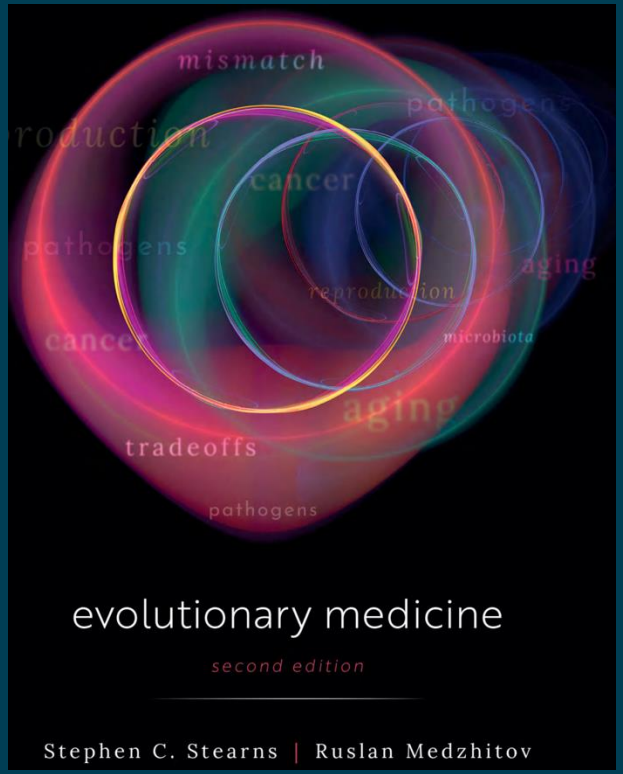


Chapter 1: Introduction to Evolutionary Thinking

Section 1: Natural Selection

A puzzle

Natural selection creates the appearance of design without having a design in mind, or a mind at all.

No agent actively “selects” anything.

How does it do that?

Natural selection occurs whenever these four necessary conditions are fulfilled:

1. There is variation in reproductive success
2. There is variation in the trait of interest
3. There is a non-zero correlation between reproductive success and trait
4. The state of the trait is heritable

When in doubt, return to these basic conditions.

Now, let's unpack them...

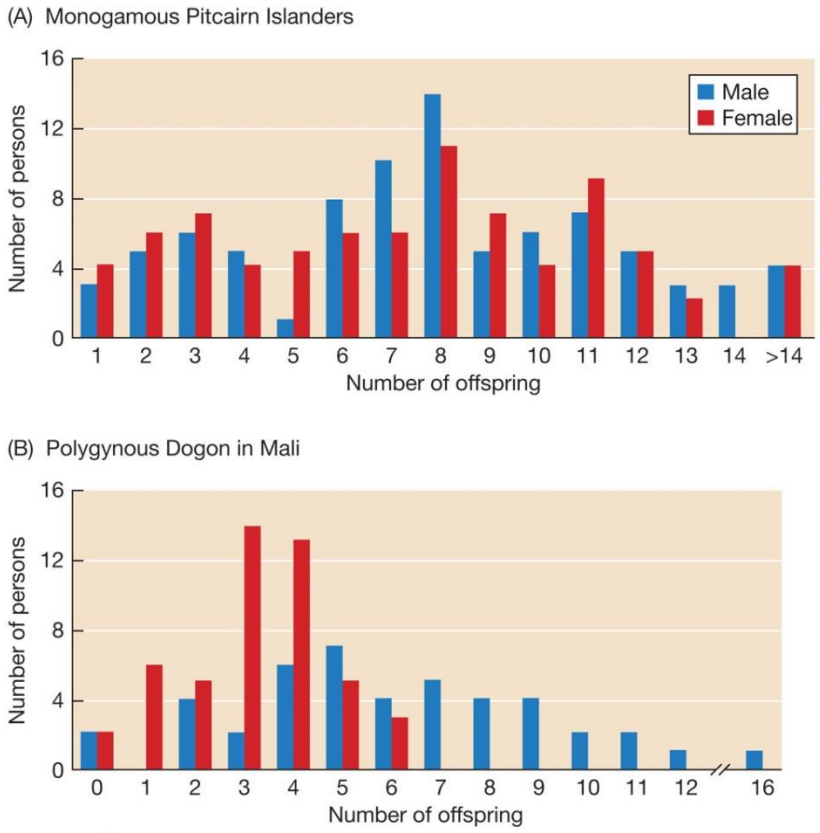
Variation in reproductive success

To a first approximation, in humans this is variation in completed family size: lifetime reproductive success (LRS), or children ever born (CEB). In bacteria and cancer cells, it is variation in time and survival between cell divisions.

To reproduce, one must survive. Thus reproductive success is a composite of survival and reproduction: the probability of surviving to reproduce × the number of offspring produced summed over reproductive events.

Note that selection acts directly via reproductive success and only indirectly via survival (i.e. to the extent that survival contributes to reproductive success).

Variation in reproductive success is universal



EVOLUTIONARY MEDICINE, Figure 1.1

Any trait that correlates with reproductive success in these populations will experience selection.

Whether it responds to selection in succeeding generations depends on whether the trait is heritable.

Variation in the trait of interest

The trait could be anything: eye color, height, the temperature dependence of enzymatic function, the structure of the ribosome, susceptibility to a disease.

If the trait does not vary, then there can be no competition for improved reproductive performance among trait variants.

Natural selection does not operate on things that do not vary.

Most traits vary among individuals. Most traits potentially experience selection.

Variation in resistance to malaria

TABLE 1.1 Variation in sickle-cell genotypes across sub-Saharan Africa

		With *S* allele		*AA* homozygotes	
Population	Region	Infected	Uninfected	Infected	Uninfected
1	Uganda	12	31	113	134
2	Kenya	131	110	154	87
3	Uganda	73	118	494	515
4	S. Ghana	42	131	270	572
5	N. Ghana	11	4	165	12
6	Nigeria	162	51	680	210
7	N. Ghana	13	6	109	18
8	Nigeria	51	40	245	97
9	Tanganyika	77	59	272	135
10	S. Ghana	34	89	176	417
Total		606	639	2678	2197
Percentage		48.7%	51.3%	54.9%	45.1%

Source: Allison 1964, Table 1, p. 138.

There are three genotypes: *SS*, *SA*, and *AA*. Sickle cell carriers were 6.2% less likely to be infected by malaria than were normal homozygotes. *SS* homozygotes suffer from complications of anemia that, without treatment, increase mortality. *SA* heterozygotes have the highest fitness in the presence of malaria.

The *S* variant is caused by a mutation in the sixth position of the β-globin chain of hemoglobin. This results in the replacement of hydrophilic glutamic acid by hydrophobic valine.

The correlation between reproductive success and the trait of interest must be non-zero

Even if there is variation in reproductive success and variation in the trait, this does not yet mean that natural selection is operating on the trait. These are necessary conditions, but they are not sufficient.

There must also be a correlation between the value of the trait and reproductive success.

For example, patients who resist disease may reproduce more often than patients who do not.

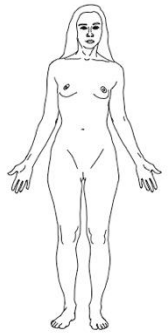
What in general generates such correlations? They are produced by myriad circumstances in the biology and, for humans, also in the culture of organisms. An important element of human culture is medicine.

There is thus no single general cause of selection. Selection occurs for a huge variety of reasons that include *anything* that causes variation in reproductive success.

Correlations of traits with reproductive success in women in Framingham, Massachusetts 1890–1960

ß is not a correlation coefficient, it is a selection gradient. It has the same sign as the correlation coefficient.

TRAIT	***N***	***ß***	***p***	Selection was acting:
Total cholesterol (mg/100ml)	2227	–0.8	<0.001	to decrease total cholesterol,
Height (cm)	2227	–4.39	<0.001	to decrease height,
Weight (kg)	2227	0.97	<0.001	to increase weight,
Age at first birth	1448	–1.2	<0.001	to decrease age at first birth, and
Age at menopause	2227	1.28	0.0035	to increase age at menopause.



The state of the trait is heritable

This is the critical genetic condition that allows what has worked in the past to be “remembered” and improvements to accumulate. It thus interacts with natural selection to generate order out of disorder.

However, inheritance must not be 100% perfect. If it was, genetic variation could not originate in the first place, and if for some reason it already existed, natural selection would eliminate it by selecting the best variants.

There must be some mutation to create the genetic variation that is the fuel on which the motor of selection runs, but not so much mutation that it destroys too much of the useful information on what has worked in the past.

Heritabilities of some human traits

Age at first birth: 0.11 (mean of 5 estimates, *n* = ca. 12,000)

Blood traits: 0.36 (mean of 66 estimates, *n* = ca. 15,000)

Age at menopause: 0.59 (mean of 24 estimates, *n* = ca. 14,000)

Height: 0.75 (mean of 115 estimates, *n* = ca. 130,000)

All of these traits will respond to selection.

Height will respond more rapidly than age at first birth.

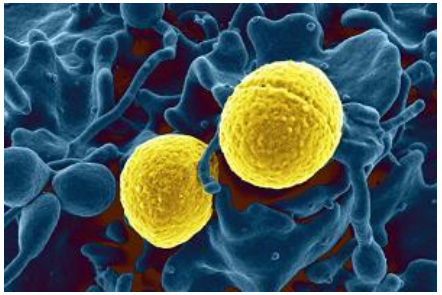
Heritabilities can vary from 0.0 to 1.0.

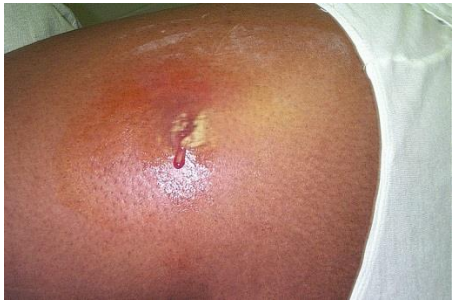
Zero means no more resemblance between relatives than people chosen at random.

One means offspring have exactly the same value as the average of their parents.

Natural selection in action: The rapid evolution of antibiotic resistance in *Staphylococcus aureus*

- 1943: Penicillin commercially available
- 1947: First resistance reported
- 1960s: Switch to methicillin
- 1980s: Methicillin resistance rising
- 1990s: 35% of isolates resistant to methicillin
- 1990s: Switch to vancomycin
- 1996: Vancomycin resistance reported
- 2000: Linezolid approved by the U.S. Food
- and Drug Administration
- 2002: Linezolid resistance reported





Antibiotic resistance: Strong selection and rapid response

Bacterial populations are huge; large numbers of genetic variants are continually generated by mutation and introduced by horizontal gene transfer, and generation times are short.

Antibiotic therapy creates huge differences in the reproductive success of resistant and nonresistant bacterial clones.

The trait that varies is resistance; that variation has a genetic basis; antibiotics select resistant clones, which have greater reproductive success.

The process is very fast and very efficient: resistance against every new antibiotic evolves within a few years.

Other examples of natural selection in clinical medicine and public health

The evolution of metastatic cancer

The evolution of resistance to cancer chemotherapy

The coevolution of pathogens with host defenses, leading to evasion and manipulation

The evolution of pathogen virulence in response to changes in transmission and to vaccination campaigns

The impacts of medical practice on human, pathogen, and cancer evolution

Summary of Natural Selection

Selection occurs whenever variation in a trait is correlated with reproductive success.

Traits experiencing selection only respond to it if their variation is heritable.

Selection produces a significant response when the events that generate it occur *frequently* and *consistently*.

Selection efficiently creates order out of disorder, producing the appearance of design that we call *adaptation*.

No agent actively selects: the process emerges, unsupervised, from any circumstances that correlate heritable variation in traits with reproductive success.

Section 2: Random evolution: The roles of chance

Why neutrality arises

Many genotypes may produce the same phenotype:

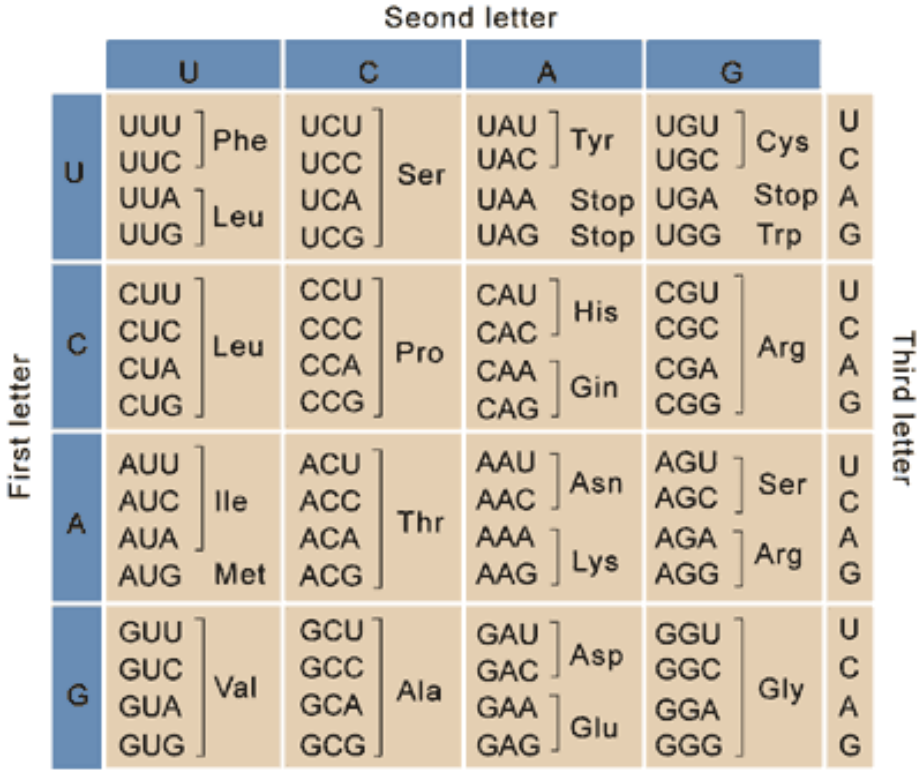
- Because the genetic code is redundant
- Because some DNA is not expressed
- Because some amino acid substitutions produce no change in the shape or charge of a protein
- Because development is canalized

Many phenotypes may have essentially the same fitness

- Because that particular trait variation makes very little difference to reproductive success
- Because the impact on fitness of a change in one trait compensates for that of a change in another trait

Let’s unpack each of those conditions.

The genetic code is redundant: 64 triplet codons with 23 meanings



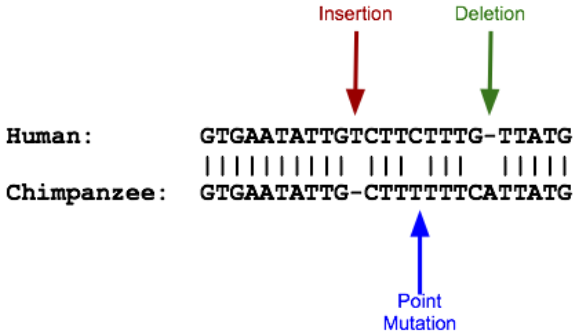
Some DNA is not expressed

Pseudogenes are genes that are no longer expressed. They result from gene duplication followed by loss of function in one copy.

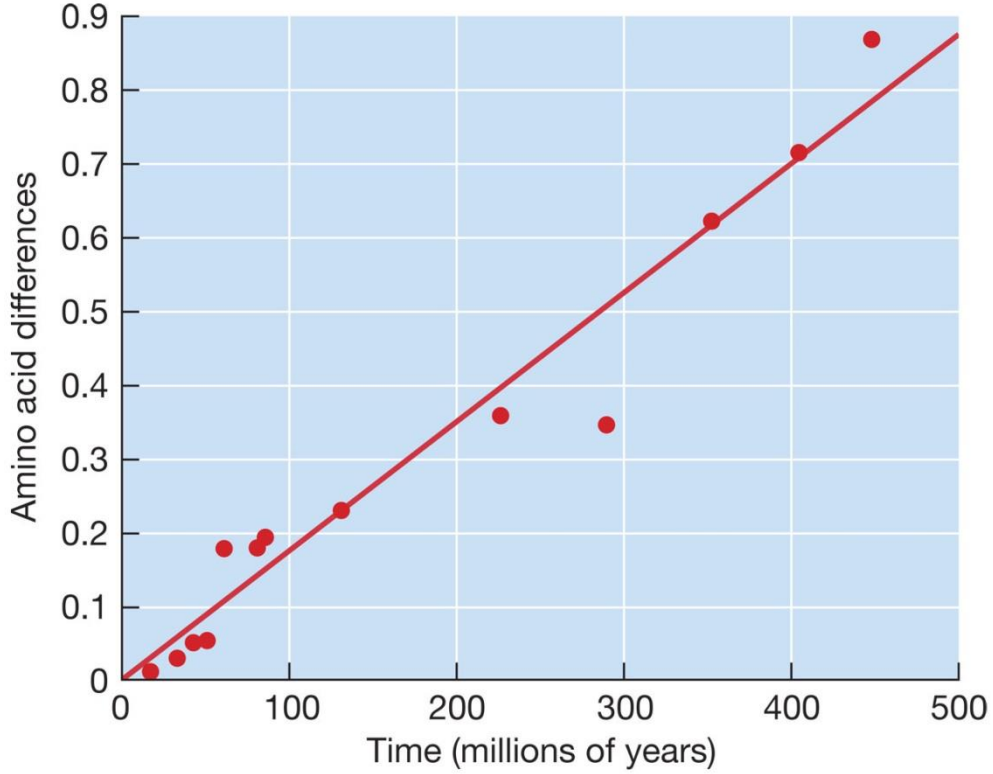
Function is lost *because* a pseudogene is not expressed: all of its nucleotides are free to diverge at random as they mutate.

Some other DNA is also neither transcribed nor translated. It is also free to accumulate mutations at random.

Example of the evolution of a pseudogene: The DNA sequence is part of a gene for an olfactory receptor. The gene is functional in chimpanzees but not expressed in humans.



α-globin evolution in vertebrates: many amino acid substitutions have been neutral



EVOLUTIONARY MEDICINE, Figure 1.2

Straight line: expectation if rate of amino acid substitution is uniform (i.e random).

The canalization of development

Canalization: the limitation of phenotypic variation by developmental mechanisms.

Canalizing mechanisms resist the tendency of variation in either genetic or environmental factors to perturb the phenotype.

Genes whose impact on the phenotype has been reduced or eliminated by canalizing mechanisms are freer to accumulate neutral variation than those whose impact is directly expressed.

Some traits canalized in tetrapods: four limbs, two eyes, one mouth, five digits. Genetic variation affects many things about those traits, but not their number.

Some phenotypic variation makes very little difference to reproductive success

The population may be too small to establish a consistent correlation between the trait and reproductive success.

The variation may simply be irrelevant, (e.g., variation in traits that cannot be detected by mates, pollinators, predators, parasites, or prey)

Variation that lies within the “normal” ranges of blood tests:

Total cholesterol: 110–150
Systolic blood pressure: 100–130
Diastolic blood pressure: 65–85

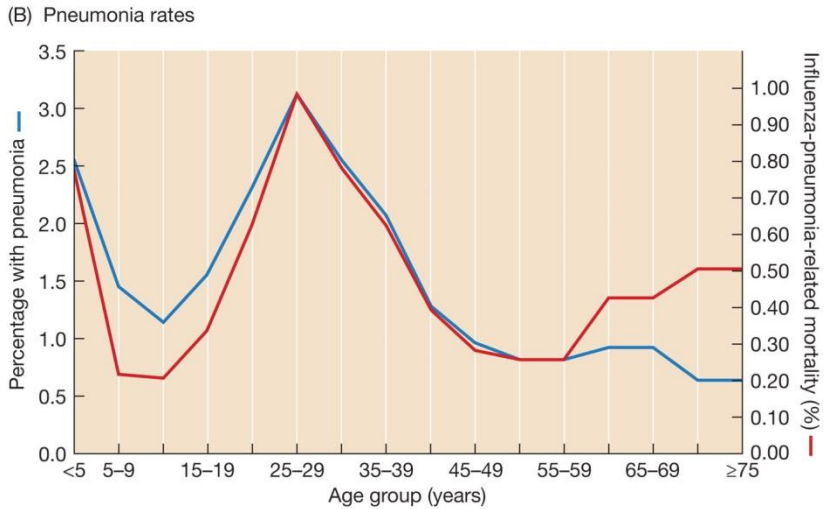
A fitness gain in one trait can compensate for a fitness loss in another mediated by a tradeoff

If the compensation is precise, the change is neutral.

This could occur, in principle, with any tradeoff, including:

- More offspring, less survival
- More success fighting for mates, less resistance to disease
- More resistance to normal infection, more costs of inflammation

In the 1918 influenza pandemic, the mortality rate was highest in young adults who had the strongest inflammatory responses. Their lungs flooded with fluid, and many died of secondary bacterial pneumonia.



EVOLUTIONARY MEDICINE, Figure 4.9 (Part 2)

Mechanisms causing random change

Mutation

Founder effects and genetic bottlenecks (passage through small population sizes)

*The Mendelian Lottery - meiosis is a fair coin

*Variation in reproductive success in populations of any size

*Drivers of genetic drift.

Mechanisms causing random change: 1. Mutations

The sense in which mutations are not random:

- They occur more frequently at some sites than others.
- The mutation rate in pathogenic bacteria increases in response to certain signals.
- Transitions (purine to purine, pyrimidine to pyrimidine) are more common than transversions.
- They do not produce random changes in phenotype space.

The sense in which mutations are random:

- *There is no systematic relationship between their phenotypic effect and the needs of the organism in which they occur.* ***Mutations are random with respect to fitness.***

Mechanisms causing random change:
2. Effects caused by small population size

Founder effect:

A few individuals found a new population with only a small portion of the genetic variation of the original stock.

Example: Genetic diseases in Quebec (Tay-Sachs), among the Afrikaaners (porphyria), and on Pitcairn Island (diabetes).

Genetic bottleneck:

A population crashes to very small size. Only a few alleles make it through because there are only a few individuals left alive to carry them.

Example: The homozygosity of cheetahs, confirmed by the ease of reciprocal skin transplants.

Correlations decrease in small samples:

If selection is real but weak, then it can only be effective in a large population; in a small population the correlation of reproductive success with the trait will be eroded by sampling error.

Pitcairn Islanders

Cheetah

Mechanisms causing random change:
3. Meiosis is a fair coin

Mendel's Law of Segregation: If there are two alleles at a locus, the probability that one of them will get into a given gamete is 50%.

In the long run, the average number of successful haploid gametes per parent in a diploid sexual species is 2. There are just two chances, two flips of the coin, because on average, individuals just replace themselves.

Mechanisms causing random change:
4. The trait or gene lands at random in families of different size

Random variation in reproductive success: If an allele randomly lands in a sequence of families with different numbers of children, it increases and decreases in frequency at random. (That is the meaning of having zero correlation with reproductive success.)

Genetic drift

Genetic drift is the random, aimless wandering of the frequencies of neutral genes. It resembles the Brownian motion of small particles pushed about by the thermal motion of molecules.

Genetic drift is driven by **the lottery of meiosis** combined with **variation in reproductive success**.

Genetic drift fixes neutral alleles faster in smaller populations but occurs in populations of all sizes.

What happens to neutral alleles?

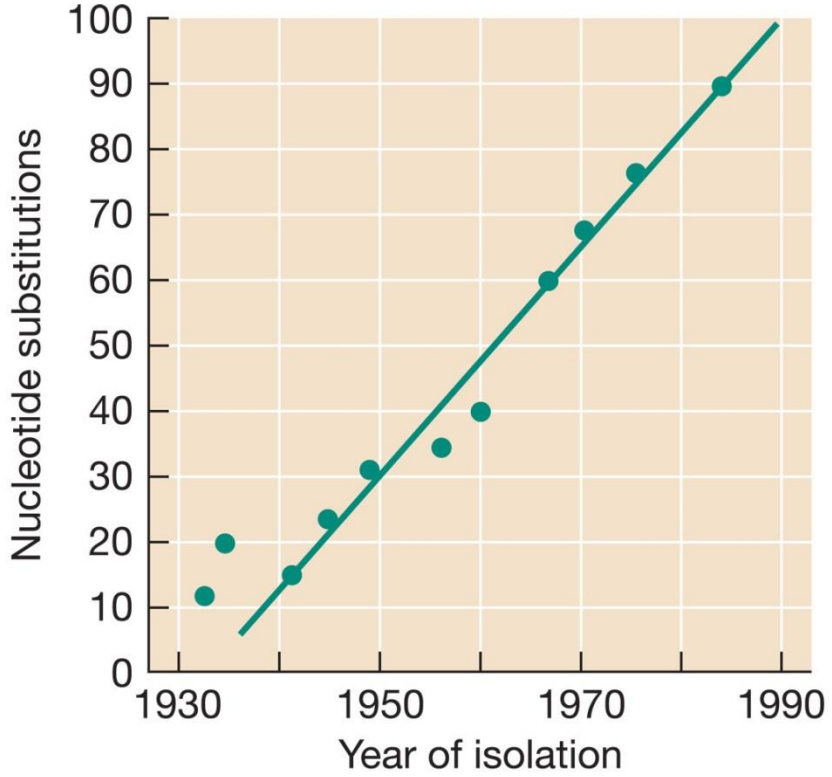
Most neutral alleles never make it to high frequency; those that do get fixed in the population **take longer** in larger populations.

But large populations also have more mutations, and this *exactly compensates* for longer fixation times.

We do not know *which* mutation will be fixed in any given period of time, but we do know *how many* will be fixed on average.

In that sense, the molecular clock is like an atomic clock driven by radioactive decay: In any given period of time, we do not know *which* atom will decay, but we do know *how many* will decay.

In both cases, the regularity emerges as a result of a very large number of independent random events. The haploid human genome consists of about 3×10^9 DNA base pairs. One mole of uranium contains 6×10^{23} atoms.



EVOLUTIONARY MEDICINE, Figure 1.3

Influenza samples: Population sizes fluctuated, but substitutions were regular.

The effect of population size on the number of new mutations introduced per generation exactly compensated for the slower rate of fixation of neutral mutations in larger populations.

If you can estimate time from number of substitutions, you have a *molecular clock.*

Summary

1. For several reasons, variation in DNA and variation in traits may make no difference to reproductive success.

2. Meiosis is like a fair coin: *The probability of getting into a specific gamete is 50%.*

3. The fixation of neutral alleles is like radioactive decay: *In neither case do we know precisely which mutation will be fixed or which atom will decay, but because there are so many of them, we know how many events will occur* on average *in a unit of time.*

4. Genetic drift fixes neutral alleles at a regular rate *independent of population size.*

5. The regularity of the fixation of neutral alleles *allows us to estimate times to last common ancestors by comparing DNA sequences.*

Section 3: Mismatch: A major cause of maladaption

Mismatch: often invoked, frequently misused

There was no single environment of evolutionary adaptation (EEA); our ancestors had many diets and lifestyles.

An argument that invokes an imagined past to support a favored hypothesis is suspect.

The paleodiet movement is guilty of suspect certainty on this point.

Mismatch occurs two ways

In time:

The environment changes faster than the population can adapt.

Human examples: agriculture, urbanization, hygiene.

In space:

Organisms move from environments where they are well adapted to environments where they are not.

Human examples: migration, immigration

Mismatches in Time

Diet before agriculture

- Lean meat, fruit, roots, nuts, seeds
- Little sugar, no refined starch, less salt, no milk after weaning

Microbiota before hygiene and antibiotics

- Almost everyone had worms
- Our gut flora was diverse and often helpful

Addictive substances and technologies rare or absent

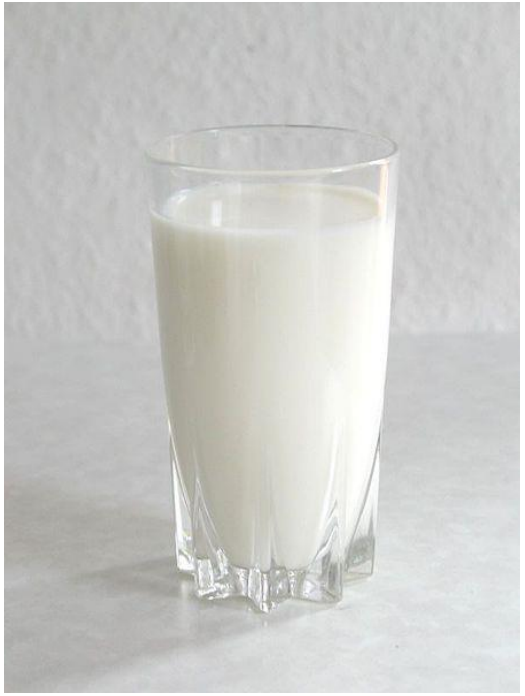
- No tobacco, alcohol, heroin, cocaine ...
- No TV, email, Twitter, Facebook ...
- No horses, bicycles, cars, planes ...

More movement, less sitting

Milk

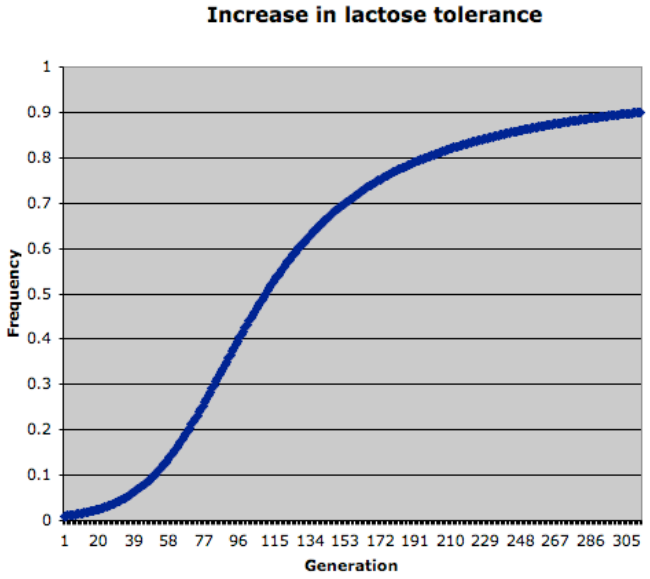
Evolution takes hundreds of generations to adjust traits to new conditions.

This lag produces serious mismatches in our reactions to novel conditions.



Evolution takes time:
Lactase persistence in adults

A mutation that enabled adults to digest lactose and gave them a selective advantage of 5% would take about 8000 years to increase from 1% to 90%.



Neolithic history was, however, more complicated than that model

There were both local responses to selection and immigration from areas where lactase persistence had already started to evolve.

Depending on the region considered and the level of immigration assumed, the selective advantage of drinking milk would have to have been between 0.5% and 3% to account for the patterns seen today and in the archeological record.

Only a few populations are now 90% tolerant.

The point of the lactose example:

The current prevalence of primary lactose tolerance ranges from 95–97% in Scandanavia to 0–10% in Eastern Asia.

Strong selection and 8000 years was not enough to fix the trait.

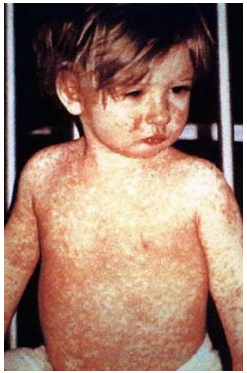
This means that mismatches to modernity are plausible for many traits, not just lactose tolerance in adults.

Mismatches in Space

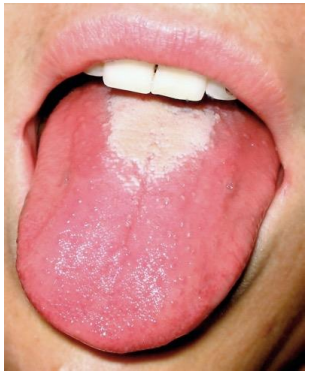
1. Migrants introduce new diseases

- Columbus' sailors brought syphilis back to Europe, where it was initially highly virulent, spreading from Naples and routing the French army that was invading Italy.
- Europeans introduced measles, smallpox, bubonic plague, influenza, typhus, diphtheria, and scarlet fever to the New World and Polynesia, causing epidemics that killed from 20% to over 90% of the natives.

Tertiary Syphilis
Musée de l'Homme, Paris



Day 4 Measles Rash
Wikimedia Commons



Scarlet Fever
Wikimedia Commons

Mismatches in Space

2. Immigrants leave pathogens and symbionts behind.

- African-Americans continue to suffer from sickle-cell anemia, which has compensating advantages only when malaria is present.
- Immigrants to developed countries suffer from atopies that may be related to shifts in their microbiomes: International adoptees and children born in Sweden to foreign-born parents used asthma medication 3 to 4 times as often as did foreign-born children.

We are adapted to things that happen frequently

Reproductive success occurs more frequently in the young than in the old, in supportive environments and healthy bodies than in threatening environments and in sick bodies.

We are adapted to circumstances that frequently led to reproductive success in the past.

Things that happen very frequently with small effects can accumulate to have large effects – for example, anything involved in protein synthesis.

We are mismatched to things that happened rarely or never before.

Summary

Although the concept of mismatch is often misused, mismatch is real.

The evolution of lactase persistence shows that mismatches in time are real.

We are mismatched to conditions encountered rarely or never before.

We can also be mismatched to things that happen in other environments but not the one in which the organism currently resides.

Section 4:
Adaptations: how to recognize them

Adaptation can be problematic

Claims of adaptation should not be accepted unexamined. Any hypothesis of adaptation needs to be tested against alternatives.

Evolutionary biologists have developed several criteria for recognizing adaptations

Here are some of them:

1. The design criterion
2. Natural selection itself
3. The perturbation criterion
4. The strategic criterion
5. The invasion-resistance criterion

1. The design criterion

Adaptation can be recognized by its complexity and conformity to *a priori* design specifications - by its resemblance to something that an engineer might design.

Any complex organ that performs a difficult function efficiently (e.g. the dark-adapted human eye, which can detect the arrival of photons produced by a single match at a distance of 10 kilometers).

2. Natural selection itself

Natural selection on a trait exists given a correlation between variation in the trait and variation in reproductive success.

A response to natural selection occurs when some variation in the trait is heritable.

You document heritable changes in the trait that result from a demonstrated correlation of trait state with reproductive success.

Example: The many cases of experimental evolution.

3. The perturbation criterion

This criterion requires both a predictive model and an experiment.

An adaptation is the state of a trait predicted by a model that is tested by using some method to perturb the phenotype from the optimal state and to demonstrate that the fitness of the perturbed phenotype is lower than the fitness of the predicted one.

Example: Clutch size experiments on kestrels.

Manipulate clutch size in kestrels
Measure reproductive success

TABLE 1.2 Impact of brood size on fitness in kestrels

	Reduced	Control	Enlarged
Brood:			
Number of broods	28	54	20
Mean number fledged	2.60	3.95	5.84
Clutch reproductive value V_c	3.16	5.25	6.99
Parents:			
Number of males and females	49	85	35
Parent local survival	0.653	0.588	0.429
Parent reproductive value V_p	10.14	9.14	6.69
Total reproductive value ($V_c + V_p$)	13.30	14.39	13.68

Source: Daan, Dijkstra, and Tinbergen 1990, Table 3, p. 97

***EVOLUTIONARY MEDICINE*, Table 1.2**

4. An appropriate strategic response

An adaptation is a change in a phenotype that occurs in response to a specific environmental signal and has a clear functional relationship to that signal that results in an improvement in growth, survival, or reproduction.

Otherwise, it does not appear.

Some pretty convincing cases

Spines and helmets in *Daphnia* are induced by dissolved molecules associated with predators whose efficacy is reduced by spines and helmets. They have a reproductive cost and are not produced in the absence of the predators.

Bent shells in barnacles make them resistant to snail predators but reduce their fecundity.

Snails parasitized by digenetic trematodes that castrate them reproduce earlier.

Lauder's Five Questions about Claims of Adaptation:

1. Have experiments been done to support the claimed function?
2. Has the performance of the trait in the fulfillment of that function been compared with alternative states of the trait?
3. Do phylogenetic analyses suggest that the state claimed to be an adaptation is repeatedly associated with the kind of natural selection needed to produce that adaptation?
4. Could the trait have been selected to this state as a byproduct of selection on other traits?
5. Is it a spandrel? Might the claim of adaptation be confounded by an inappropriate abstraction of a piece of the organism from the larger whole in which it is naturally embedded?

5. The ESS or invasion-resistance criterion

Think of a population with a trait that is a candidate adaptation.

To test the adaptation claim, allow the population to be systematically and repeatedly invaded by all possible alternative states of the trait in all orders and combinations.

If the candidate adaptation can resist invasion by alternative states, then we can say that it is an adaptation in the sense of an evolutionary strategy that resists invasion by competitors.

Cases not covered by the ESS criterion

A beats B beats C beats A → eternal cycles (e.g. rock-paper-scissors game).

The state that resists all invaders is not attainable in phenotype space.

Negative frequency-dependence yielding an adapted set of phenotypes, not a single best-adapted phenotype.

Cases where the invasion challenge is hard to arrange and the ability to resist invasion has not been convincingly tested.

Summary on adaptation

Criterion	**Comment**
Natural selection observed	The best
Perturbation	Convincing
Function	Induced responses convincing
Design	Plausible if Lauder's questions answered
Invasion resistance	Only as good as the mutants tried

Bottom line: adaptation is only problematic if not tested or testable.
Beware untestable claims of adaptation.

Section 5: Styles of thought: Typological, population, and tree thinking

Understanding arguments

What implicit assumptions are being made?

What different meanings are being assigned to words?

What issues are hanging unexpressed in the background?

In brief, where are people coming from?

Typological Thinking

The most important thing to know about something is the kind of thing - the category - that it represents: the “normal” condition.

This derives from Plato’s theory of Ideals and Aristotle’s theory of Types.

The Type embodies the essence of the thing.

Scientific examples: *the* hydrogen atom, *the* vertebrate kidney, *the* eukaryotic ribosome.

If you’ve seen one, you’ve seen them all.

Typological Thinking is Useful...

... whenever the average properties of a thing are much more important than its variation.

- This is sometimes the case in molecular biology, cell biology, and physiology - but not always.

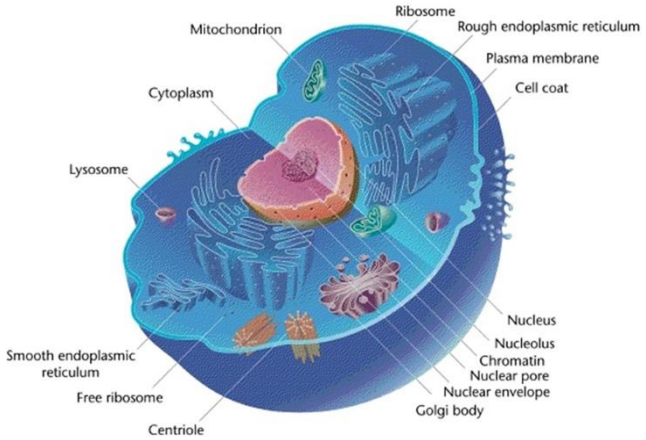
Typological thinking is a powerful simplification that makes life easier.

The important thing is to know when you can get away with it.

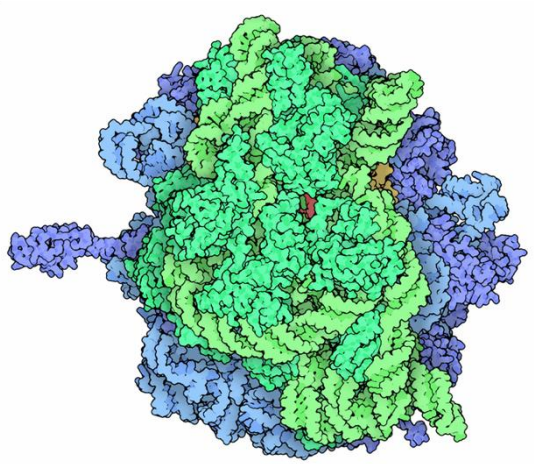
It will mislead you when thinking about evolution, or the adaptive immune system, or ... many other things.

Typological thinking is useful in cell and molecular biology

Animal Cell



Ribosome



Population Thinking

The most important thing to know about something is the variation in the population from which it is drawn.

This is tied to Darwin's insight into the central role of variation in natural selection.

Examples: Gene frequencies, relative risk of heart disease stratified by sex and lifestyle, personalized medicine.

This view emphasizes variation in the population and the processes that change it, with individuals seen as samples whose traits can be estimated from population frequencies.

Population thinking is useful ...

... whenever it is important to know whether and how fast something will evolve, including:

antibiotic resistance,

pathogen virulence,

cancer malignancy,

and anything related to the microbiota.

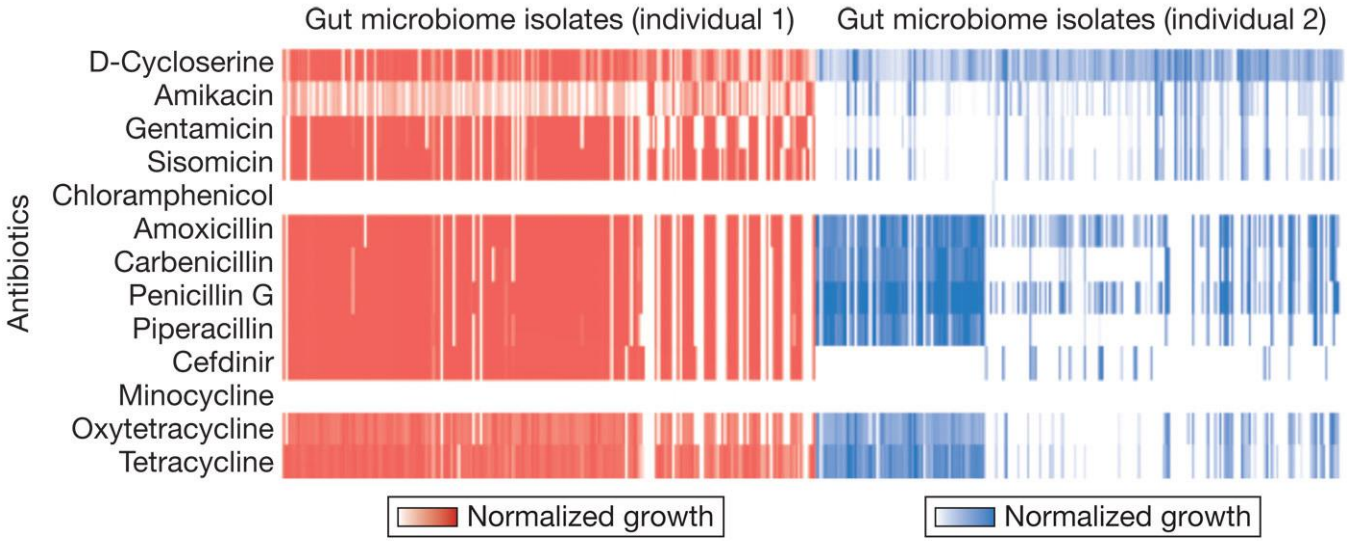
Population thinking forces us into conceptualizing frequency distributions, patterns of variation in space and time, and probabilities rather than certainties.

Population thinking about antibiotic resistance

Gut microbiome isolates from two humans differ in the percentages of isolates that are resistant to single and multiple antibiotics.

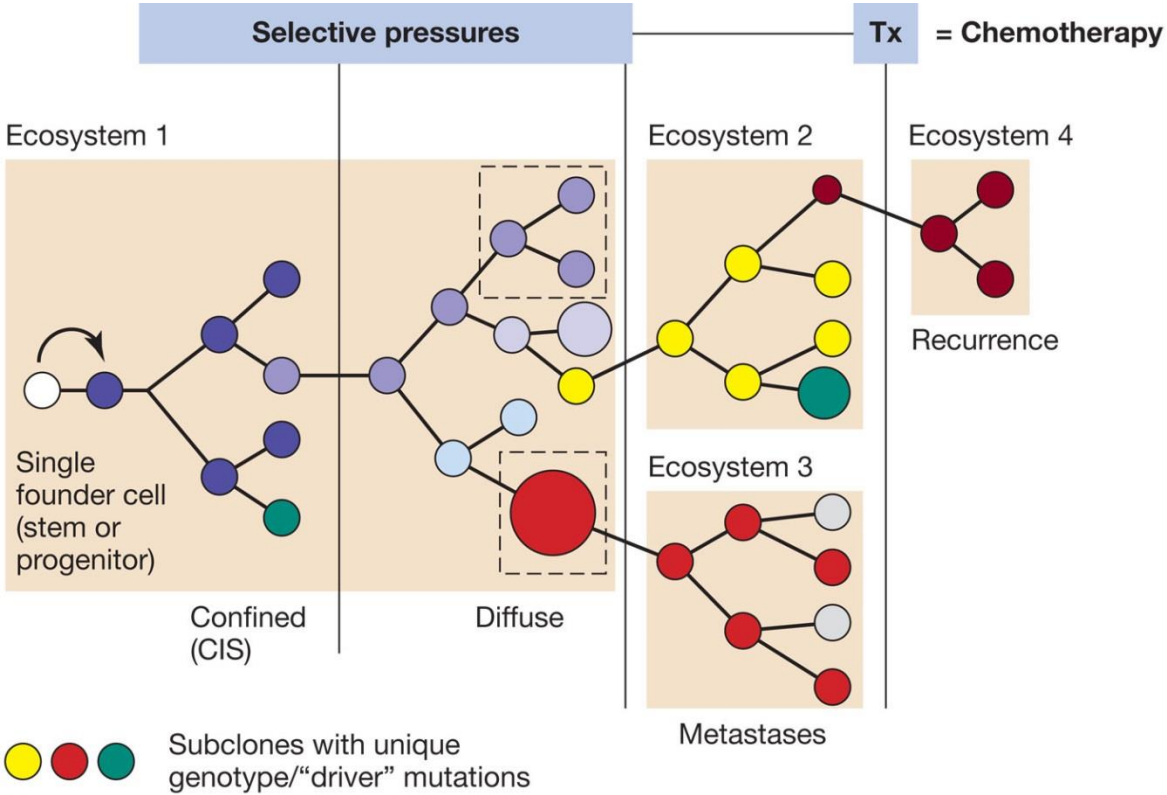
The humans are two samples from a large population.

The gut microbes are 572 samples from huge populations.



***EVOLUTIONARY MEDICINE*, Figure 1.4**

Population thinking about cancer



EVOLUTIONARY MEDICINE, Figure 1.6

Every cancer arises as a population of clones that differ in their history of mutations.

Selection allows some clones to expand; others go extinct or into dormancy.

Ecosystems are different tissues to which different clones become adapted.

Chemotherapy selects for resistant clones.

Tree Thinking

The most important thing to know about something is its position in a phylogenetic tree.

This derives from the insight that all species are related in a single "tree of life."

Species are not independent replicates within a larger class but are connected within a phylogenetic tree.

This emphasizes explanations within the context of phylogenetic trees in which differences arise by divergence from the last shared ancestor.

Tree thinking is useful ...

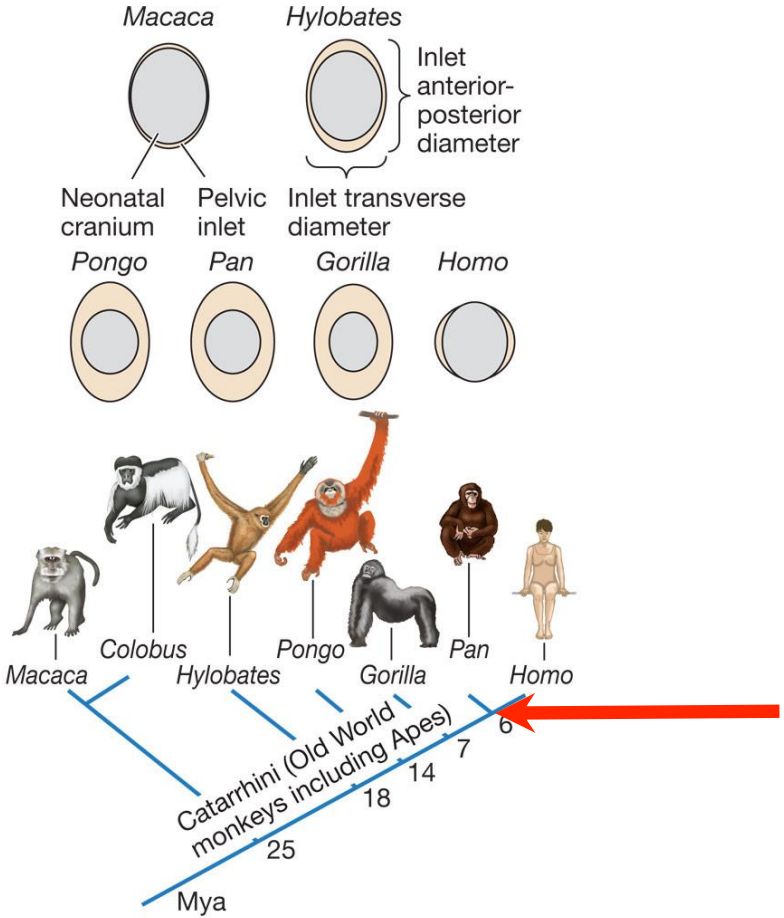
... whenever there is insight to be drawn from comparisons among species.

In evolutionary medicine, such comparisons suggest insights into issues that include:

- The association of invasive placentas with metastatic cancer.
- The association of upright posture with problems of childbirth.
- Why whales and elephants do not all die of colon cancer as teenagers.
- Why African green monkeys have SIV but not AIDS.
- Why heart disease presents differently in chimpanzees than it does in humans.

Knowing where on the tree of life a condition is present or absent immediately gives us clues to its correlates and possible causes.

Tree thinking about birth

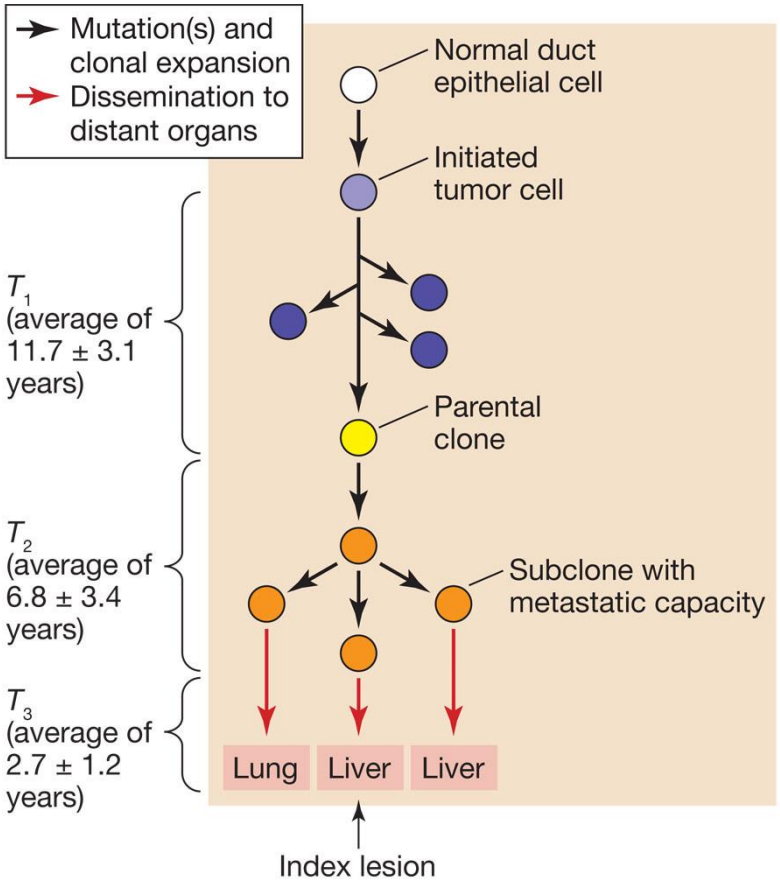


EVOLUTIONARY MEDICINE, Figure 1.7

The relationship between the size of the maternal pelvic inlet and the neonatal head in primates.

Looking at the phylogenetic tree immediately tells us which is the key comparison: Between chimpanzees and humans, not between gibbons or macaques and humans.

Tree thinking about cancer



EVOLUTIONARY MEDICINE, Figure 6.7

The metastases of a pancreatic cancer can be genotyped, allowing estimates of relationship and age.

These cancers originated about 18 years before they were detected. Knowing this gives us new ideas for methods of detection that could prevent growth and spread.

Summary

People think about problems in profoundly different ways.

It is important to match the way you think to the problem you are trying to solve.

Population and tree thinking are standard in evolutionary biology.

- They emphasize the importance of variation in populations, frequencies, probabilities, history, and comparisons.