"Nothing in biology makes sense …
… except in the light of evolution"
(Theodosius Dobzhansky, 1973)

Why not?

Living things are extremely *complex*, *adapted*, and *diverse*.

The ***problem*** is how to explain this, scientifically.

At present, the ***best solution*** we have is the "theory of evolution".

Bumper-sticker version:

Natural selection (among variants in populations) drives ***descent with modification*** (from shared ancestors)

To understand, test, and use this idea we need to learn:
"population thinking"
(about correlations between genotypes, phenotypes and fitnesses);
"tree thinking"
(about change along the branches of a phylogeny).

The logic as a set of propositions (syllogism)

There is heritable phenotypic variation in all populations.
[Mendel]

Ecological limits on reproduction cause a "struggle for existence".
[Malthus]

As a consequence, natural selection inevitably occurs.[1]
[Darwin[2]]

This causes *adaptation*, *speciation*, and *evolutionary divergence*.[3]
[Darwin[4]]

[1] "Survival of the fittest" is a *definition* of selection; yes *of course* it's "tautological"!
[2] Wallace independently discovered natural selection; he and Darwin published it together.
[3] This claim is *not* tautological; it's a scientific proposition because it could be proved *false*.
[4] And amazingly, Darwin came up with this in *ignorance* of Mendel's discovery of *genes*!

Evolution = change in inherited properties of populations

OK, but mechanistically, how does it happen? What are the pieces?

Reproduction with inheritance. Living things (including viruses) make babies that resemble themselves.

Random mutation. Inheritance is *not perfect*. Mutations accumulate within populations, causing variation, and between populations, causing divergence. (Darwin never understood the source of variation.)

Natural selection. Within populations, the variants best able to survive and reproduce *under current conditions* become more common. Thus individuals and populations become *adapted* to those conditions.

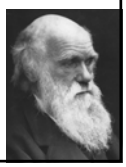
Lots of time, and exponential growth. All three of these processes operate continuously and cumulatively over millions of years. Thus the principle of "compound interest" can slowly but surely turn slight advantages into dramatic evolutionary changes.

Evidence reviewed in *On the Origin of Species* (1859)

For ***natural selection*** [*mechanism of evolutionary change*]:
resemblance of offspring to their parents (heredity)
variation of structure (within and between populations)
variance of survival and reproductive success (fitness)
modification of domestic species (artificial selection)

For ***descent with modification*** [*fact and consequences of evolution*]:
fossils (including imperfection of the geologic record)
biogeography (distributions of related species)
comparative anatomy & embryology (e.g. vestigial organs)
modification of domestic species (dogs, pigeons, cows, etc.)

We'll review more up-to-date versions of this evidence (about the ***history of life***, and about the ***process of selection***) in the next two lectures.



Some important scientific implications

Adaptation involves modification of ancestral structures and habits (parts made over or recycled).

New species (like new genes and functions) arise by splitting and divergence.

Thus organisms and their properties (down to proteins and genes) are products of *history* ("they have a past"), and can't be properly understood apart from that history.

Organisms and their mechanisms *appear* to have been designed to achieve or serve *"purposes"*, but this is an illusion.

Instead, they have *functions*, which arise inevitably from the blind, opportunistic process of natural selection (i.e., without foresight).

The scientific study of life requires analysis of both "*proximate*" causation (how does it *work*?) and "*ultimate*" causation (how did it *come to be that way*, and what is its *function*?).

A huge philosophical implication: no more *essentialism*

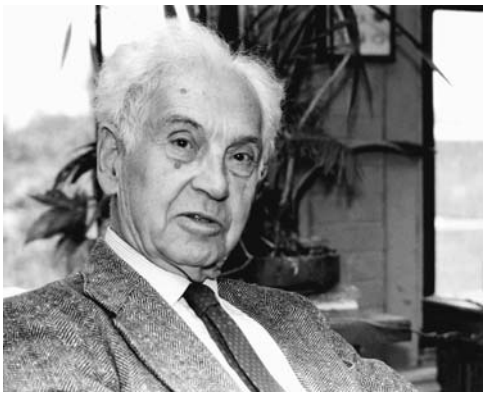
For thousands of years, western thought had accepted the Platonic view that an object's ultimate reality was its *essence* or *ideal type*.

Essentialism in biology meant that species were thought to be held together by their underlying, unchanging "types" or ideal forms. On this view, individual variations are *departures* from the essence of a species; thus they are *imperfections* that make individuals less representative of the true nature of their species.

Darwin completely destroyed essentialism in biology and replaced it with a radical new idea: variationism.

Variationism holds that species are united only by *recent common ancestry*. Thus every individual is *equally* representative of the species; the *average* phenotype is just a statistical abstraction, *not* the reflection of some higher, more pure, or more ultimate reality.

Ernst Mayr (1904-2005), "The 20th century's Darwin"



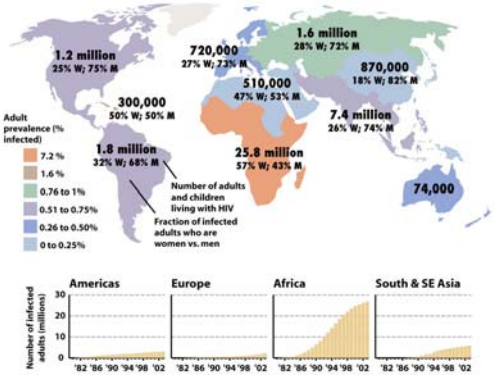
"It was quite overlooked, in the uproar over evolution, religion, and man's place in nature, that Darwin had introduced **a new way of thinking.** Darwin himself was apparently unaware of it… Philosophers found it exceedingly difficult to deal with this new thinker, but none of the new concepts caused them more trouble than **population thinking:**

"What is this population thinking and how does it differ from typological thinking, the then prevailing mode of thinking? Typological thinking, no doubt, had its roots in the earliest efforts of primitive man to classify the bewildering diversity of nature into categories. The *eidos* of Plato is the formal philosophical codification of this form of thinking. According to [the concept of the *eidos*], there are a limited number of fixed, unchangeable ideas underlying the observed variability, with the *eidos* (idea) being the only thing that is fixed and real, while the observed variability has no more reality than the shadows of an object on a cave wall, as it is stated in Plato's allegory. Most of the great philosophers of the 17th, 18th, and 19th centuries were influenced by the idealistic philosophy of Plato, and this school dominated the thinking of the period.

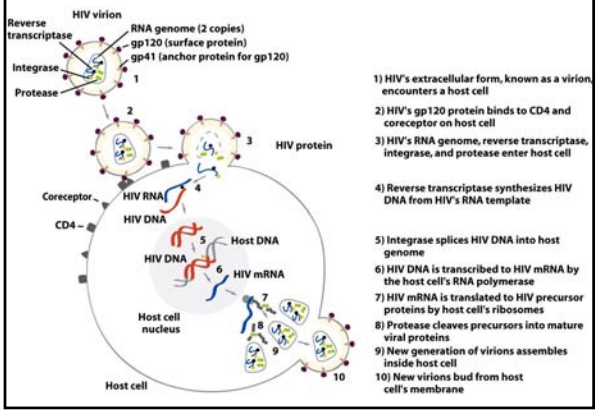
"The assumptions of population thinking are diametrically opposed to those of the typologist. The populationist stresses the uniqueness of everything in the organic world. What is true for the human species - that no two individuals are alike - is equally true for all other species of animals and plants. All organisms and organic phenomena are composed of unique features and can be described collectively only in statistical terms. Individuals, or any kind of organic entities, form populations of which we can determine the arithmetic mean and the statistics of variation. Averages are merely statistical abstractions, only the individuals of which the populations are composed have reality. The ultimate conclusions of the population thinker and of the typologist are precisely the opposite. For the typologist, the type *(eidos)* is real and the variation an illusion, while for the populationist, the type (average) is an abstraction and only the variation is real. No two ways of looking at nature could be more different."

Ernst Mayr (1959) in *Evolution and Anthropology;* also in his Introduction to *On the Origin of Species* (facsimile of the 1st edition, Harvard University Press, 1964).

HIV/AIDS: probably the worst epidemic in human history



HIV's RNA genome is copied to DNA by reverse transcriptase (RT)



Questions about HIV that require evolutionary analysis

Where did HIV come from?

When did it arrive in the human population?

Why does HIV cause AIDS and eventually kill people?

Why can't HIV be less virulent (more benign)?

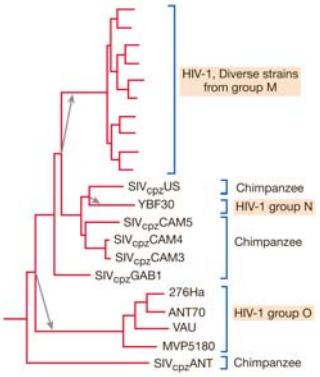
Why are some people naturally resistant to HIV?

Why have therapies such as AZT become ineffective over time?

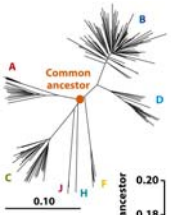
Where did HIV come from?

HIV belongs to a group of retroviruses that infect old-world monkeys and apes.

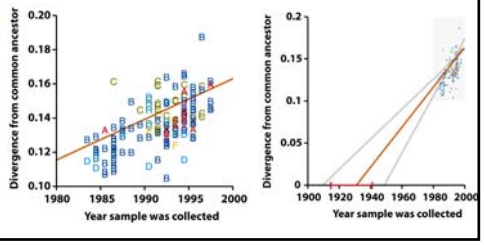
Phylogenetic analysis implies that HIV-1 (the highly virulent form that causes AIDS) jumped from chimpanzees to humans more than once.



When did it arrive in the human population?



Most HIV-1 infections belong to the diverse "M" group. Bette Korber and colleagues (*Science* **288**, 1789-1796, 2000) sequenced the envelope protein genes of 159 different viruses from this group, then inferred their evolutionary history (left) and used the *dates* when they were collected to estimate the *rate* at which the *env* gene evolves (below).



Why does HIV cause AIDS and eventually kill people?

It infects immune-system cells (macrophages and helper T cells) that express the CD4 protein on their surfaces.

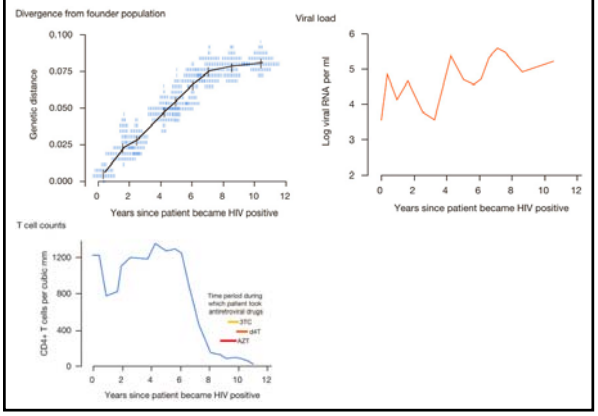
The immune system attacks and kills those cells when they become infected.

But this doesn't clear the infection, because HIV *evolves very rapidly*, temporarily evading immune-system recognition and infecting more macrophages and helper T cells.

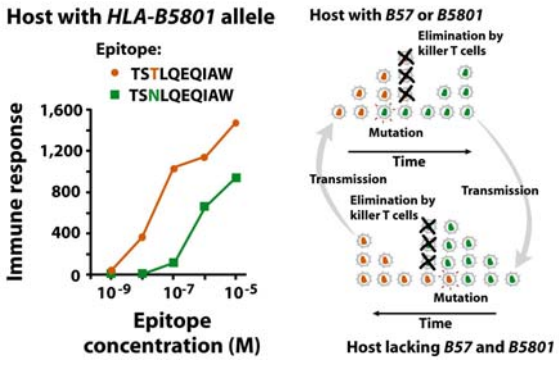
The immune system fights back, but eventually the population of CD4 helper T cells is depleted and the immune system collapses.

The host succumbs to a variety of opportunistic secondary infections.

History of a patient who carried the infection for 11 years



Host-genotype specific evolution of HIV's gp120 protein



Why can't HIV be less virulent (more benign)?

Hypothesis 1: It simply *can't* multiply at a lower rate. (No, the SIVs and HIV-2 are much less virulent, as are other viruses that infect CD4 cells.)

Hypothesis 2: There isn't any genetic variation in virulence for selection to act on. (No, the mutation rate is extremely high, and particular mutations that increase and decrease virulence have been identified.)

Hypothesis 3: Selection favors virulence because it increases transmission of HIV. (Probably. A higher viral load in the blood may increase the probability of transmission to an uninfected host, given blood-blood contact.)

Upshot: The way to defeat HIV is to *change human behavior* (no unprotected sex outside strict partner fidelity; no needle sharing).

This *directly* reduces transmission, and also *selects for lowered virulence* (because the host must remain alive if the virus is to have any chance of transmitting itself).

Vaccines, by contrast, are unlikely to work because HIV is so rapidly evolving and diverse.

Why are some people naturally resistant to HIV?

HIV uses a host cell-surface protein called CCR5 as the co-receptor (part of its "doorway" into the cell).

Some people carry a mutant form of CCR5 which blocks entry of HIV.

This allele is most common (9%) in populations of European ancestry, and may have been favored during the Black Plague (14th Century), by conferring resistance to the plague bacillus.

Analogous resistance alleles exist at other genetic loci. They too may have been favored by past epidemics, and are probably being favored again, by HIV.

But at what cost? (*Tradeoffs!*)

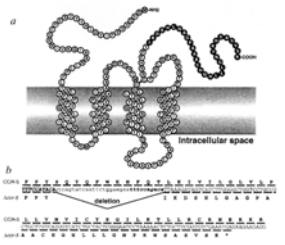
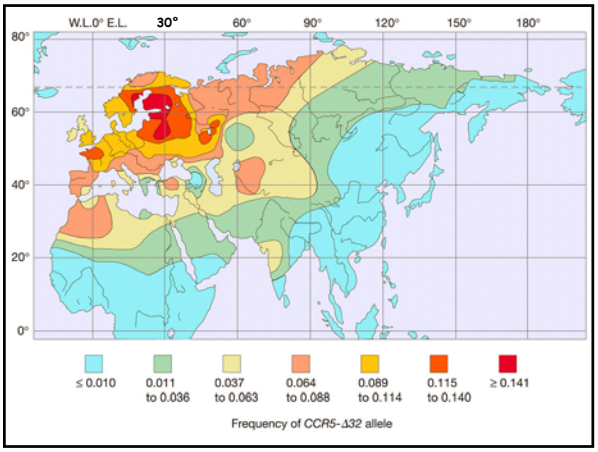


FIG. 1 Structure of the mutant form of human CCR-5. *a*, The amino-acid sequence of the non-functional Δccr-5 protein. The transmembrane organization is given by analogy with the predicted transmembrane structure of the wild-type CCR-5, although the correct maturation of the mutant protein up to the plasma membrane has not been demonstrated. Amino acids represented in black correspond to unnatural residues resulting from the frame shift caused by the deletion. The mutant protein lacks the last three transmembrane segments of CCR-5, as well as the regions involved in G-protein-coupling. *b*, Nucleotide sequence of the CCR-5 gene surrounding the deleted region, and translation into the normal receptor (top) or the truncated mutant (Δccr-5, bottom). The 10-bp direct repeat is represented in bold italics.

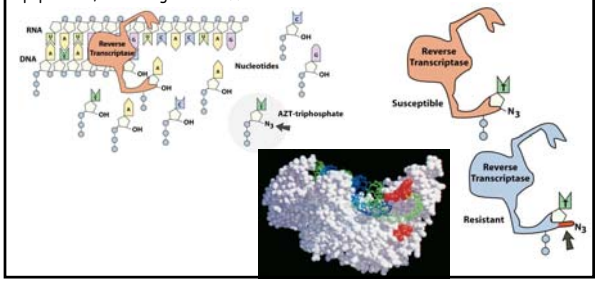
Samson *et al.* (1996) *Nature* **382**, 722-725



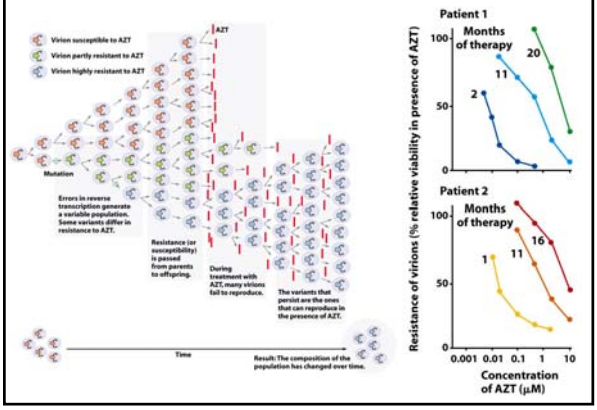
Why have therapies such as AZT become ineffective over time?

AZT (azidothymidine) is a chain-terminating dT analog that is accepted by the HIV reverse transcriptase (but not by human DNA polymerases).

HIV's mutation rate is so high that resistant (discriminating) RT mutants appear within a few years *in the HIV population of a single infected host*. These mutations are highly beneficial to the virus, and quickly take over the population, rendering AZT ineffective.



AZT-resistance: predictable consequence of a *population* process!



Review:
Questions about HIV that require evolutionary analysis

Where did HIV come from?

Its ancestors were Simian Immunodeficiency Viruses (SIVs) of chimpanzees.

When did it arrive in the human population?

The predominant M strain appeared around 1930.

Why does HIV cause AIDS and eventually kill people?

It overwhelms the immune system by evolving rapidly within an individual. This may illustrate the principle that evolution is "blind" (without foresight).

Review, continued…

Why can't HIV be less virulent (more benign)?

If many carriers engage in unprotected promiscuous sex or share needles, then HIV's fitness may be increased by high densities in the bloodstream which increase the rate of transfer to uninfected individuals.

Why are some people naturally resistant to HIV?

A mutant allele of the *CCR5* gene prevents the virus from entering helper T cells. This allele may have been favored in the past by conferring resistance to a different pathogen (e.g., the plague bacillus).

Why have therapies such as AZT become ineffective over time?

AZT is a deoxythymidine analog that "tricks" HIV's reverse transcriptase. Unfortunately, mutant forms of RT arise that can discriminate between AZT and "genuine" dT, and these are strongly favored by natural selection in patients who are being treated with AZT.

… and what was that implication about "purpose"?

"Organisms and their mechanisms *appear* to have been designed to achieve or serve "purposes", but this is an illusion."

"Instead, they have *functions*, which arise inevitably from the blind, opportunistic process of natural selection (i.e., without *foresight*)."

Does this mean that *humans* don't have purposes?

NO! Of course we do!

It just means they come from our *values* and *visions* …

… *not* from our *genes*.

For example: Let's defeat HIV!