ANBI 139

Evolution of Human Disease
Pascal Gagneux Spring 2019

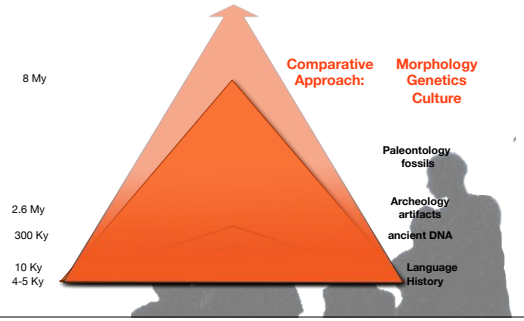
ANBI 139

Evolution of Human Disease

Lecture 1: What is a Disease and How Sick Are We?

https://www.pascalgagneux.com/

Looking back on deep history



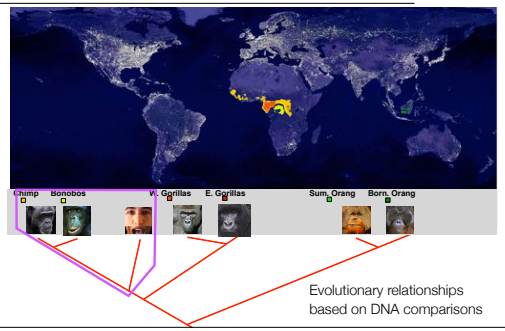
Evolutionary biology is also a historical discipline with very limited experimental options, the comparative approach is essential as are different perspectives from different fields: physical, biological, social, and computational sciences.

Your world map, your ancestral heritage

Draw a world map with major continents and place pins where you parents, grandparents and great-grandparents were born

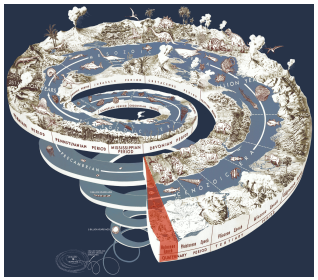
---

Distribution of great apes and humans



An extra terrestrial view of our planet reveals a stark contrast in the distribution of humans and our closest living relatives.Despite genetic similarity, but life is more than genetics. What allowed our species to reach such a planetary dominance?

Deep Time: 3 billion years



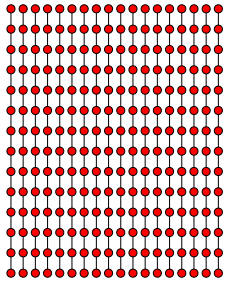
Holocene Trap

The 10 thousand years since the last major ice age are known as the Holocene. Most data we have comes from this time. Especially the last 5 thousand years since writing was invented.

Requirements for Evolution ?

- Replicating entities.
- Heritable variation between entities.
- Differential survival and reproduction.

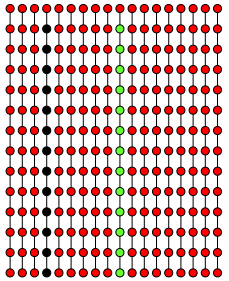
Principles of Evolution



Inheritance:

"entities make copies of themselves – they replicate"

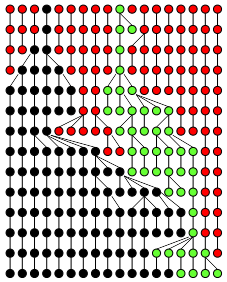
Principles of Evolution



Variation

that is heritable, comes about by random mutation

Principles of Evolution



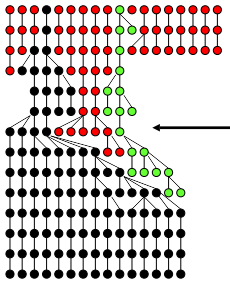
Differential
reproductive
success

Due to differences in mortality and/or fertility, highly deterministic, not random.

Changes of frequency over time:
Evolution
a population level phenomenon

Evolution is a phenomenon of populations! Individuals are born, grow up and sometimes reproduce, then die. Frequencies of variants within the population are changing: the population evolves, not the individual!

Principles of Evolution



Population size
(numbers of copying entities)

"Bottleneck"

Small populations undergo more rapid changes in frequencies of variable units.

In small populations, frequencies can change more rapidly due to chance as well as to natural selection. Population bottlenecks can accelerate evolution. The population evolves, not the individual!

An important Asymmetry:

- Once extinct, a lineage never returns.
- Currently existing copies descend from ancestors, which were successful, lucky or both.
- Every copy alive today by definition, descends from a common ancestor.

Evolution in a nut shell:

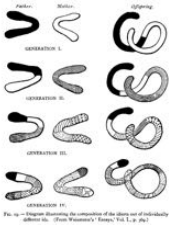
- Replicating entities.
- Heritable variation between entities.
- Differential survival and reproduction.

Replicators?

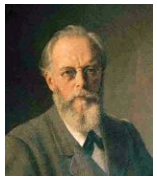
cells, organisms, viruses, nucleic acids/ genomes

Evolution by natural selection, drift, and sexual selection is **the** organizing principle of modern life sciences.

Soma and Germ Line



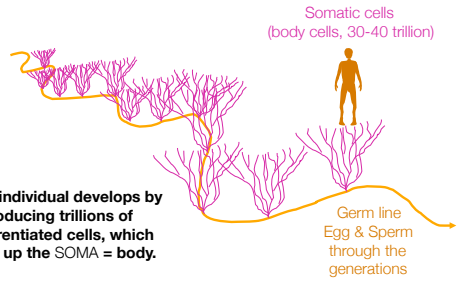
"idants in worm eggs"



August Weismann,1893
Germ Plasm a Theory of Heredity

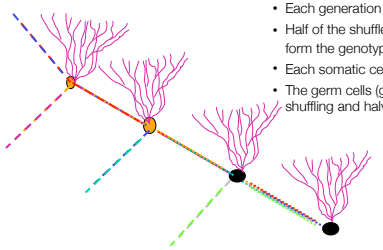
Weismann realized that certain cells are specialized for generating potentially immortal line of descent: the germ line.

Germ Line and Soma



Every individual develops by producing trillions of differentiated cells, which make up the SOMA **= body.**

The Germ Line is not a simple line:

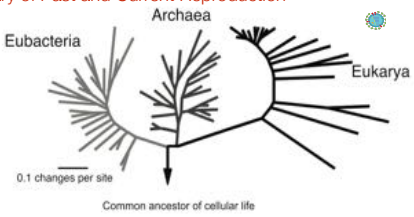


- Each generation shuffles the parental genes.
- Half of the shuffled genes from both parents form the genotype of the offspring.
- Each somatic cells carries this genotype.
- The germ cells (gametes) are formed by shuffling and halving the genotype once again.

The germ line is made up of shuffled pieces of DNA that meet and get taken apart again by sexual recombination.
WE ARE DYNAMIC MOSAICS!

Three Domains of Cellular Life

Grand Summary of Past and Current Reproduction

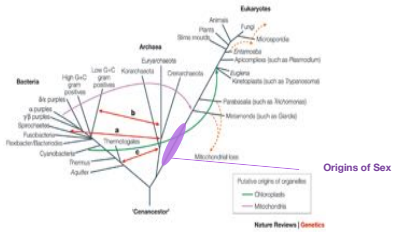


Redrawn from Olson & Woese 1993. *FASEB* 16s rRNA based phylogeny and James Brown, 2003. *Nature Reviews Genetics*

The tree of cellular life is a phylogeny
It represents a grand summary of past reproduction and gene exchange
No one knows the precise evolutionary relationship between viruses and cellular life. Viruses can shuttle DNA from one branch to the next.
Practice Question: Why is the evolutionary tree of life made up of branches?
B'cause most of the time, once two populations or organisms have stooped exchanging DNA, they become incompatible and cannot start exchanging DNA again.

Why is it impossible to place viruses on the tree of life?
Because viruses do not contain any DNA that can be directly compared to the DNA in cellular life.

Phylogenetic trees of the three domains of cellular life



James Brown, *Nature Reviews Genetics* (2003)

How is it possible to compare mammals with bacteria or archea?

which parts of the organism allow comparisons?

DNA sequences coding for ribosomal RNA

Sex involving recombination of chromosomes and later dedicated sexual cells (gametes) evolved at the root of eukaryotes (organisms with a nucleus in each cell).

FIGURE 19.1. Phylogenetic trees of the three domains of cellular life (*upper panel*) and of the multicellular Eukarya (*lower panel*). The universal tree of life (*upper panel*) is inferred from maximum likelihood analysis of 1620 homologous nucleotide positions of small-subunit ribosomal RNA sequences from each organism. (The tree is redrawn, with permission, from Barns S.M. et al. 1996. *Proc. Natl. Acad. Sci.* **93:** 9188–9193, ©National Academy of Sciences, U.S.A. The eukaryotic phylogeny is redrawn and modified, with permission, from Pollard T.D. et al. 2007. *Cell Biology*, 2nd Edition. Saunders, New York, ©Elsevier.) Common eukaryotic "model" organisms are indicated. Except for the sponge, all indicated species have had their genomes sequenced. (*Gray dotted rings*) Approximate time before present (mya = millions of years ago). Major groups are indicated by different colors and refer to specific chapters (see text for discussion). The unicellular alveolates (e.g., trypanosomes) and slime mold diverged more than 1 billion years ago. Thus, their branching points are not shown.

Mechanisms of Evolution

Natural selection
"survival of the fittest"
Neutral evolution….drift
"survival and reproduction of the luckiest"
history and geography…islands
Sexual selection
"reproduction of the sexiest"

Not all diversity is adaptive

Convergent Evolution:

Molecules, Anatomy, Behavior

Similar or even identical things can evolve multiple times

Practice Question: What does convergent Evolution mean?
Independent evolution leading to similar outcomes (biochemistry: caffeine, anatomy: spindle shaped swimmers, behavior: paternal care of the young)

Disease

A disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms or that affects a specific location and is not simply a direct result of physical injury.

'bacterial meningitis is quite a rare disease'

Oxford English Dictionary

"Health": equally tricky to define

Normality, abnormality, disability, infirmity, having an impairment, another way of being, disruption to ongoing personal identity, e.g. deaf vs Deaf,

Diseases that you hope to learn about:

Hepatitis B
Human Papilloma Virus
Human Immunodeficiency virus
Rubella virus
dementia
diabetes
Alzheimer's disease
Schizophrenia
hydrcephalus
pregnancy
osteoporosis
sickle cell anemia
obsessive compulsive disorder
other mental disorders
plague (Yersina pestis)
tuberculosis
cancer
ebola virus
yellow fever virus
huntington's disease
(Lou Gehrig's disease amyotrophic lateral sclerosis, ALS)
Spinal muscular atrophy (SMA)
vector-borne disease
malaria
syphillis
spinocerebellar ataxia
West nile virus

Noticeable: no polio, no cholera, no typhoid, no helminth (worm) caused diseases…

Types of Diseases

1. Diseases with genetic cause.
Cystic fibrosis, Severe combined immunodeficiency, PKU, Tay-Sachs

2. Diseases with environmental cause.
Infection, dysbiosis, malnutrition, poverty

3. Diseases that are byproducts of defense systems.
Autoimmune diseases, rheumatoid arthritis, Asthma, panic disorders

4. Diseases of homeostasis.
obesity, heart disease, type 2 diabetes, addiction

5. Diseases caused by lack of maintenance.
age related cancers, neurodegeneration, cardiovascular disease,

6. Diseases caused by stochastic developmental problems
Trisomy 21, premature birth, preeclampsia

7. Diseases of pregnancy and early development caused by maternal-fetal or maternal paternal conflicts.
Fetal growth restrictions, imprinting disorders, some autism spectrum disorders.

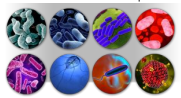
attempt to classify diseases according to their causes

Perspectives on Disease

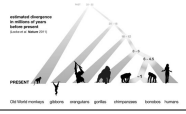
Patient:
suffering

Physician/Health professional:
abnormal condition

Evolving pathogen:
pathogen adaptation,
unintended consequences

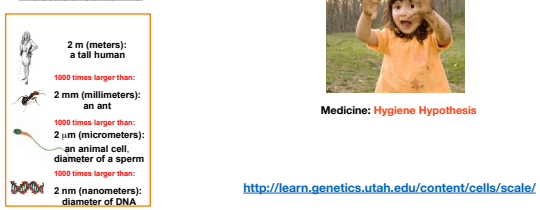


Evolving Host:
byproducts of infection,
host defense adaptations



Each disease can be explored though multiple different perspectives.

Mechanistic versus Evolutionary Explanations



Crohn's disease
GWAS: NOD2 protein
IL-10
T cells
Microbiome

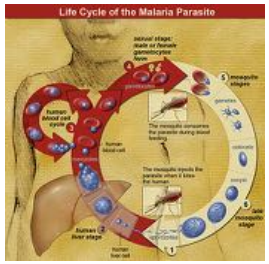
Loss of Microbial diversity
Loss of "Old Friends"

Medicine: Hygiene Hypothesis

http://learn.genetics.utah.edu/content/cells/scale/

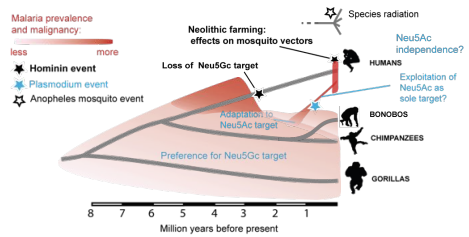
Why questions can aim at the mechanisms or proximate reasons for a disease, i.e. genetic changes, infections, exposure to toxins or
at ultimate reasons having to do with altered evolutionary environments

Malaria (protozoan parasite)



Malaria is a the major disease of humanity. It is caused by a protozoan parasite that lives in mosquitoes, where it reproduces sexually, and in mammalian hosts, where it reproduces asexually (clonal reproduction).

Human Sialic Acids & Malignant falciparum Malaria



Modified from

Varki, A and Gagneux, P. 2009. ***Proc. Natl. Acad. Sci. USA.***106:14739

Changes in the glycocalyx (the sugar coat) of human cells may have been selected by malarial parasites of the distant past.

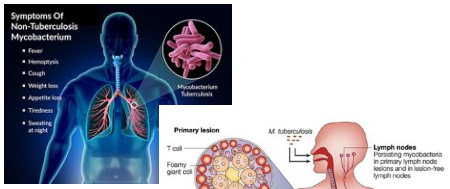
Genetic Diseases

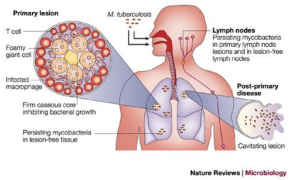
Over 4000 human diseases caused by a single gene defect.

Disorder prevalence (approximate)	
Autosomal dominant	
Familial hypercholesterolemia	1 in 500
Polycystic kidney disease	1 in 1250
Neurofibromatosis type I	1 in 2,500
Hereditary spherocytosis	1 in 5,000
Marfan syndrome	1 in 4,000[2]
Huntington's disease	1 in 15,000[3]
Autosomal recessive	
Sickle cell anaemia	1 in 625
Cystic fibrosis	1 in 2,000
Tay-Sachs disease	1 in 3,000
Phenylketonuria	1 in 12,000
Mucopolysaccharidoses	1 in 25,000
Lysosomal acid lipase deficiency	1 in 40,000
Glycogen storage diseases	1 in 50,000
Galactosemia	1 in 57,000
X-linked	
Duchenne muscular dystrophy	1 in 7,000
Hemophilia	1 in 10,000
Values are for liveborn infants	

mutations in single genes can cause disease! Most diseases involve many different genes, not just a single mutation.

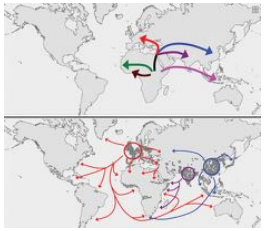
Tuberculosis (bacterium)





Tuberculosis (TB) is caused by a bacterium *mycobacterium tuberculosis,* that infect human immune cells. ~ a third of humanity carries the TB bacteria, but only a small fraction ever develop disease. What determines why only some of use develop disease is not known.

Spread of Tuberculosis (bacterium)



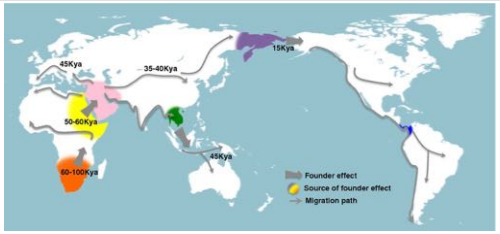
out of Africa with Homo sapiens

out of Europe with colonialism

Comas *et al.*, 2009. ***Nature Genetics*** 2013

Genetic studies of TB reveal that it has infected humans for at least a hundred thousand years. TB strains infecting our African ancestors left Africa with modern humans and went everywhere people migrated.

Early Spread of Modern Humans Outside Africa



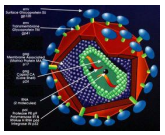
Ancient dispersal patterns of modern humans during the past 100,000 years

(exact timings uncertain)

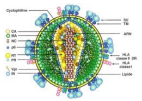
Brenna M. Henn et al. *PNAS* 2012;109:17758-17764

Ancient dispersal patterns of modern humans during the past 100,000 y. This map highlights demic events that began with a source population in southern Africa 60 to 100 kya and conclude with the settlement of South America approximately 12 to 14 kya. Wide arrows indicate major founder events during the demographic expansion into different continental regions. Colored arcs indicate the putative source for each of these founder events. Thin arrows indicate potential migration paths. Many additional migrations occurred during the Holocene.

HIV1 (retrovirus)



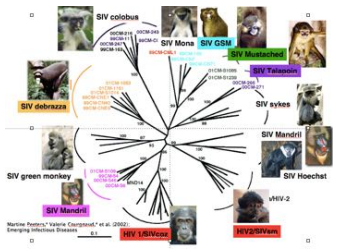
out of Africa with *Homo sapiens*



One of the major viral diseases of humankind is HIV, human immunodeficiency virus. infection of humans with this virus is very recent (about 100 years old). The virus is transmitted sexually or through blood contact and infect human immune cells, eventually leading to the demise of the host's immune defenses.

All other African primates have their own SIV

SIV in > 30 species of primates



Humans only acquired HIV from African primates at the beginning of 1900s.

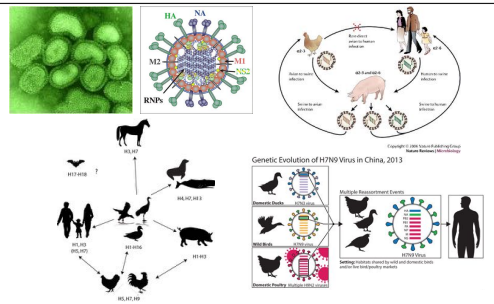
Peeters *et al.* 2002. *Emerg. Infect. Dis.*

Most African non-human primates each have their own versions of HIV, named SIV (simian immunodeficiency virus, a misnomer, as most other African primate species do not get sick).

Practice question: why is the name SIV a misnomer?

Answer: B'cause the virus does not cause immunodeficiency in most non-human primates.

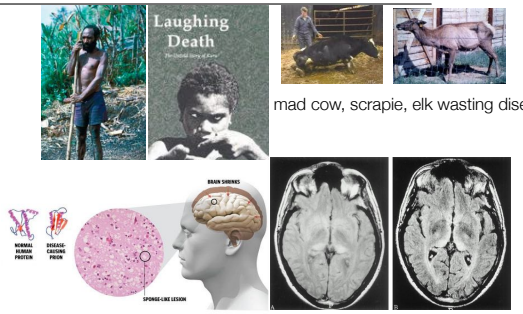
Influenza A (RNA virus)



Influenza A is a virus with an RNA genome broken into 8 segments. Many different strains exist in water birds and so it is impossible to eradicate this virus. Each year, there are new rounds of infections around the world.

Practice question: Why is it impossible to rid the world of influenza A virus?
Answer: there is a huge and diverse reservoir of influenza viruses in wild water birds.

Prion Diseases : Kuru, Creutzfeld Jakob's disease

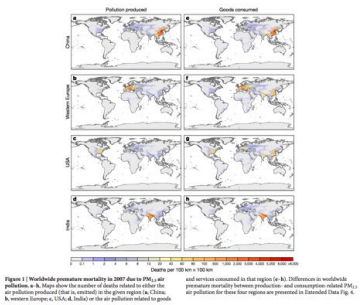


Kuru and Creutzfeld Jakob's disease are caused by a protein that is misfolded and can cause other proteins to misfold! In animals, a similar protein causes mad cow disease, scrapie in sheep or elk wasting disease.

Practice question: What is unusual about prion diseases?
Answer: they are cause by a misfiled protein, not by a living, replicating organisms.

Prion Diseases : naturally protective variants, prevent aggregation and disease

Environmental Disease



Environmental pollution by industry or intensive agriculture can cause widespread disease.

Obesity

"Venus" figurines from the middle stone age Lespugue, Dolni Vestonice and Willendorf, 26, 28 24 ky

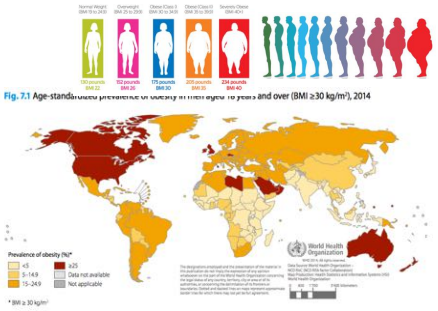
Fat Buddha: Contentment and Abundance
Bu Dai 布袋

Xiao Fo 笑佛

The Tuscan General
Alessandro del Borro, attributed to Charles Mellin, 1645

Obesity went from revered status symbol to pathological condition and social stigma.

Obesity

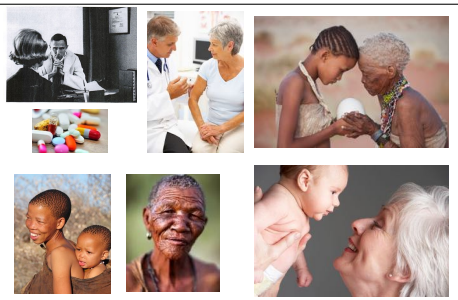


Homosexuality

1973: APA depathologizes homosexuality, out of DSM

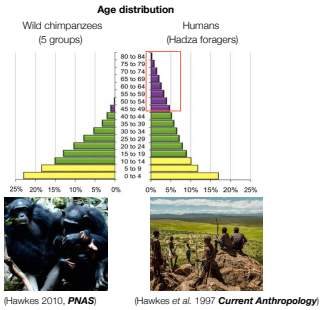
Changing definitions of diseases can make diseases vanish into thin air!

Menopause: disease or adaptation?



Some “diseases” are actually adaptations! menopause, the cessation of ovulation often followed by three decades of productive life is what made grand-motherhood possible

Aging and survival



(Hawkes 2010, ***PNAS***)

(Hawkes *et al.* 1997 ***Current Anthropology***)

Hadza grandmother at work

Humans populations have many individuals who survive long after the period of reproduction. In Most other animals, when reproduction ceases, most individuals tend to die. Due to the bias favoring female survival , many more older females survive. Up to 25% of living adults in a given social group can be post-reproductive females. The grandmother hypothesis proposes that these females benefit their younger relatives buy provisioning children with food, care and knowledge.

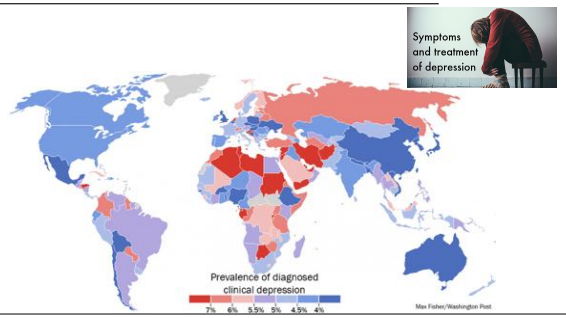
Hysteria: Non-fulfillment of natural desire?

Diseases like hysteria have almost completely disappeared.

Hysteria: the movie

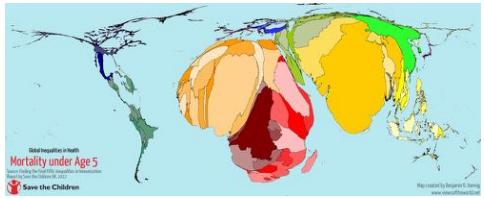
Very fun movie about the insane history of hysteria and attempts at curing it!

Mental Health: Depression



Others, like depression have massively increased in many places around the world.

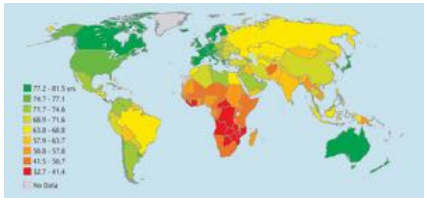
Child Mortality



"If we are the future and we're dying, there is no future." Mary Phiri, 2001

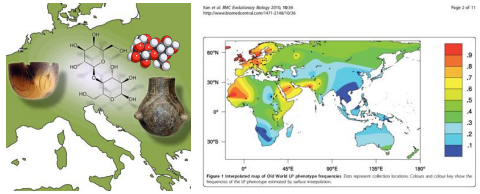
Child mortality due to diseases, poverty/neglect, malnutrition and armed conflicts remains very high in many places.

Life Expectancy



Digesting lactose as adults

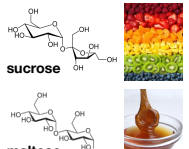
Lactase persistence phenotype frequency

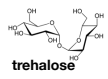


Yuval Itan, Mark Thomas
UCL, UNITED KINGDOM
Joachim Burger, Johannes Gutenberg-University, DE

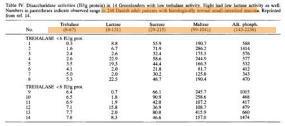
7500 years ago, when early animal herders discovered that one could steal milk from other species, a cultural process began to select for lactase persistence. Lactose intolerance is not a disease, but rather the normal state for any primate…..those of us who can still digest milk sugar as adults are the freaks (the mutants), but also living proof that cultural habits can change human biology

Sucrose/Maltose and Trehalose intolerance





"use it or lose it!"
Sucrase/isomaltase deficiency in up to 1/20 Greenland Inuits

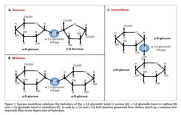


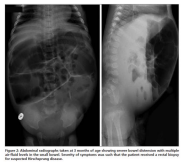
E. Gudmand-Høyer & H. Skovbjerg (1996) Disaccharide Digestion and Maldigestion, ***Scandinavian Journal of Gastroenterology***, 31:sup216, 111-121

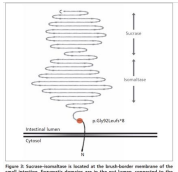
Arctic hunter gatherers like the inuit do not find plant sugar or even starch in their natural environment, many of them have lost the capacity to digest sucrose or starch. Even therapies, a disaccharide in mushroom cannot be digested by them

---

Mutation in Sucrase/isoMaltase Gene:



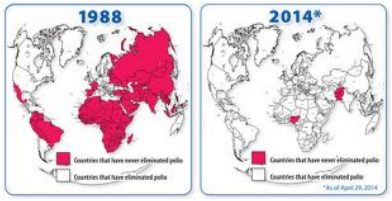




Marcadier et al. Congenital sucrase–isomaltase deficiency: identification of a common Inuit founder mutation. ***CMAJ***, February 3, 2015, 187(2) CMAJ 2015

The enzyme most of us use to digest sucrose, starch and therapies is called sucrase isomaltase. A loss-of-function mutation in this enzyme has become rather common among the inuit because there is not penalty for the individuals that inherit this mutation. If these individuals start consuming a typical European or American diet, the children fail to thrive and have massive digestive issues.

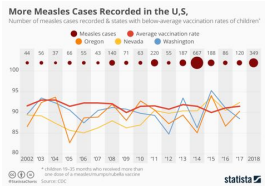
Fighting Disease



Poliomyelitis virus infections

Immunizations work! Polio is almost eradicated. This virus infects nerve cells and our immune system's defenses often result in permanent nerve damage that can lead to paralysis.

Losing the fight: Measles back on the rise



Anti-vaccine misinformation is causing new outbreaks of preventable disease.

Summary

Evolution: populations change over time due to random mutation and non-random differences reproductive success.

Studying evolution is studying past history. We know most about the last few moments, much less about distant past.

All living organisms have disease.

Diseases have several different causes, both internal and external to the organism.

A brief introduction to major diseases: Malaria, TB, Flu, HIV, Kuru, obesity, poverty, industrial pollution, depression.

Human cultures can consider anything a disease: homosexuality, menopause, hysteria, lactose intolerance….

Immunizations are one of the most successful weapons against many diseases.