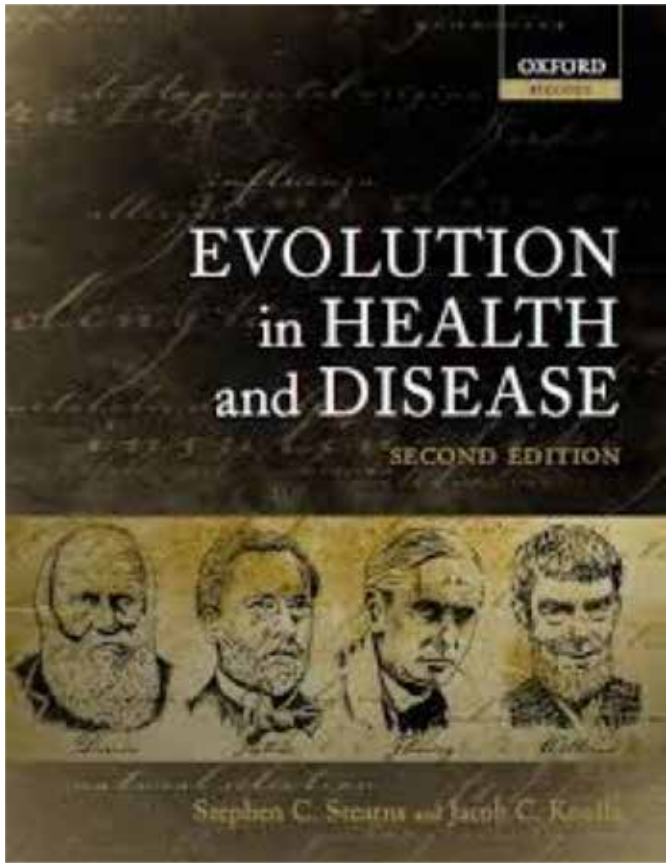
1994

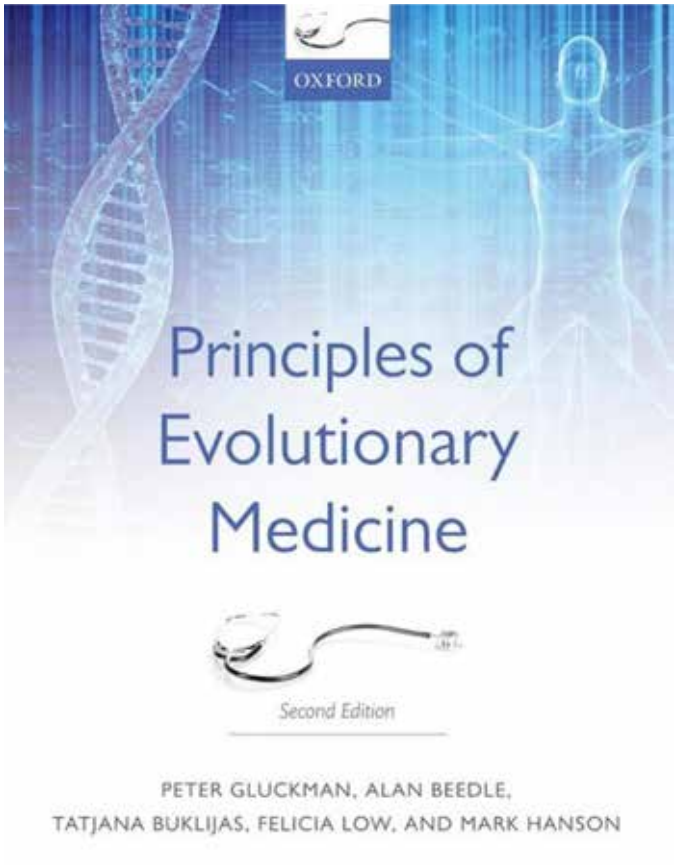
What is evolutionary medicine?

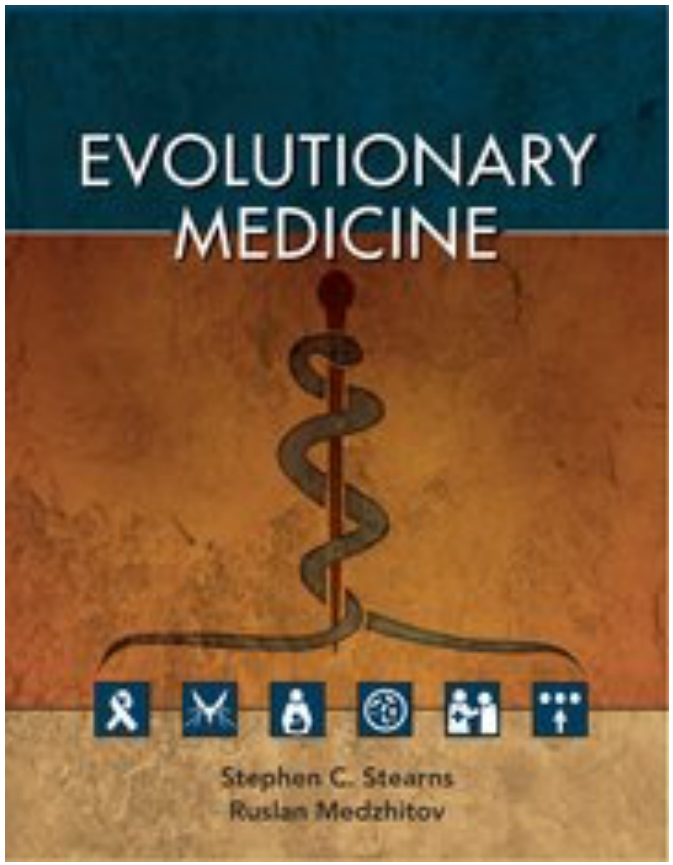
Evolutionary medicine or **Darwinian medicine** is the application of modern **evolutionary** theory to understanding health and disease.

Wikipedia 2018

Evolutionary medicine textbooks







Disease – anybody without?

Who has…

- Lactose intolerance?
- Myopia (nearsightedness)?
- Allergies?
- …ever experienced iron deficiency?

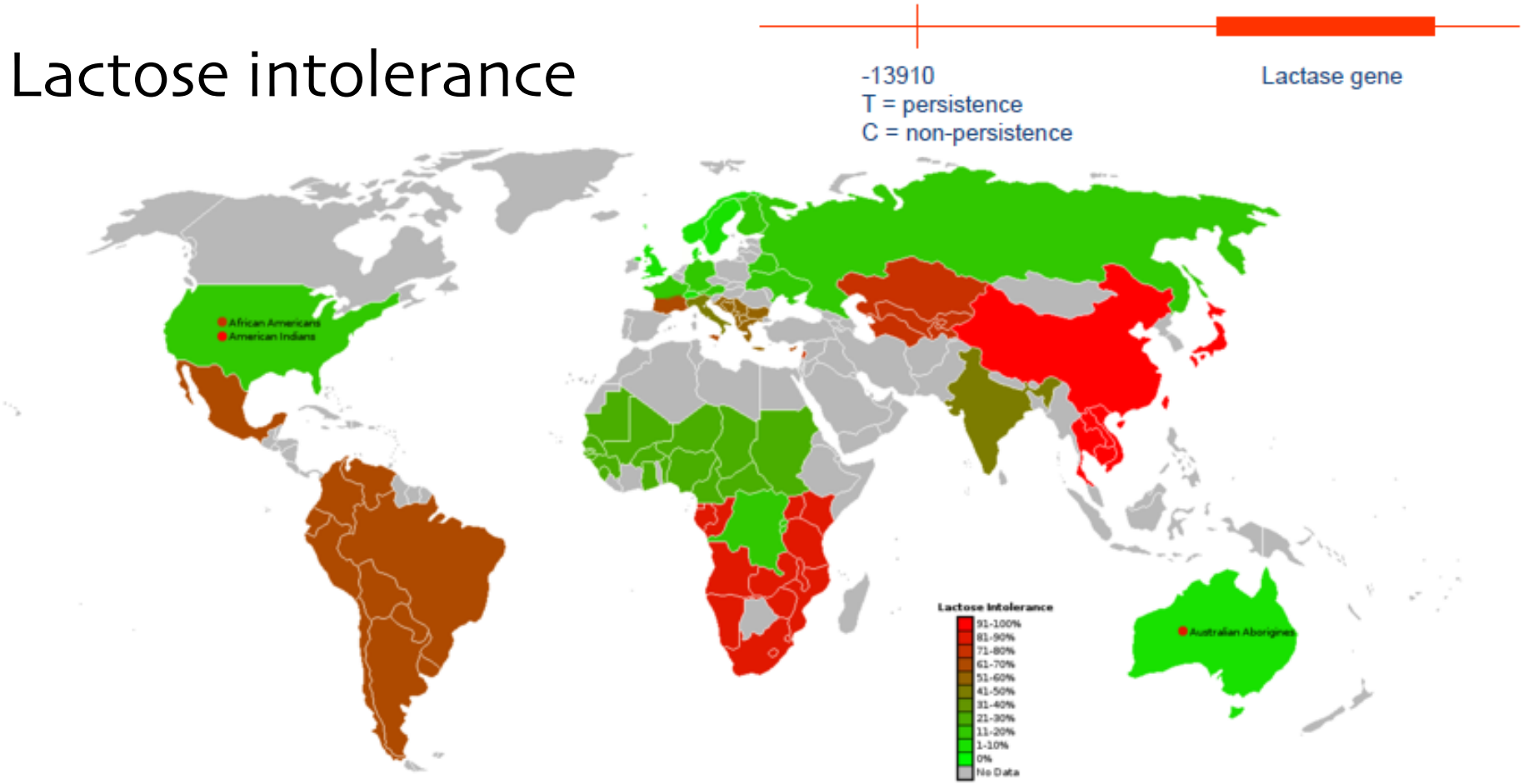
Evolutionary medicine

A brief introduction:

1. What is disease?
2. The human body – not intelligently designed…!
3. Rare diseases
4. Common diseases
5. Infectious diseases
6. Allergies
7. Does evolutionary medicine help us?

1. What is disease?

Lactose intolerance

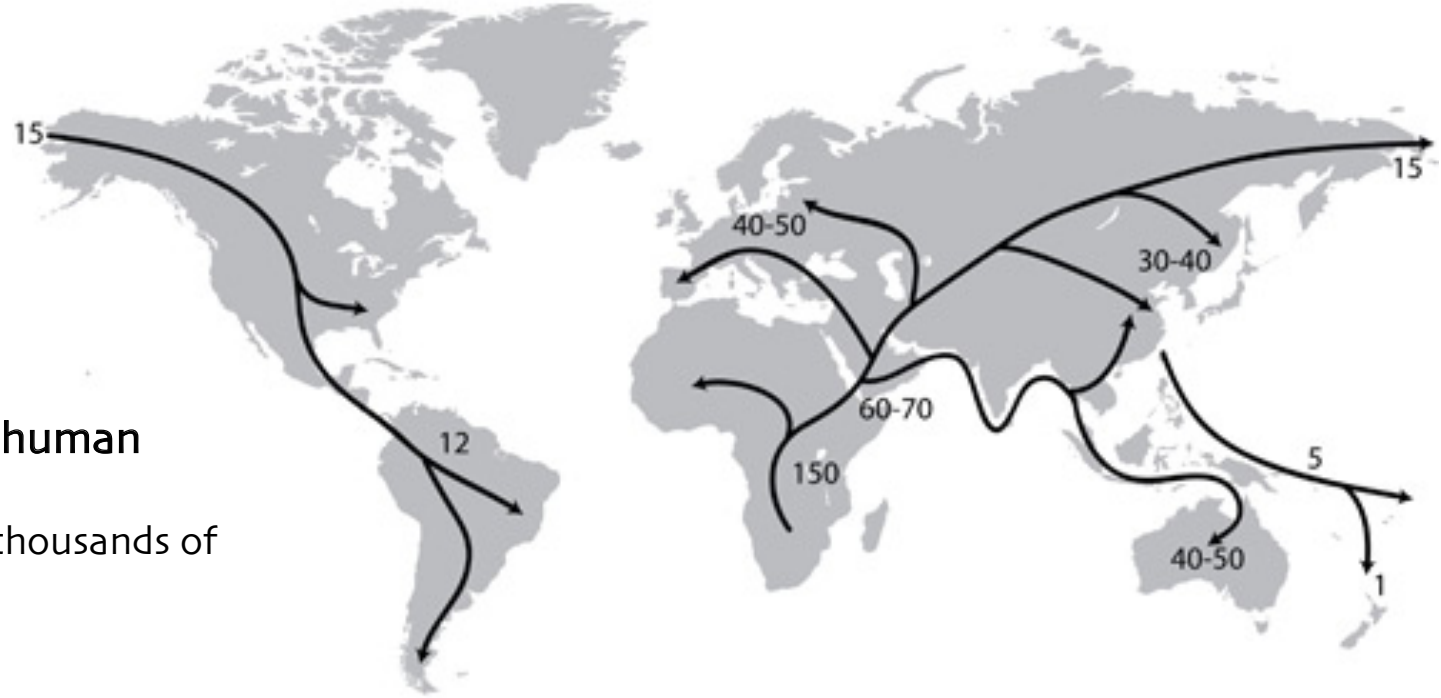


- Lactase persistance: Mutation 5.000-12.000 years ago
- Coevolution of nature and culture (agriculture: ruminant milk use)
- 'Disease' is dependent on the environment to which adaption has occurred

http://www.uneeda-audio.com/nomilk/800px_lacintol-world2.png

Human evolution

- last common ancestor with chimpanzee and bonobo:
  c. 5-6 million years ago
- "Out of Africa": Evolutionary origin of modern humans in Africa
- Adaptive evolution: humans adapted locally to the selective pressures of climate, food sources and pathogens
- Neutral evolution: bottleneck, higher diversity in Africans



Routes of human migration
(numbers: thousands of years ago)

http://evomedicine.org/the-book/human-evolution-and-the-origins-of-human-diversity/

Evolution of „health“?

- Selection maximizes fitness
- Fitness = reproductive success
- Not necessarily health or long lives
- “Classical” medicine defines as healthy a mean-valued human being
- It often doesn’t take into account the natural range of human variation

Human genetic variation

- Diploid human genome: about 6 billion base pairs
- Whole genome sequencing showed 4 million differences between two unrelated individuals (Venter and Watson – although from same ethnic group), corresponding to over 7000 protein coding differences
- Mutation rate of approximately 30 changes per generation per genome (shown by whole genome sequencing of a family)

The causes of disease

- Proximate Explanation: *What? How?*
  - anatomical, physiological, genetic, and developmental
  - Aim: mechanistic intervention

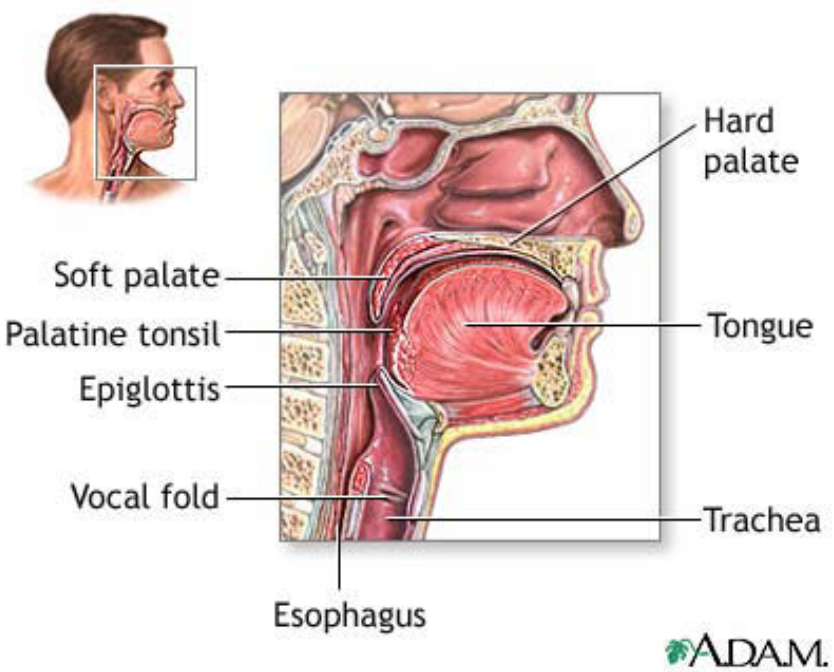
- Ultimate Explanation: *Why?*
  - historical, evolutionary
  - Aim: understanding adaptive value of traits

> The human body is a bundle of contradictions — simultaneously extraordinarily precise and unbelievably slipshod — that can be understood only through an evolutionary perspective of health and disease.
>
> Nesse and Williams 1994, p. 5

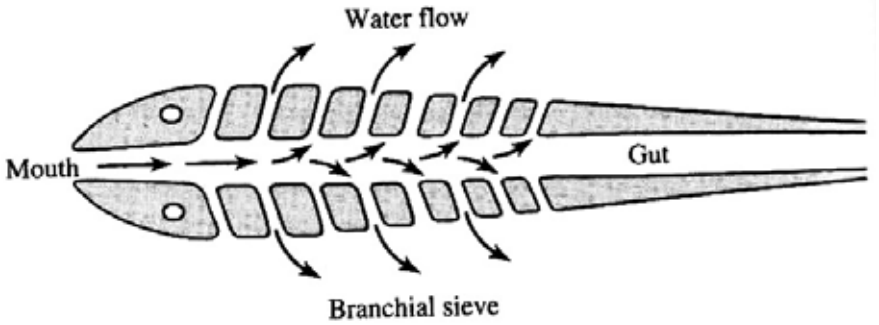
http://ottawaquitsmoking.com/images/body.jpg

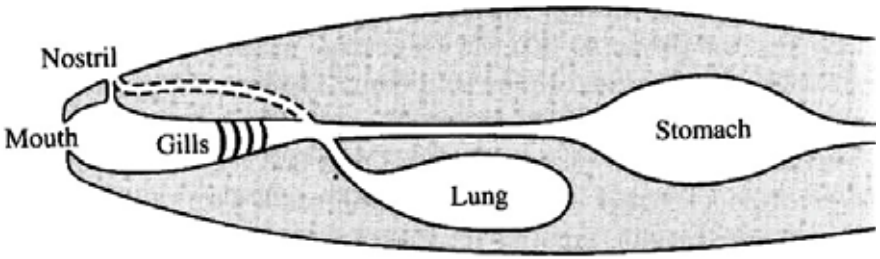
2. The human body – not intelligently designed

Evolutionary 'design' constraints



Can be understood from evolutionary history:



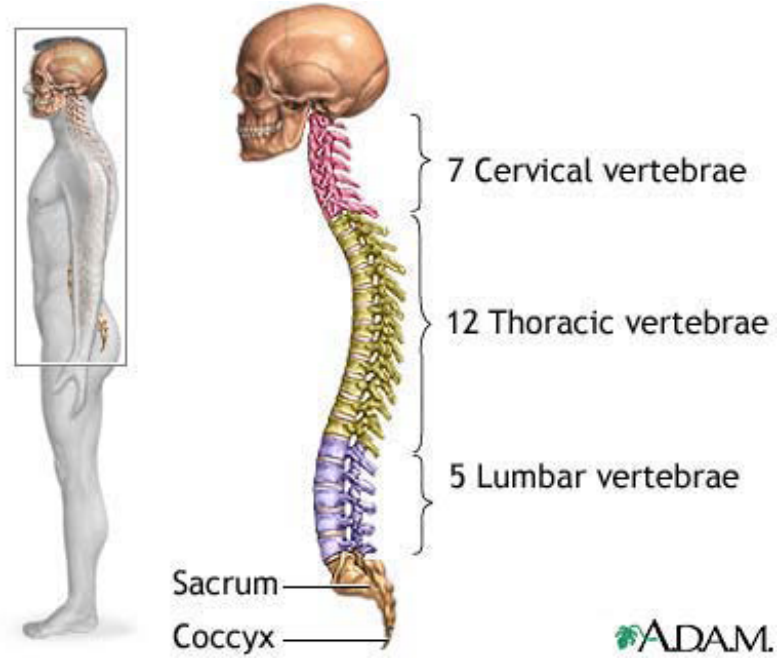


Flawed design:
crisscross of air and food ways

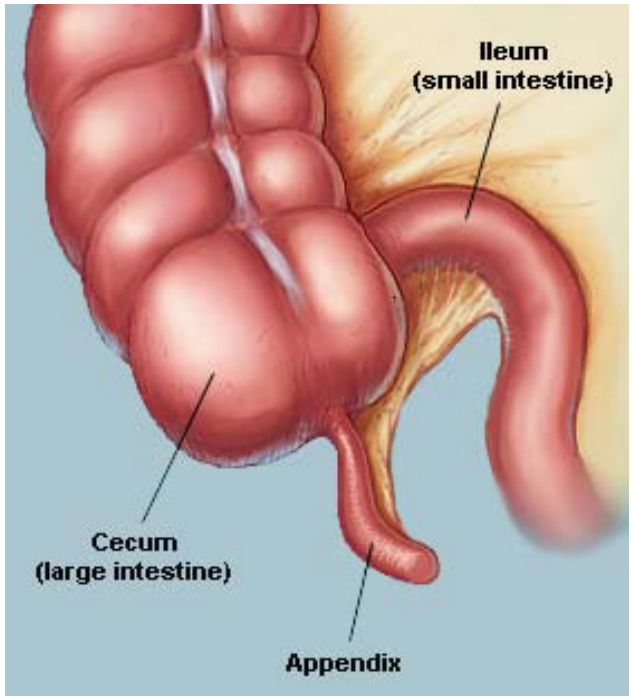
- Risk of choking
  (1 / 100.000 death per year)

Evolutionary constraints

Further examples…



Spine problems



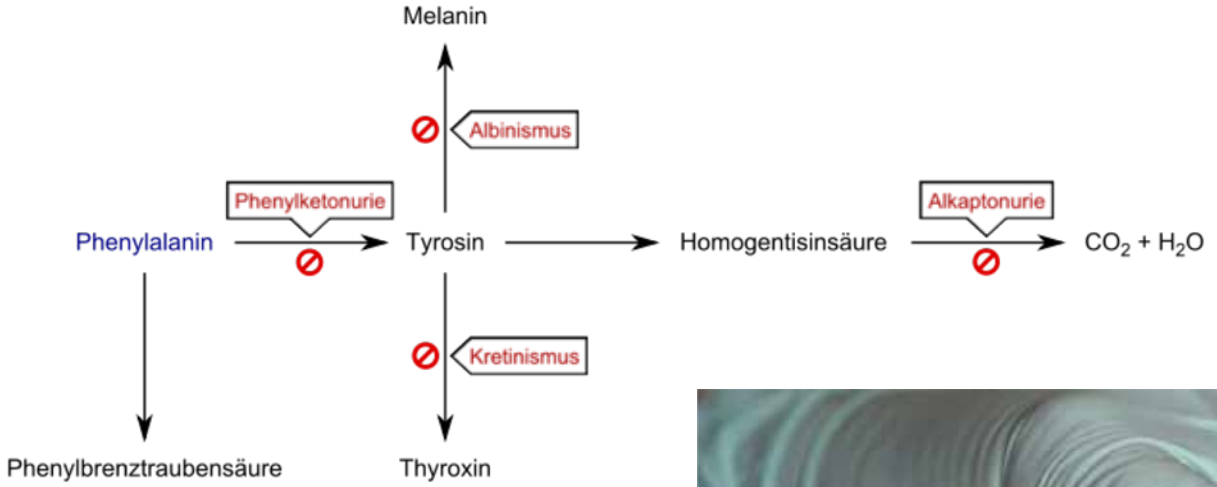
Appendicitis

3. Rare diseases

- < 1 : 10.000 for each disease, collectively 1% of people
- often simple (Mendelian) inheritance
- mostly recessive:
  selection is not very effective against recessive deleterious alleles, because there is no selection against heterozygotes
- new mutation:
  mutation-selection balance
- disease genes might have (sometimes unknown) benefits, often in the heterozygous state, in the ancestral or modern environment

PKU – a relatively common rare disease

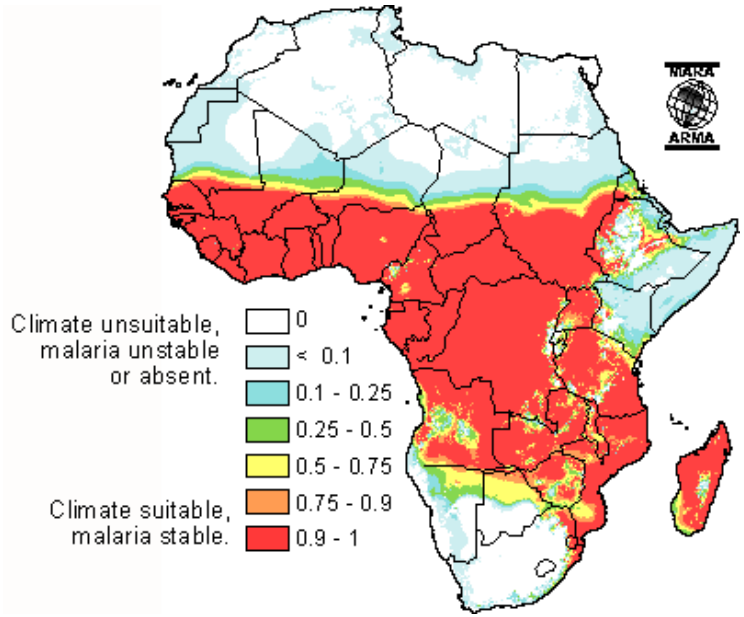
- PKU = Phenylketonuria; autosomal recessive; incidence 1:8000, i.e. 1/90 persons carry gene
- inability to metabolize amino acid Phenylalanine to Tyrosine
- accumulation of Phenylpyruvate, -acetate, - lactate



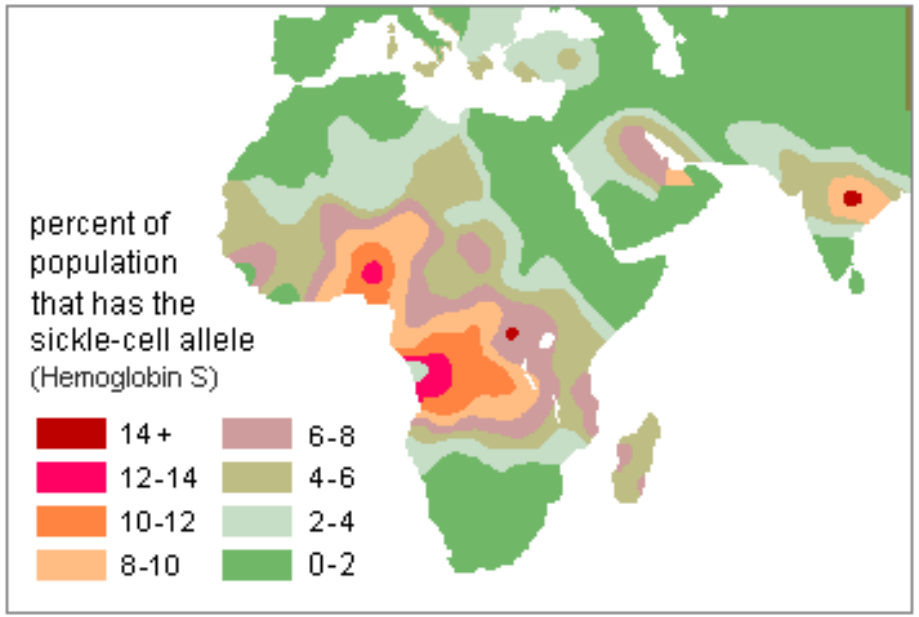
- newborn screening
- completely preventable by diet
- gene may reduce miscarriage

Balancing selection

Sickle cell anemia and malaria: Heterozygote advantage



Distribution of malaria in Africa



Distribution of sickle cell allele

http://microbewiki.kenyon.edu/images/e/e1/Picdistr.gif

http://anthro.palomar.edu/synthetic/images/map_of_sickle_cell_frequencies.gif

Huntington's disease

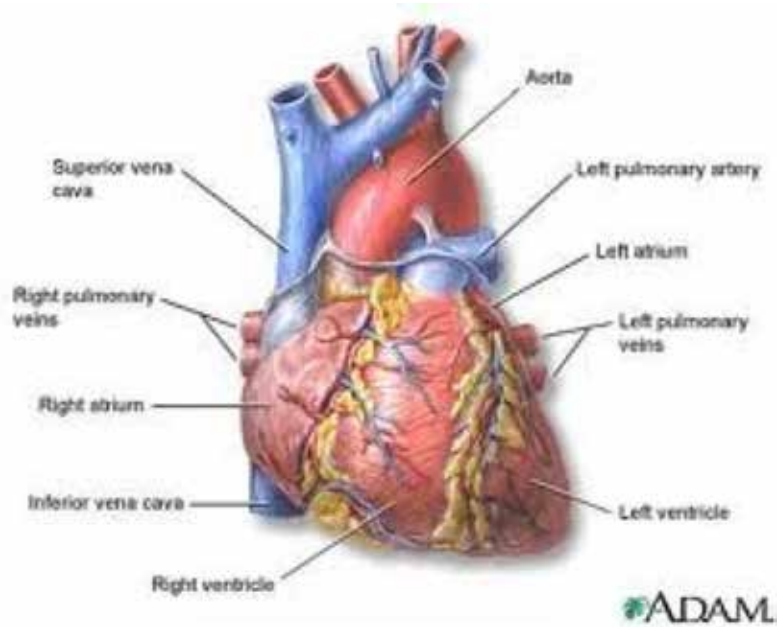
- Very severe neurodegenerative disorder
- Symptoms normally start in the age of c. 40
- Autosomal *dominant*
- Prevalence 5-10 per 100.000
- Why so relatively frequent?

Cortical atrophy

- ➢ Reproduction often has occurred before disease starts
- ➢ Selection maximizes fitness, not health!

3. Common diseases

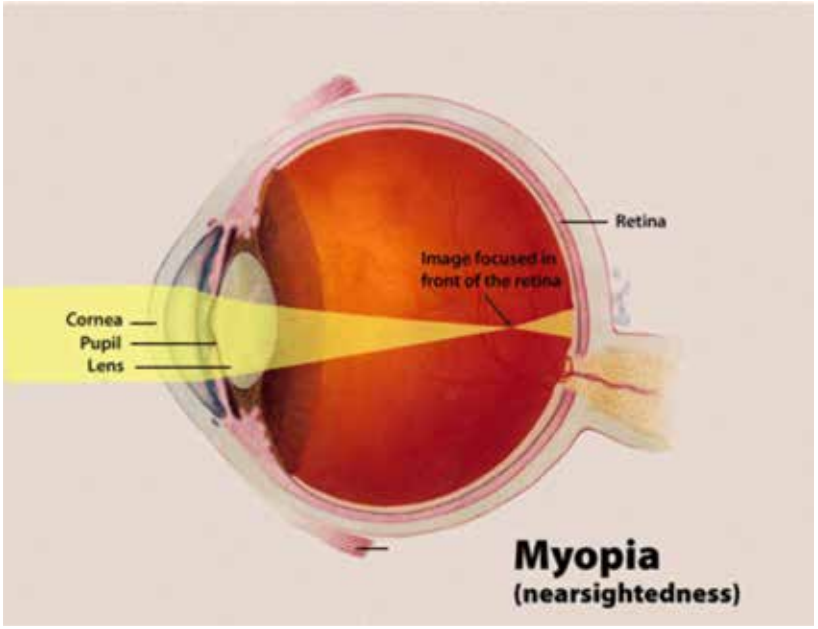
Heart diseases, diabetes, cancers, psychiatric diseases,…



- Complex causation
- Interaction of many genes
- Genetic hitchhiking
- Gene – environment interaction

Myopia (nearsightedness)

- Very high incidence: ca. 25%
- High heritability: ca. 80%
- Clear disadvantages
- Why so common?

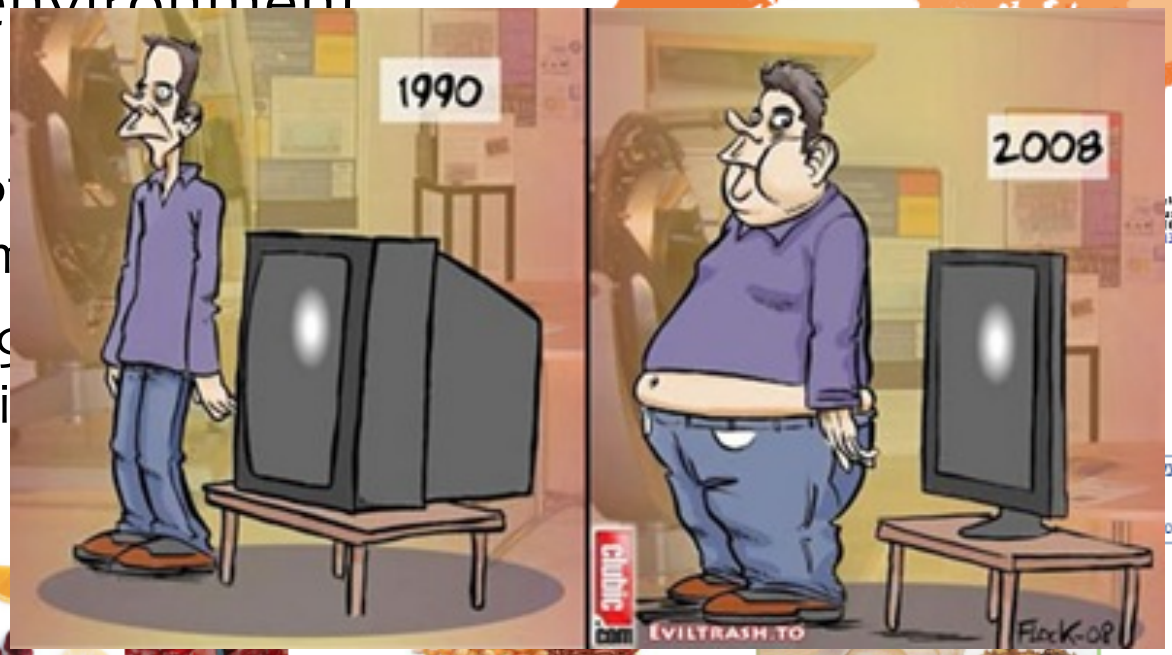


- Native people are rarely nearsighted, but when children attend school, they often become myopic
- No new genes, but new environment
- Gene – environment interaction!

Diabetes (type 2)

Mismatch between genes and environment

- Maladap
  environm
- Changing
  metaboli



Modern hunter-gatherer (Paleolithic?)

Neolithic

Contemporary

Diabetes:
Insulin resistance as an adaptation?

Insulin resistance in cavefish as an adaptation to a nutrient-limited environment Riddle et al. *Nature* 2018

Depression vs. happiness based on a plasticity gene rather than a risk allele?

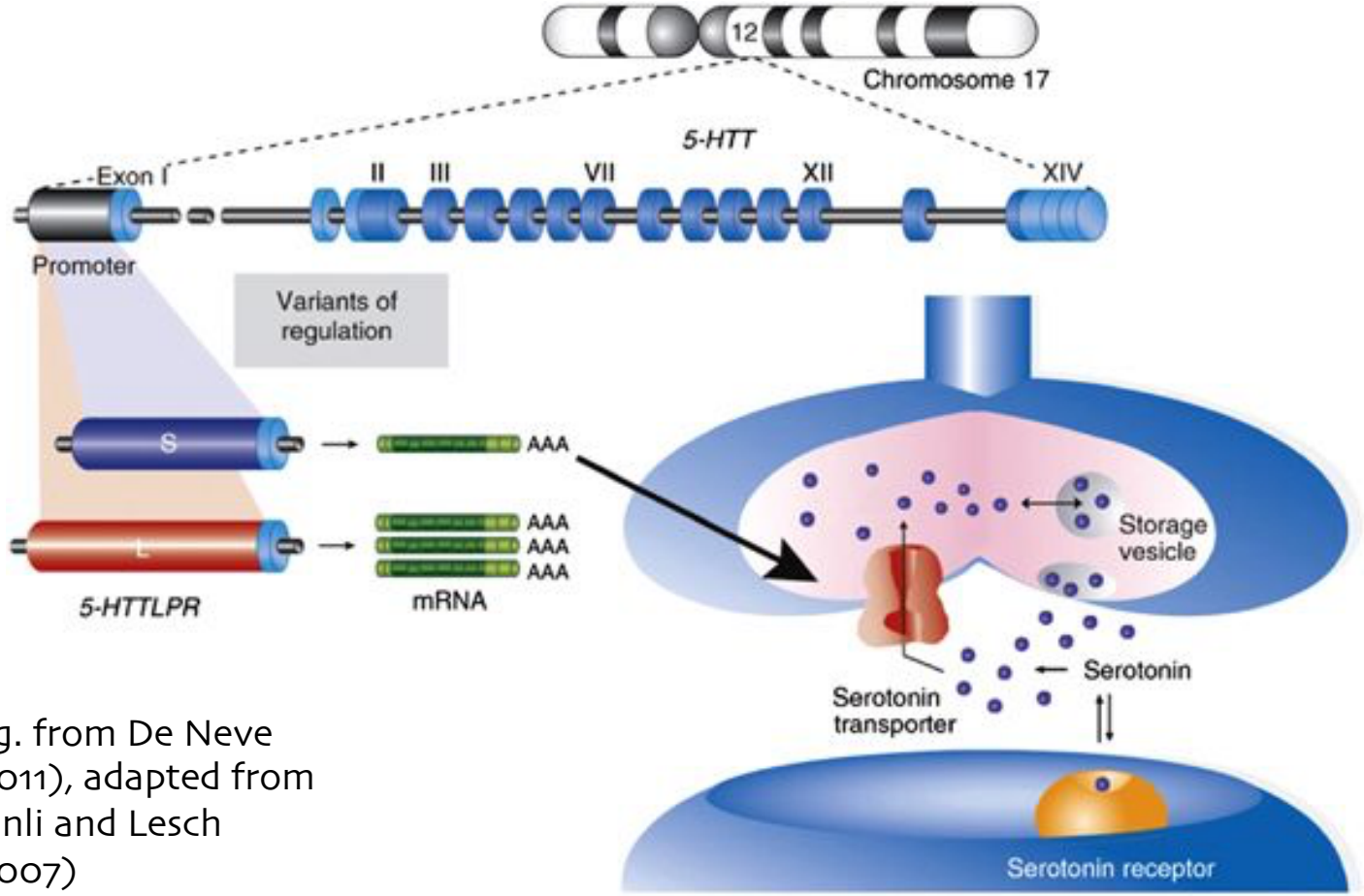
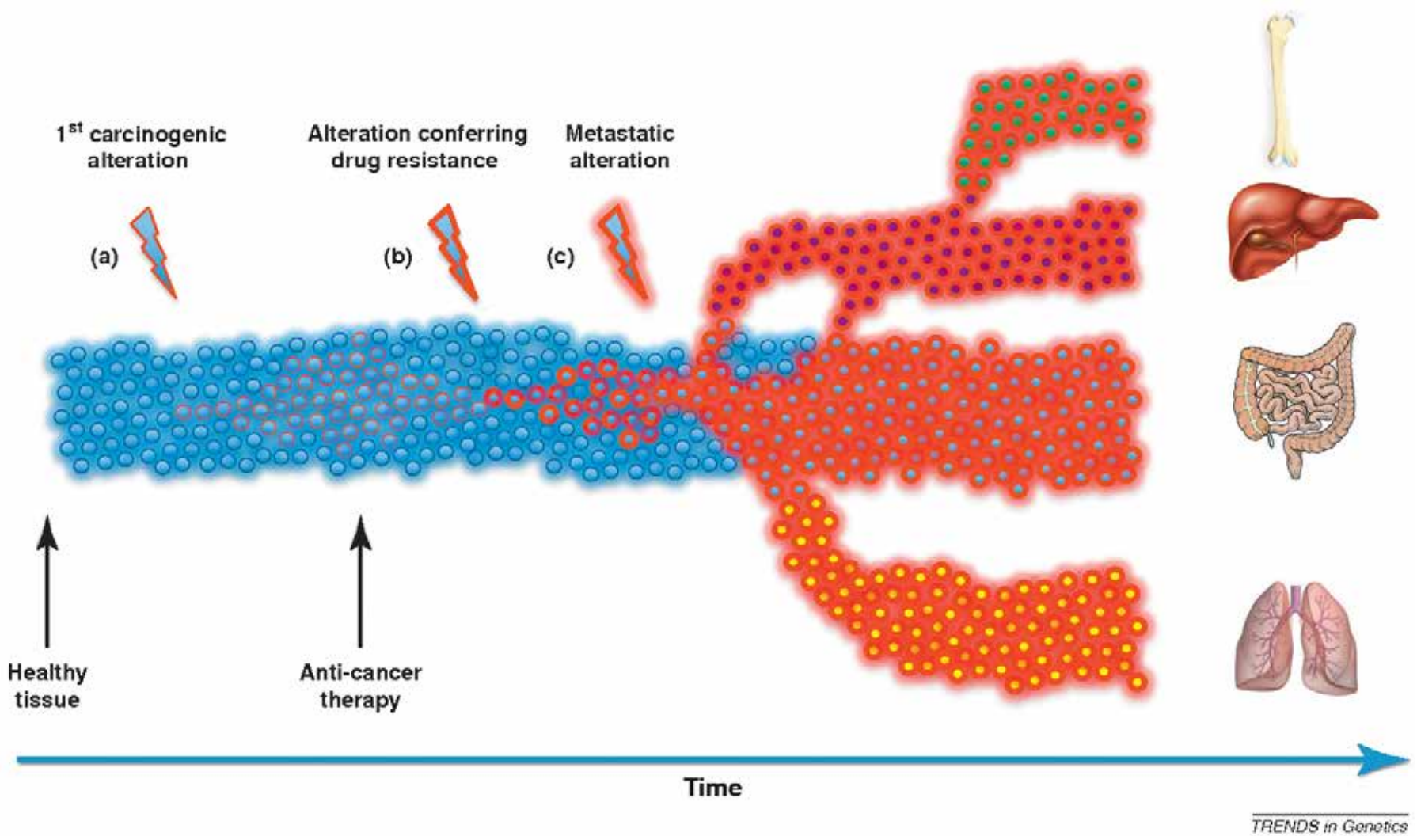


Fig. from De Neve (2011), adapted from Canli and Lesch (2007)

Variation in the promotor region of the serotonin transporter gene: Carriers of a short gene variant who have experienced negative life events are more susceptible to depression; however, this susceptibility is reversed after predominantly positive experiences.

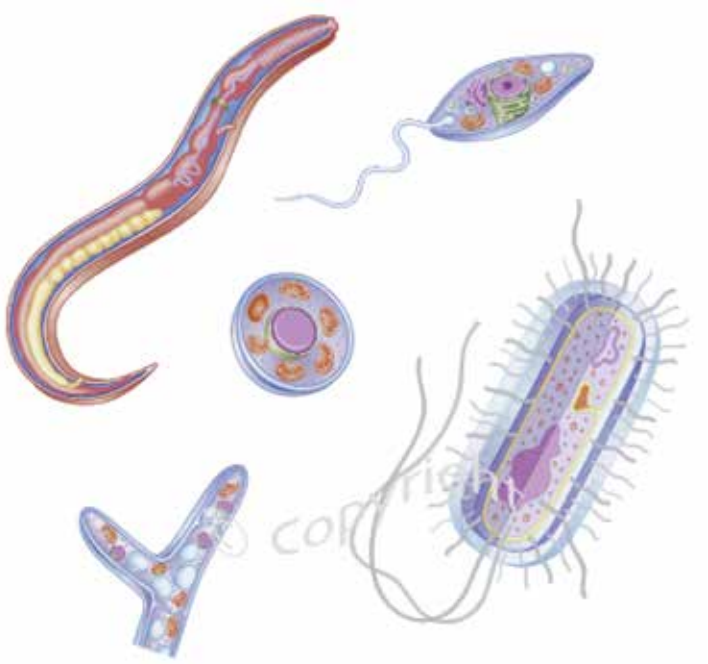
Cancer as an evolutionary process



Podlaha et al TiG 2012

5. Infectious diseases

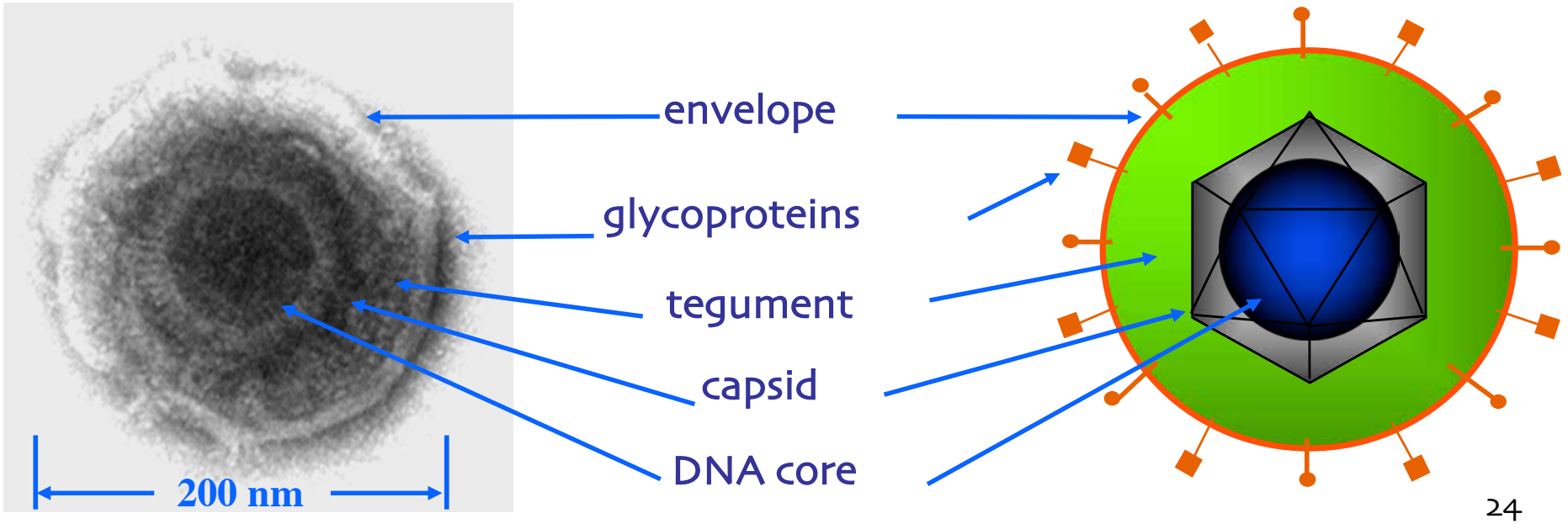
Caused by parasites:
viruses, bacteria, fungi,
protozoa, helminths etc …



- Coevolution
- Arms races, "Red Queen"
- Resistance evolution
- Often, long history of adaptations and counter-adaptations

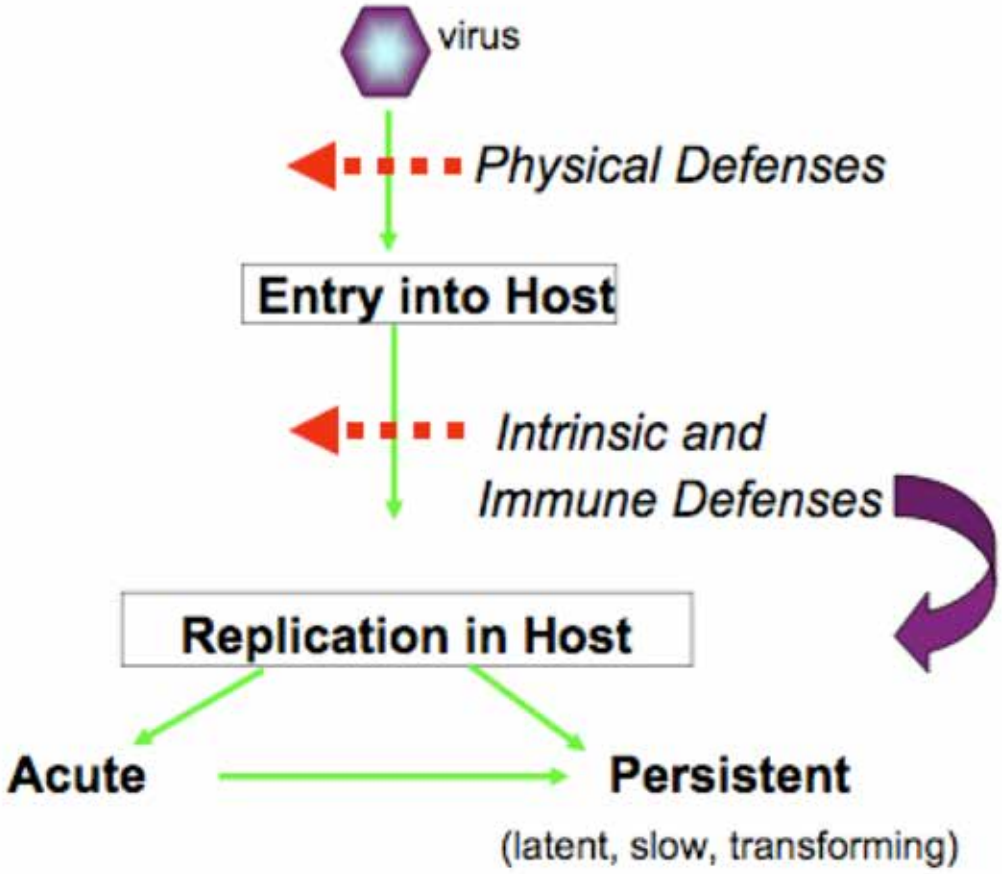
The human herpes virus

- Causes latent infections
- Human herpes virus has evolved with us since before the invertebrate-vertebrate split



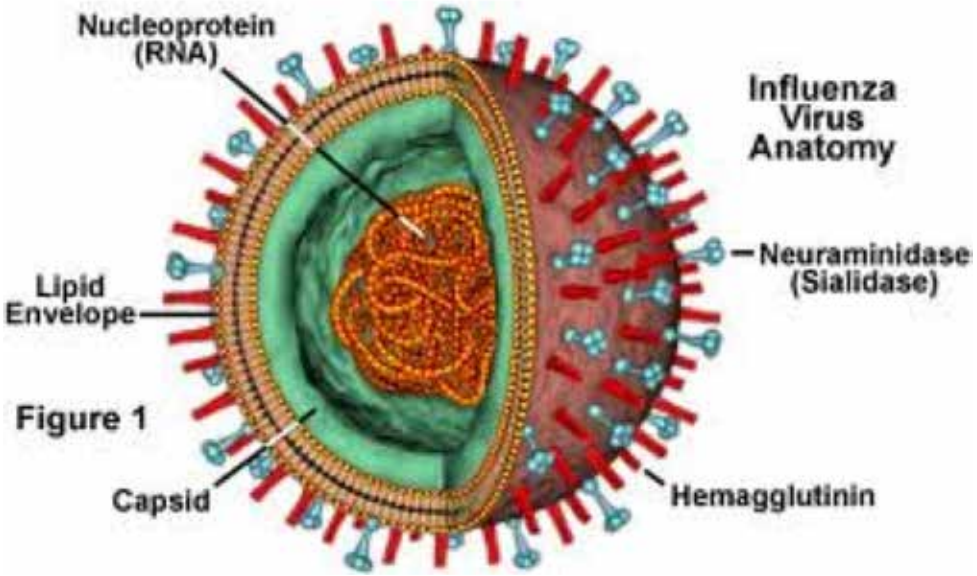
The human herpes virus

- Persistent infections, in otherwise healthy individuals rarely fatal
- Elaborate interaction of virus and host traits



Influenza virus

Very dynamic evolutionary history, host shifts, etc.



6. Allergies

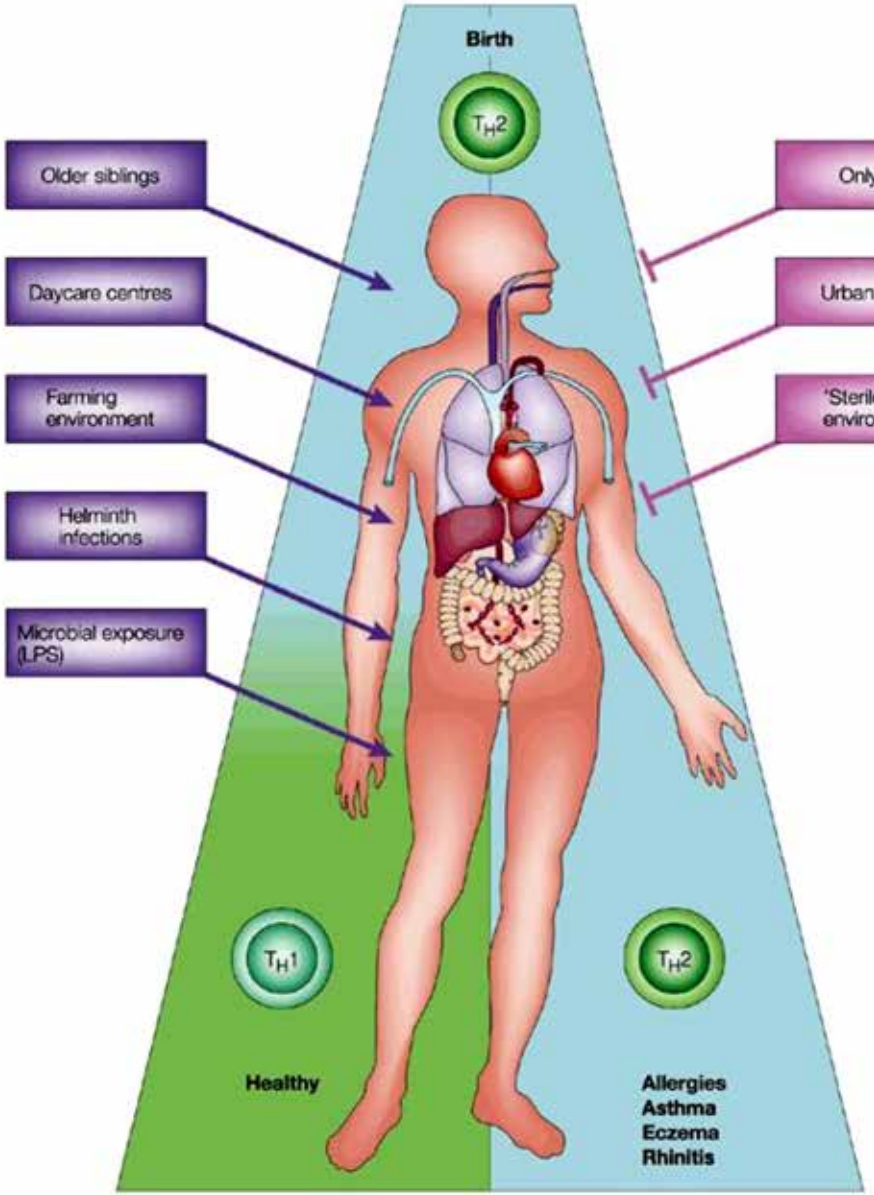
Hypersensitivity disorder of the immune system

IgE dominated immune reactions

- Dramatic increase in industrial countries, while relatively rare in developing countries
- Why?

Hygiene hypothesis

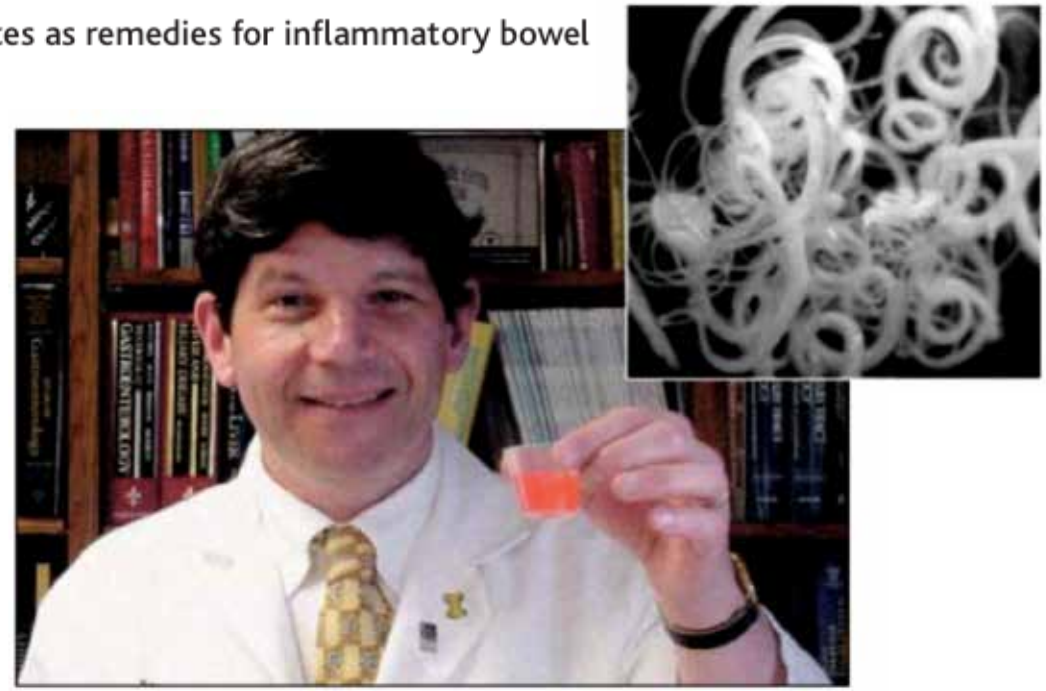
More parasites = less allergies?



Hygiene hypothesis

Can Worms Tame the Immune System?

Researchers are investigating the use of parasites as remedies for inflammatory bowel disease and other disorders of hyperimmunity

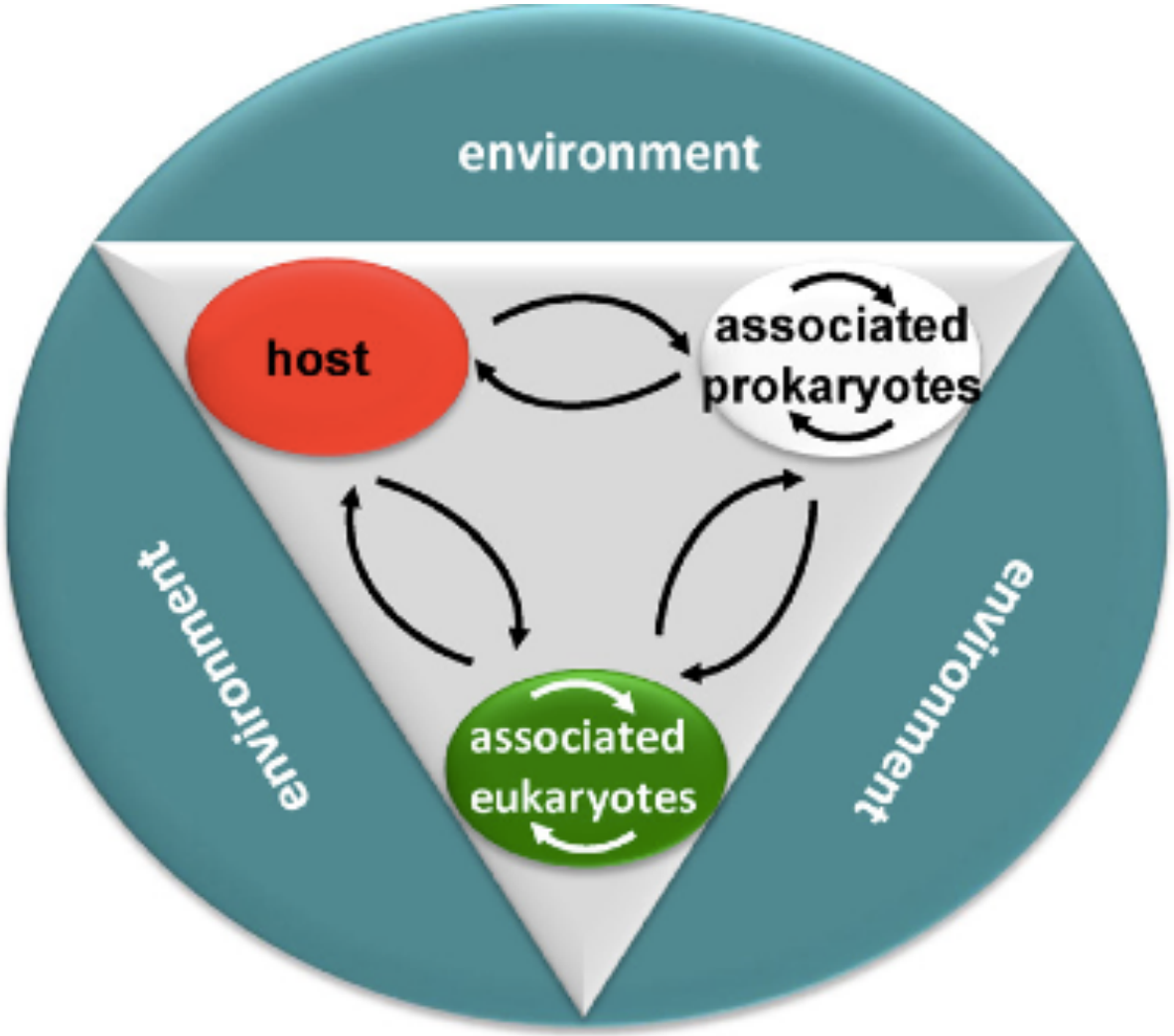


Man and his worm. Joel Weinstock holds a dose of eggs from *Trichuris suis* (*inset*), which he is using to treat inflammatory bowel disease.

Science 2004

'Old friends' hypothesis
(relevance of specific parasites instead of general hygiene)

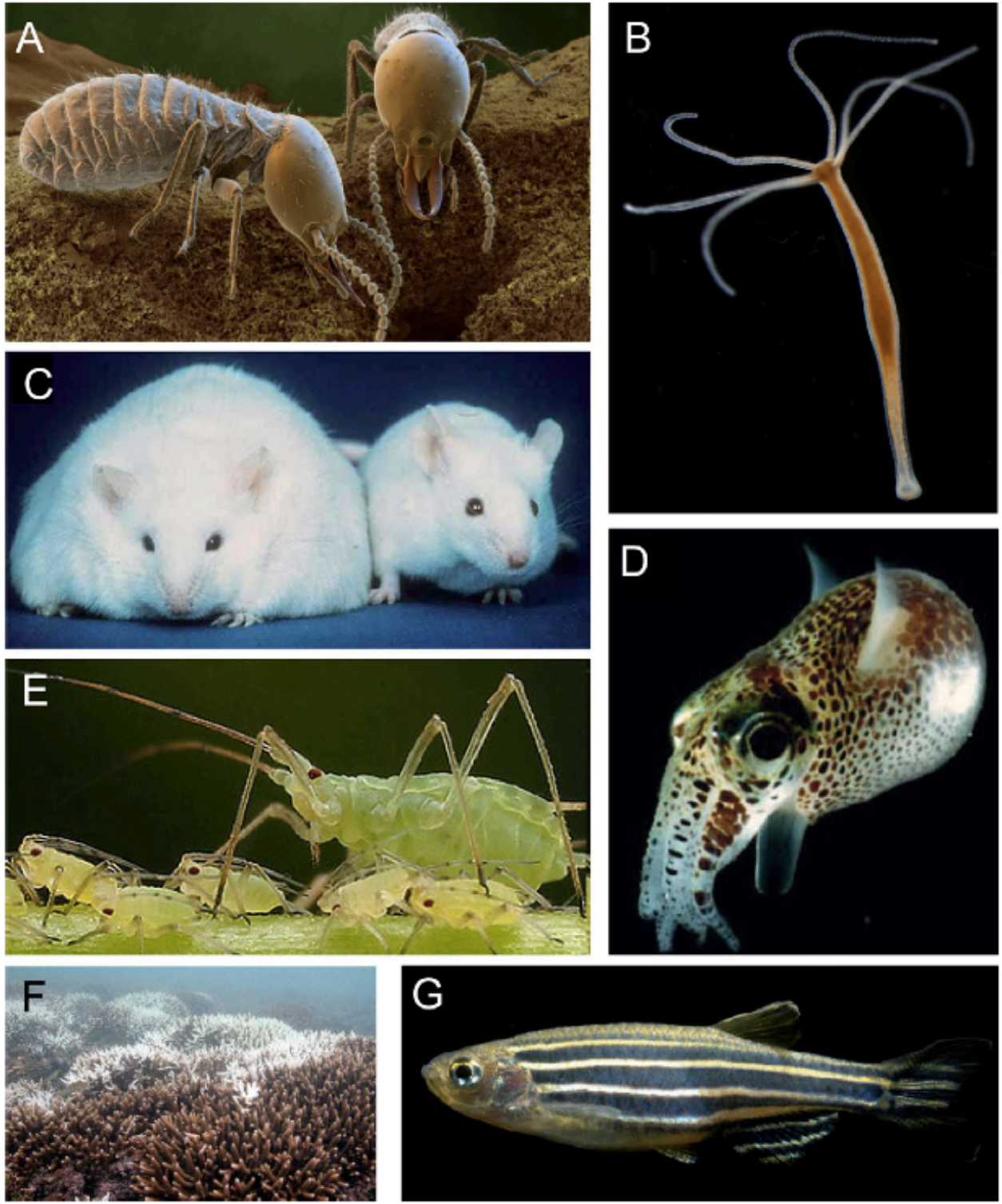
The idea of the 'metaorganism'



Bosch & McFall-Ngai Zoology 2011

The idea of the 'metaorganism':

Some examples



Bosch & McFall-Ngai Zoology 2011

Program Snapshot

The Common Fund's **Human Microbiome Project (HMP)** aims to characterize the microbial communities found at several different sites on the human body, including nasal passages, oral cavities, skin, gastrointestinal tract, and urogenital tract, and to analyze the role of these microbes in human health and disease. HMP includes the following initiatives.

- Development of a reference set of microbial genome sequences and preliminary characterization of the human microbiome
- Elucidation of the relationship between disease and changes in the human microbiome
- Development of new technologies for computational analysis
- Development of new tools for computational analysis
- Establishment of a data analysis and coordinating center (DACC)
- Establishment of resource repositories
- Examination of the ethical, legal and social implications (ELSI) of HMP research

Read More...

Program Highlights

Access the HMP data:

View the genomes of 100s of HMP reference strains in Gen Bank:
http://www.ncbi.nlm.nih.gov/bioproject/28331

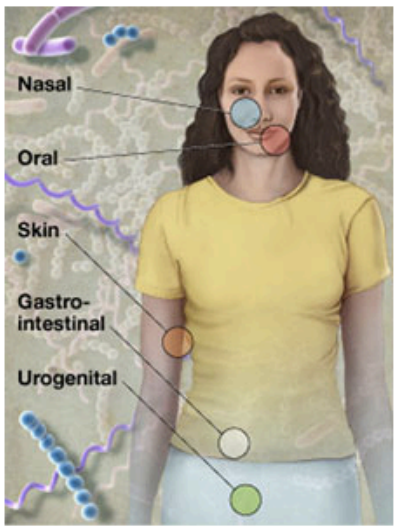
Order an HMP reference strain:
http://www.beiresources.org/

View the HMP BioProjects page at NCBI with sequence and phenotype data:
http://www.ncbi.nlm.nih.gov/genomeprj/43021

Visit the HMP Data Analysis and Coordination Center (DACC) site:
http://www.hmpdacc.org

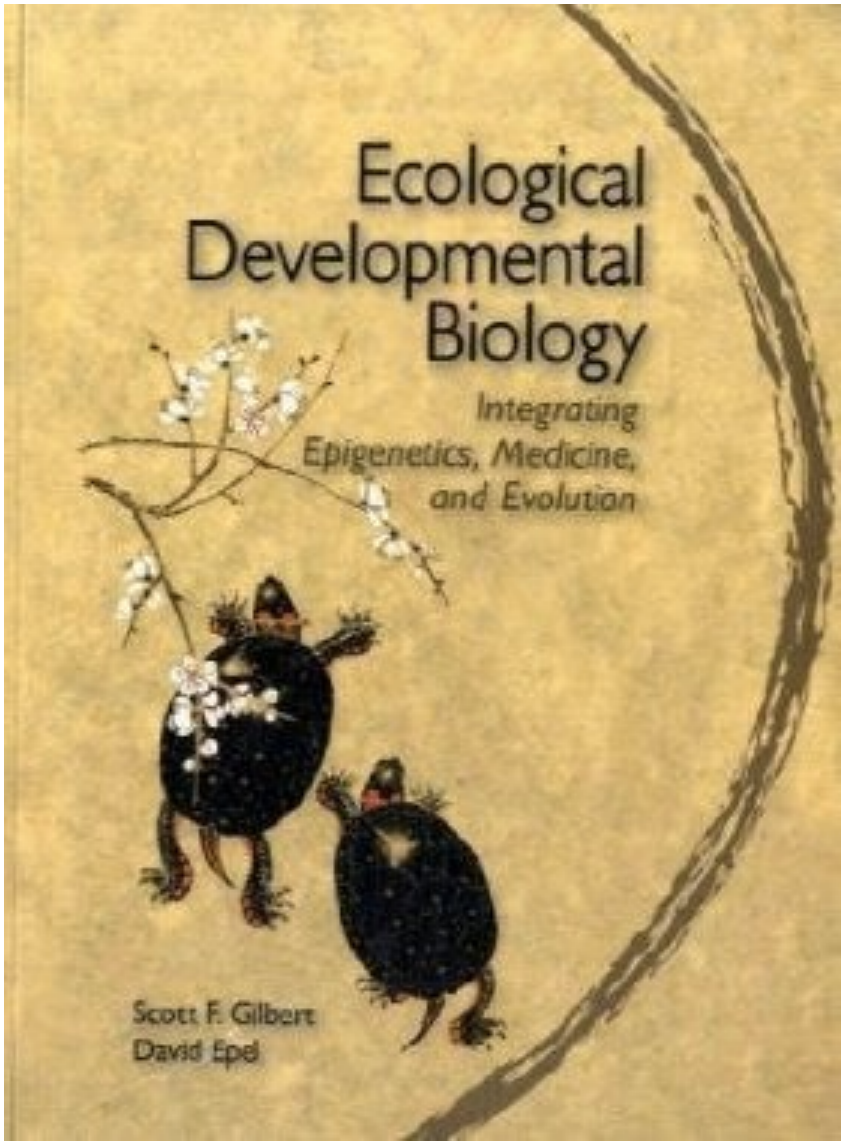
WANTED: DEAD or ALIVE!

THE HUMAN MICROBIOME PROJECT (HMP) NEEDS YOUR HELP!!!



Researchers in the HMP are sampling and analyzing the genome of microbes

Ecological developmental biology and disease



- Bacterial regulation of immune defences and development
- Role of gut bacteria for obesity
- Epigenetic origins of diseases
- Endocrine disruptors and infertility

7. Does evolutionary medicine help us?

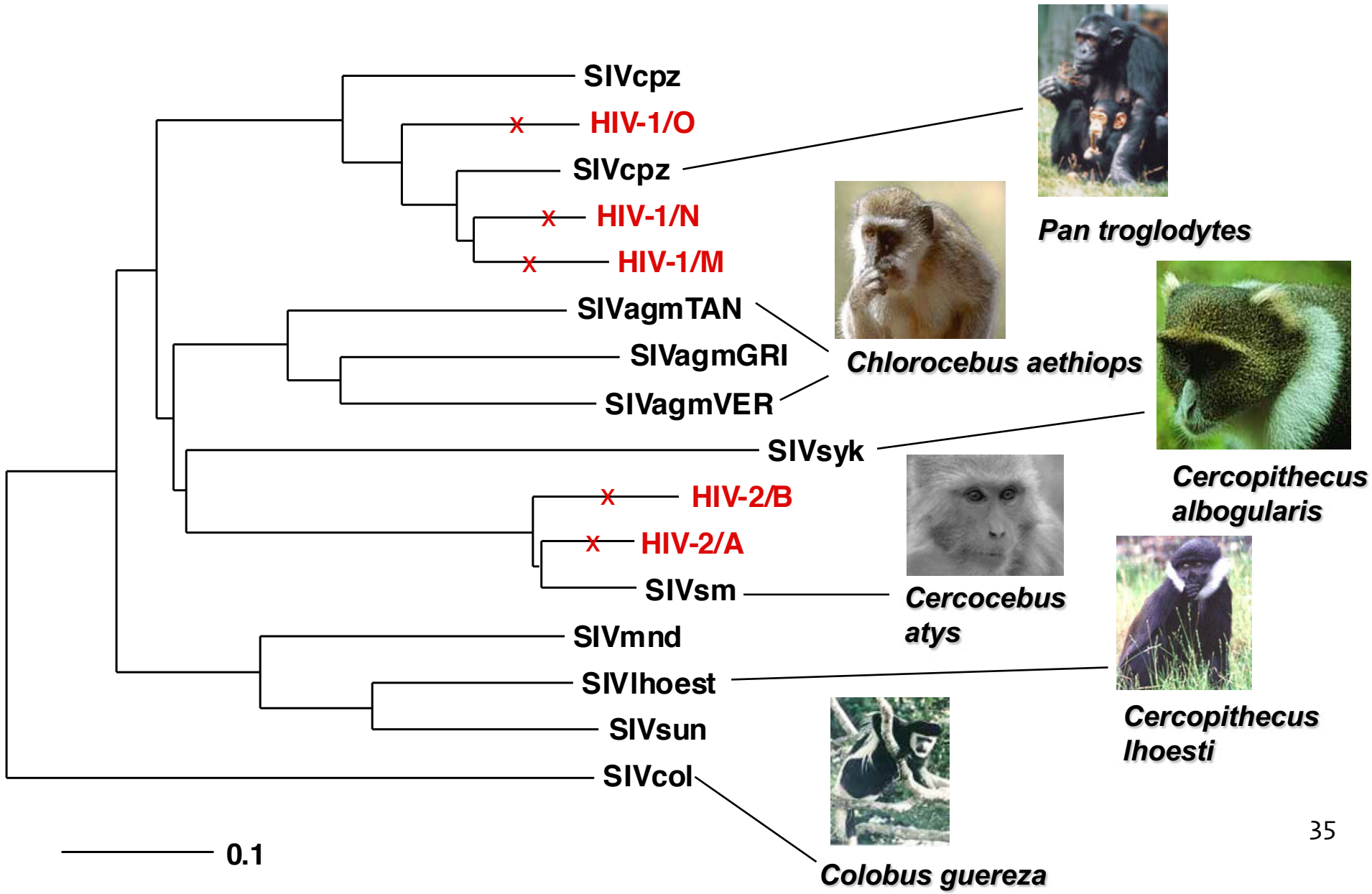
Understanding diseases:
Symptoms of disease could be defenses!

- Fever
- Iron deficiency
- Morning sickness
- …

"Respect the evolved wisdom of the body"

Nesse & Williams 1994

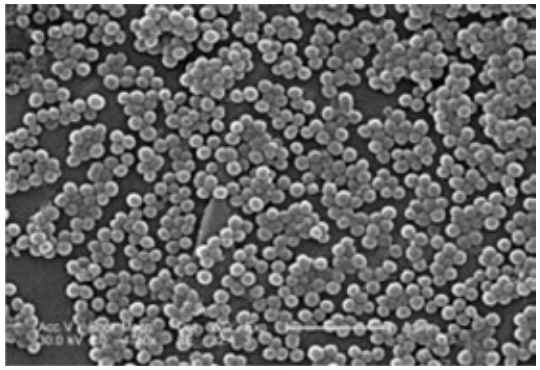
Understanding disease evolution: HIV

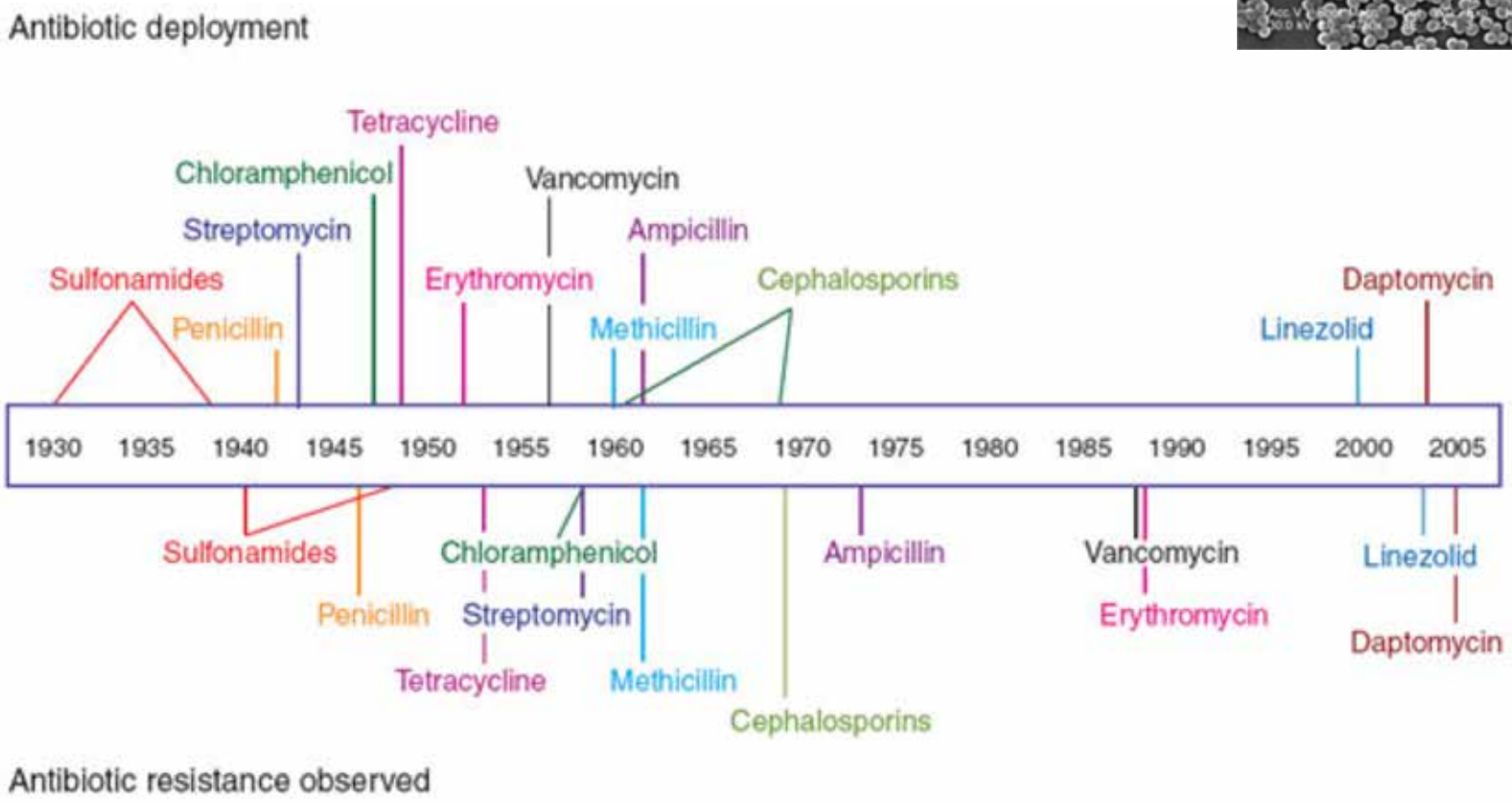


Antibiotic resistance evolution

Methicillin-resistant *Staphylococcus aureus*

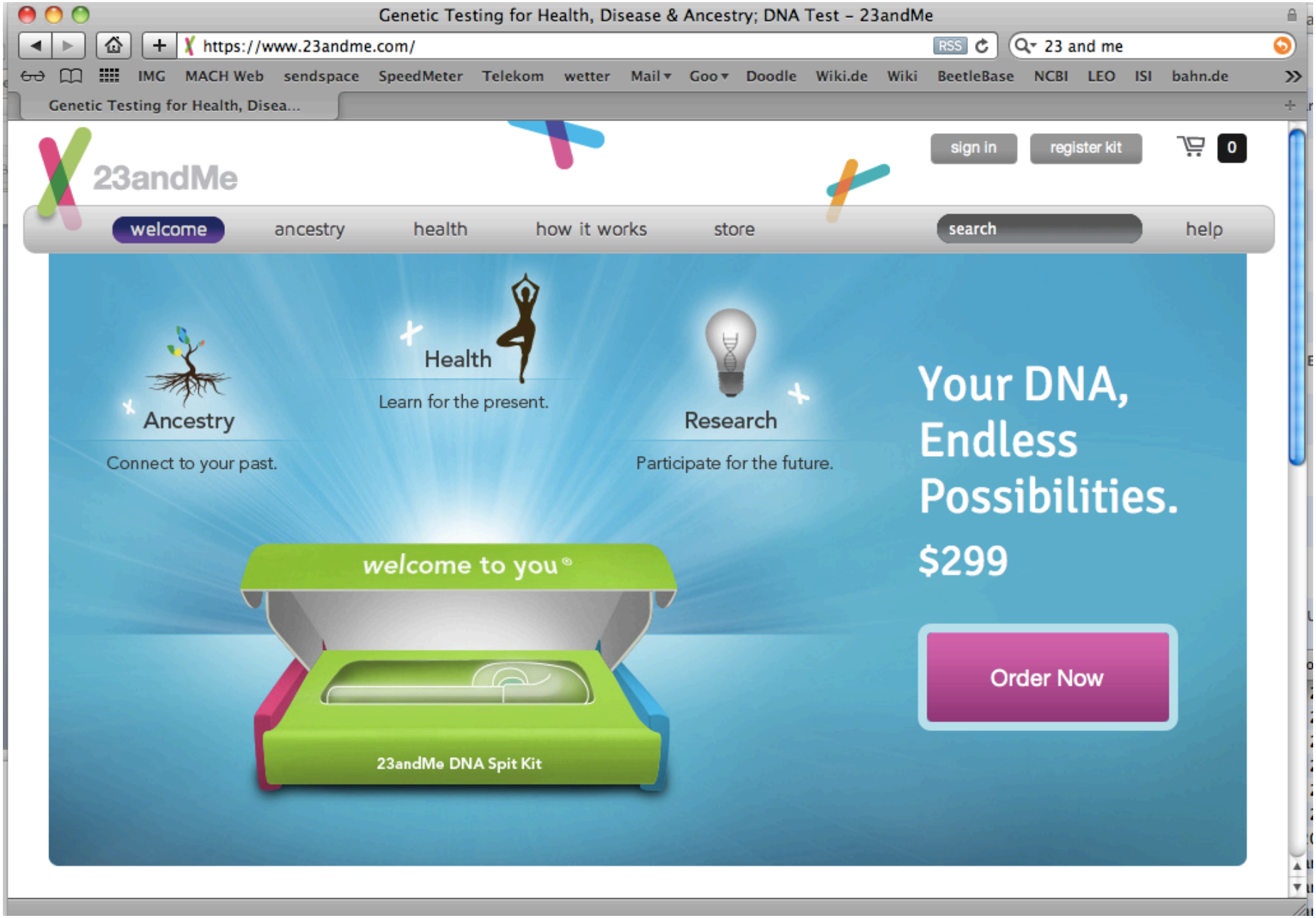
Evolved resistance to beta-lactam antibiotics which include the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins.



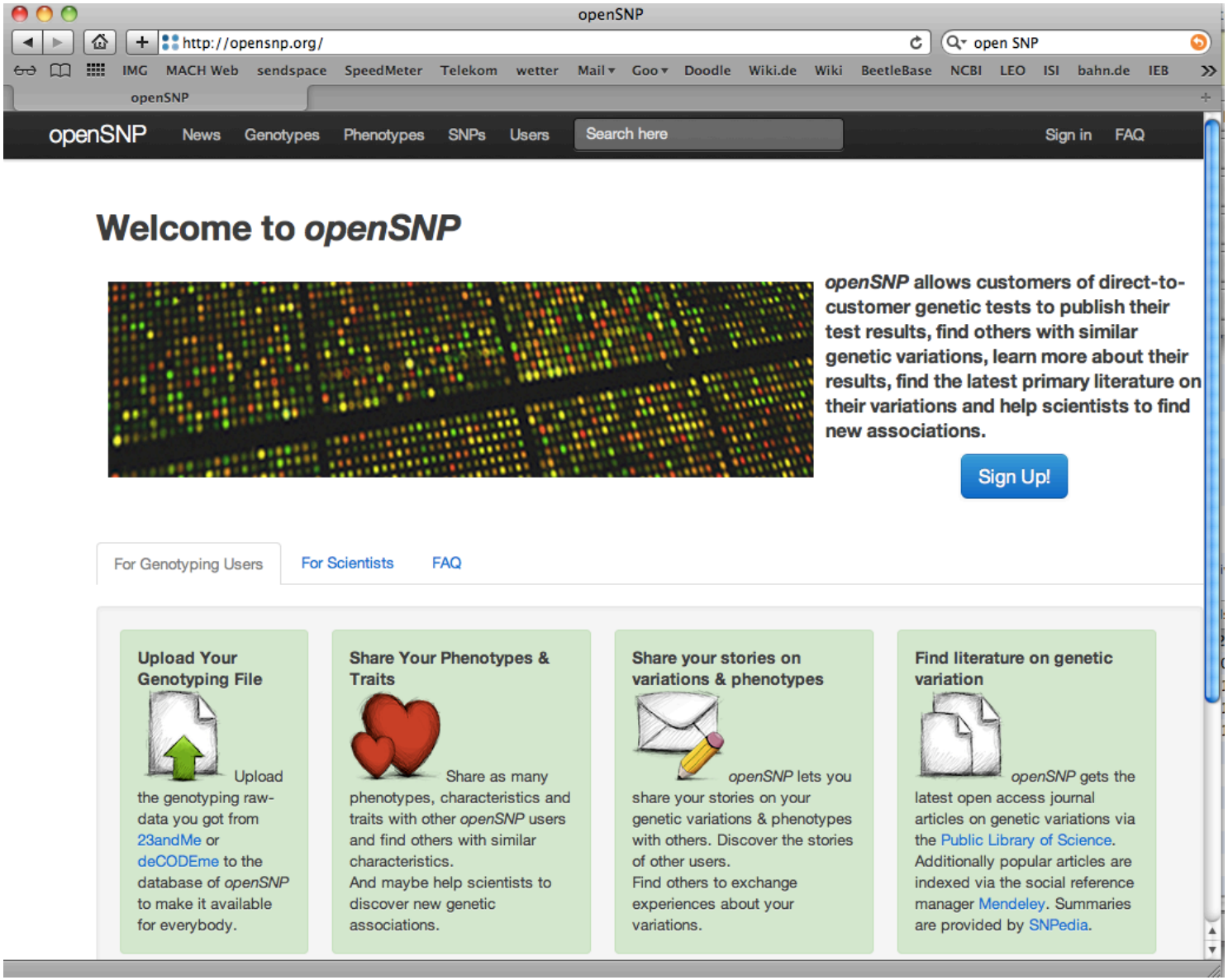


From Clatworthy et al (2007) Nat. Chem. Bio.

Human genetic screens: A Box of Pandora?

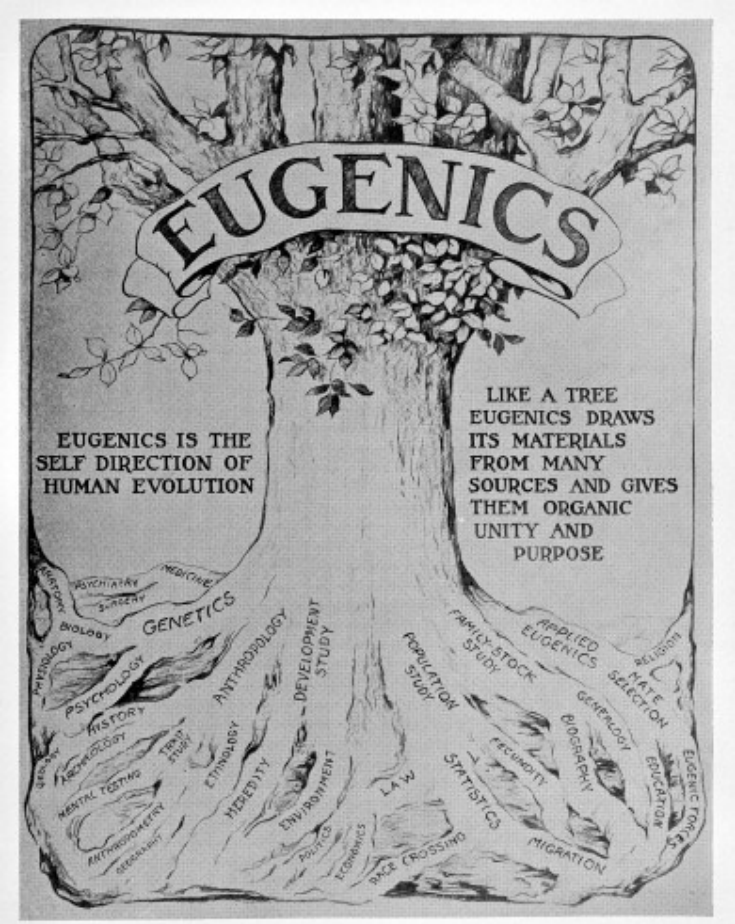


Genetic variation: What should we do with all the knowledge?



Dangerous misunderstandings

- Eugenics:
  ethically condemnable
- … and, as evolutionary medicine shows, also scientifically mostly wrong!
- The goal of medicine is to help the sick, not the species
- Evolutionary theory (as any scientific theory) cannot give any moral guidelines



THIRD INTERNATIONAL EUGENICS CONGRESS, NEW YORK CITY, AUGUST 21–23, 1932
Introductory Wall Panel "The Relation of Eugenics to Other Sciences," based on a paper by Dr. Harry H. Laughlin, Cold Spring Harbor, Long Island, New York

http://evomedicine.org/the-book/evolutionary-medicine-and-society/

Evolutionary medicine is a wide and diverse field!

- … unified by the fact that evolutionary thinking is introduced to medically relevant questions
- … many aspects have not even been touched in this lecture (e.g. anthropology, psychology…)
- … there are now good sources of up-to-date information, e.g. http://evmedreview.com

Thanks your listening!

Questions?