HIV : Human Immunodeficiency Virus
SIV : Simian Immunodeficiency Virus

HIV and SIV are kinds of retrovirus

Retrovirus - RNA virus with DNA intermediate produced via reverse transcriptase

Howard Temin

David Baltimore

These are two of the three people who shared 1975 Nobel Prize in Physiology or Medicine. They are credited for co-discovering reverse transcriptase.

"CENTRAL DOGMA" OVERTURNED?

HIV causes AIDS (Acquired Immune Deficiency Syndrome)

HIV infects a variety of cell types in the immune system (especially a problem because it kills $CD4^+$ T cells and this damages ability of a body to fight infections)

HIV has 9 Genes, total genome length is about 10,000 bases

HIV point mutation rate is about 3×10^{-5} per site per generation (in contrast, human rate is about 10^{-8} to 10^{-9})
HIV generation time estimated to be about 2.6 days

Estimated that untreated infected HIV patient has about 10^{10} new virion particles made each day

Human Immunodeficiency Virus (HIV)

About 32 million people have died due to HIV. Roughly the same number of additional people infected but still living.
(see http://www.who.int/gho/hiv/en/)

HIV1-M is name given to viruses most associated with HIV epidemic

HIV1-M believed to have originated from SIV-cpz (Simian Immunodeficiency Virus) that infects chimpanzees

Figure taken from http://faculty.ycp.edu/~kkleiner/EvolBio/EvolBioImages/CaseforEvol/HIVphylogeny_2013.jpg

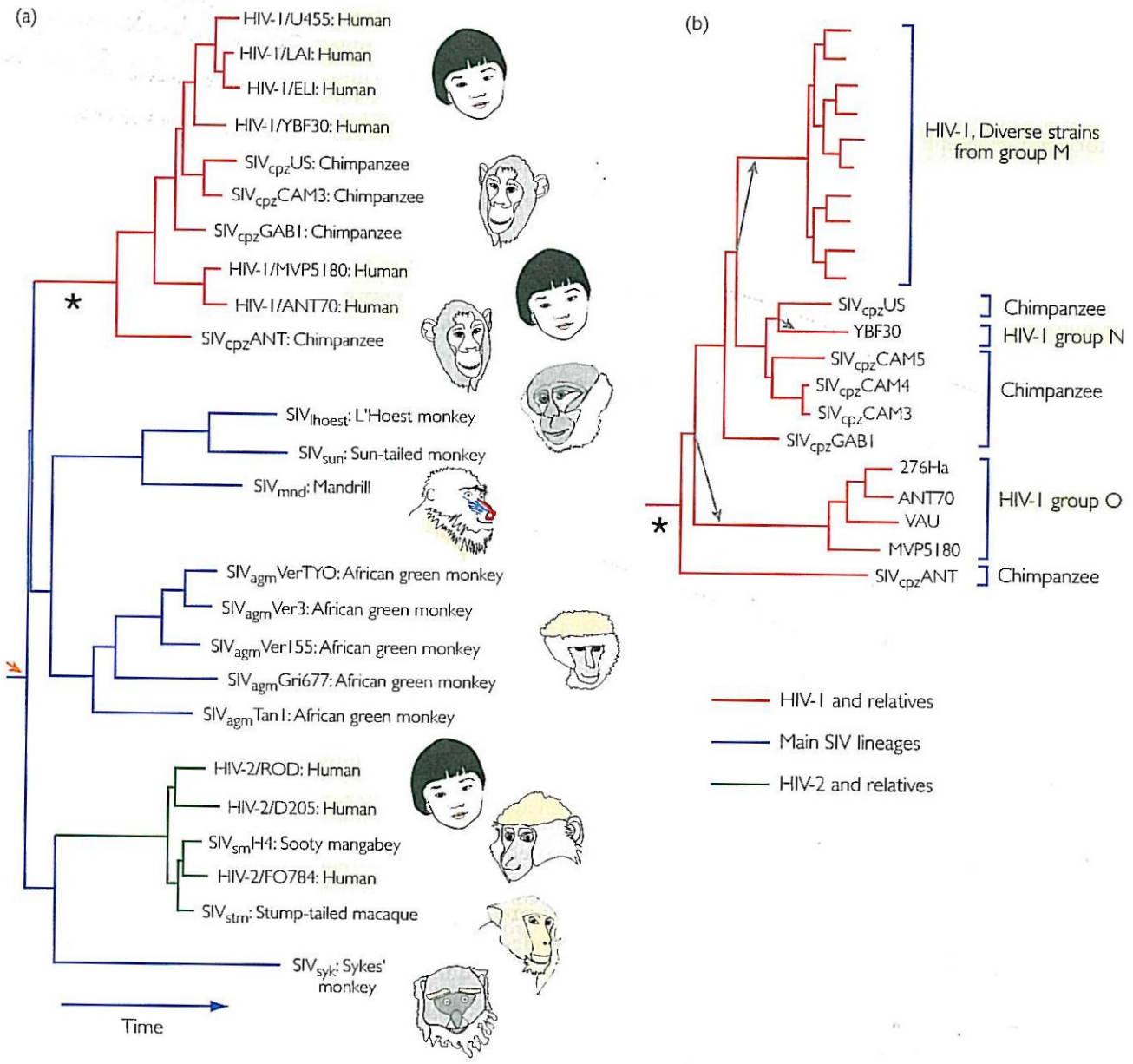


Figure 1.21 **The family tree of HIV and related viruses** (a) This tree shows the evolutionary relationships among the two major forms of HIV, called HIV-1 and HIV-2, and the immunodeficiency viruses that afflict nonhuman primates. Note that the viruses that branch off near the orange arrow at the base of the tree parasitize monkeys. Based on this observation, researchers conclude that virus strains jumped from monkeys to humans. (b) This tree shows a more detailed analysis performed by Hahn et al. (2000). (The asterisk marks the same branch point on both trees.) The arrows indicate the places on the tree where immunodeficiency viruses were transmitted from chimpanzees to humans. According to this tree, each major strain of HIV-1 originated in a different transmission event from a chimpanzee host, as represented by the gray arrows. Redrawm from Hahn et al. (2000).

Red ring shows where chimps have been found with SIV strains that are most similar to HIV-1 group M.

Kinshasa area is where the most HIV-1 group M diversity has been found.

Red ring is about 700 kilometers from Kinshasa area ...

FIGURE 1A. Origin of pandemic HIV-1.
From the following article:
AIDS: Prehistory of HIV-1
Paul M. Sharp & Beatrice H. Hahn
Nature 455, 605-606(2 October 2008)

Where did HIV1-M arise from SIV-cpz?

Partial Answer: Somewhere in Africa

When did HIV1-M arise from SIV-cpz?

Partial Answer: 1959 or before (Dr. Arno Motulsky of the University of Washington collected a blood sample that was later conclusively identified as HIV positive, exactly 1 positive of 672 total samples, positive sample from person in Democratic Republic of Congo)

How did HIV1-M arise from SIV-cpz?

Conventional Explanation: “Natural Transfer” (butchered chimp?, chimp bite?, sex with chimp?)

Oral-Polio Vaccine Explanation: About a million doses of one oral polio vaccine given to Africans between 1957-1960 ... cultured on chimp kidney cells? Other oral polio vaccines also in Africa in 50’s

“The River” by Edward Hooper

(image taken from
http://www.vaccineenterprise.org/conference/2010/images/plenary-bette-korber.jpg)

Bette Korber and her colleagues decided to examine oral polio vaccine hypothesis using available sequence data from HIV genomes ...

How did they do this?

[image taken from wikipedia]

Christian Anfinsen

Shared 1972 Nobel Prize
for work (specifically with ribonuclease A protein)
that showed protein sequence has
the information that determines the three - dimensional protein structure.

"Anfinsen's Dogma"

"Levinthal paradox states that the number of possible conformations available to a given protein is astronomically large, such that even a small protein of 100 residues would require more time than the universe has existed ... to explore all possible conformations and choose the appropriate one"

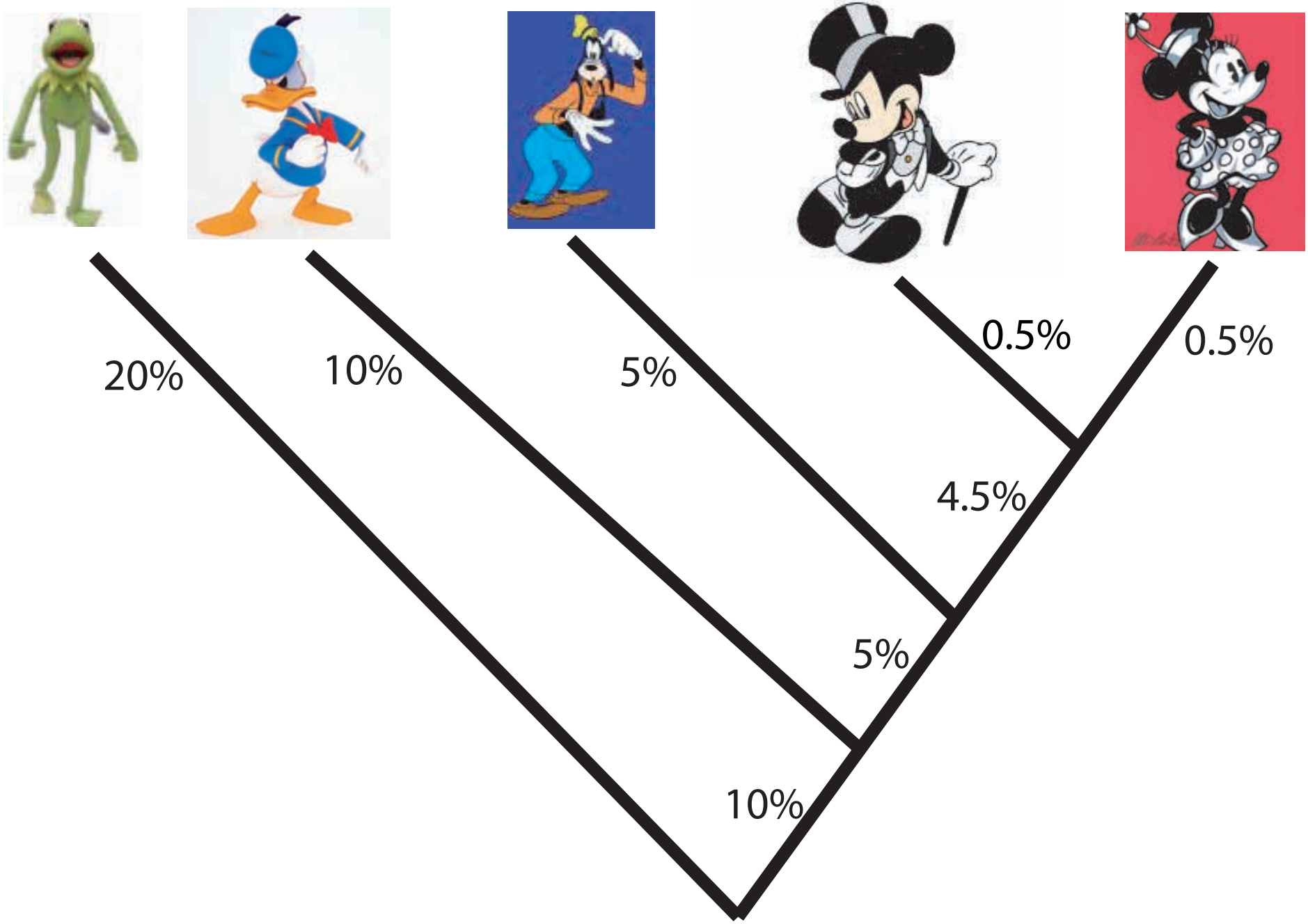
[image and quote taken from wikipedia]

"A comparison of the structures of homologous proteins ... from different species is important, therefore, for two reasons. First, the similarities found give a measure of the minimum structure for biological function. Second, the differences found may give us important clues to the rate at which successful mutations have occurred throughout evolutionary time and may also serve as an additional basis for establishing phylogenetic relationships."

From p. 143 of

The Molecular Basis of Evolution

by Dr. Christian B. Anfinsen (Wiley, 1959)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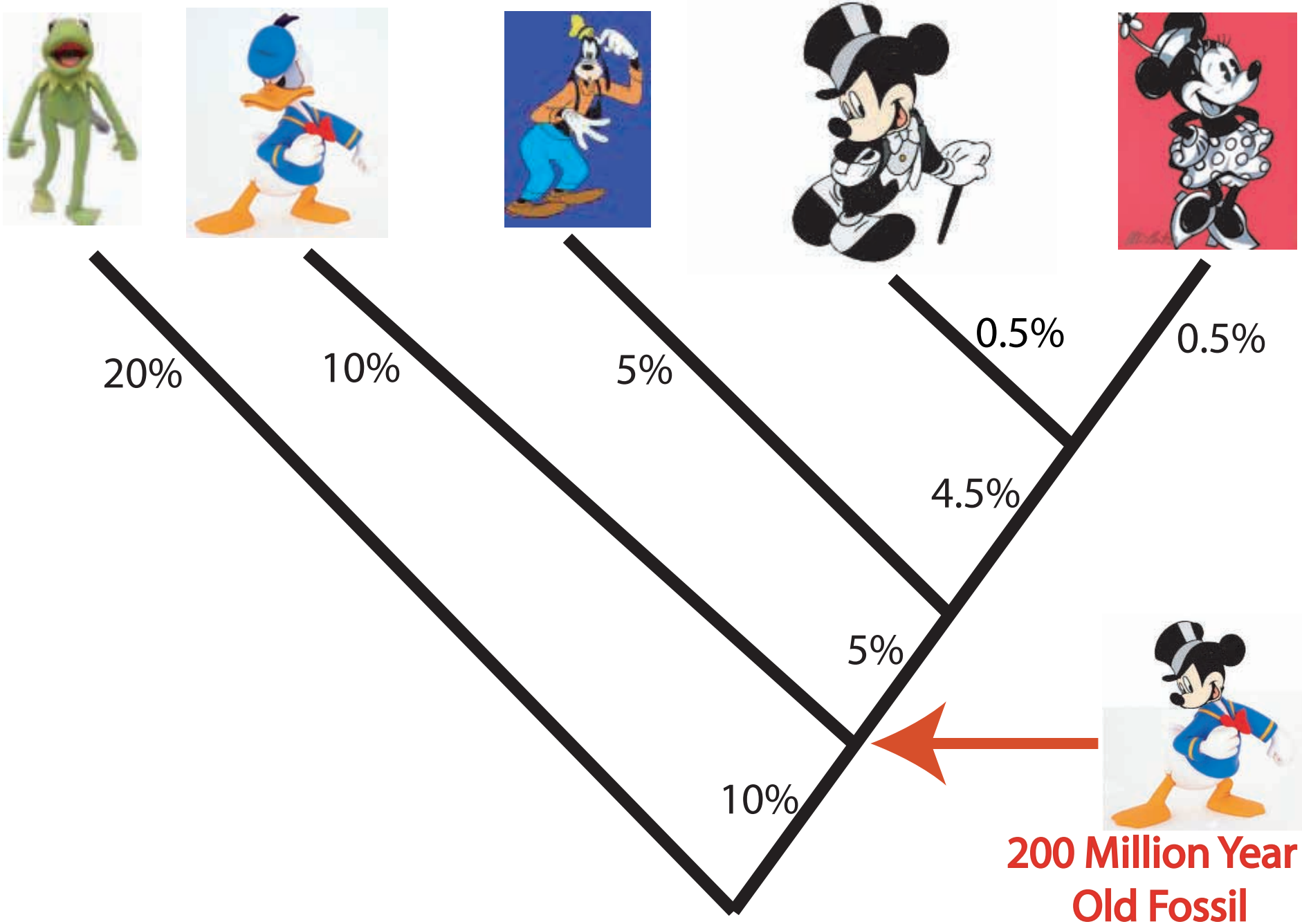
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200 Million Year
Old Fossil





20%

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10 Million

4.5%

100 Million

5%

10%

400 Million

20% Sequence Divergence in 200 Mill. Years means 1% divergence per 10 Mill. Years

200 Million Year Old Fossil

The "Clock Idea"

Christian Anfinsen

images courtesy of wikipedia.

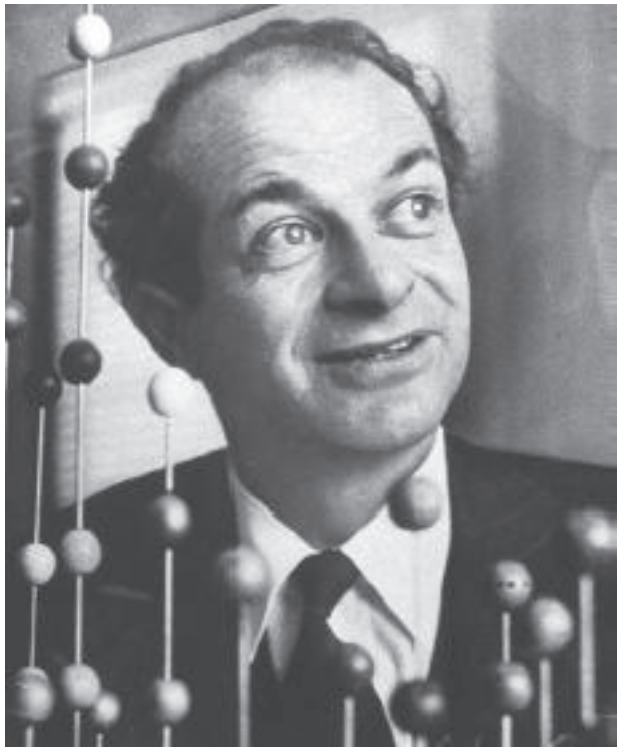
Christian Anfinsen

Ernst Mayr - Taxonomist, Evolutionary Biologist, ... Influential work includes that on how to define species and how speciation works. Very prolific author. Lived more than 99.5 years. Contributed to "modern synthesis" of Darwin's and Mendel's ideas.

images courtesy of wikipedia.

Christian Anfinsen

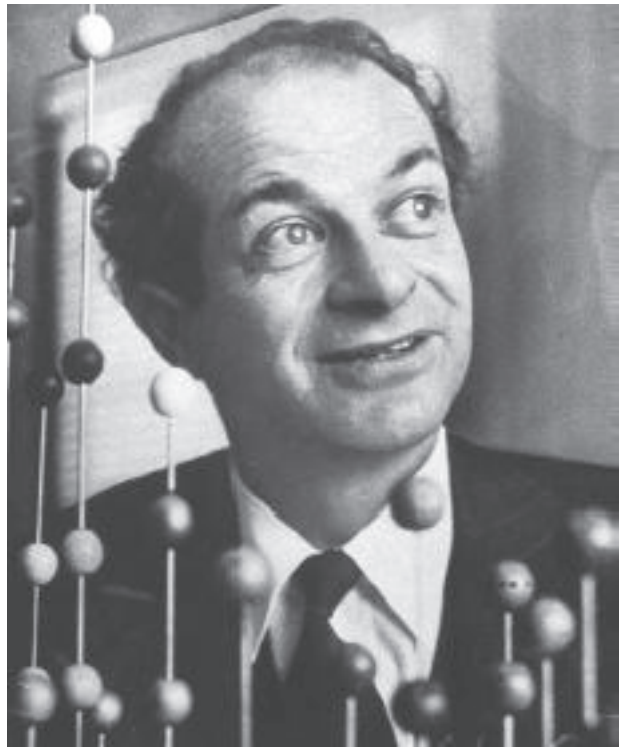
Ernst Mayr



images courtesy of wikipedia.

Christian Anfinsen

Ernst Mayr



Linus Pauling

1954 Nobel Prize in Chemistry for "nature of chemical bond"

1962 Nobel Peace Prize for opposition to nuclear weapon testing

(worked on structure of DNA)

Molecular Clock!

Vitamin C !

images courtesy of wikipedia.

"Ernst Mayr recalled at this meeting that there are two distinct aspects to phylogeny: the splitting of lines, and what happens to the lines subsequently by divergence. He emphasized that, after splitting, the resulting lines may evolve at very different rates... How can one then expect a given type of protein to display constant rates of evolutionary modification along different lines of descent?"

(Evolving Genes and Proteins. Zuckerkandl and Pauling, 1965, p. 138).





20%

10%

5%

0.5%

0.5%

10 Million

4.5%

100 Million

5%

10%

400 Million

A problem with the "Clock Idea": Rates of Molecular Evolution Change Over Time !!

200 Million Year Old Fossil





20%

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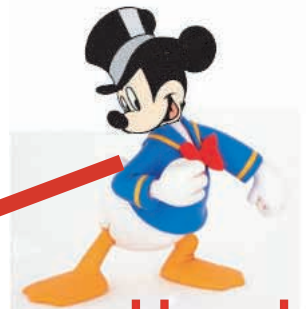
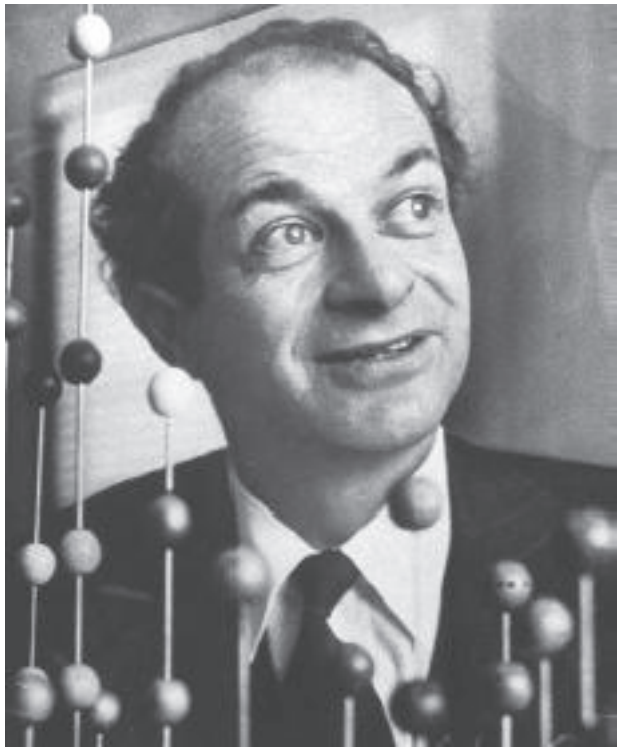
Another problem with the "Clock Idea": Fossils are unlikely to represent same organism as genetic common ancestor.



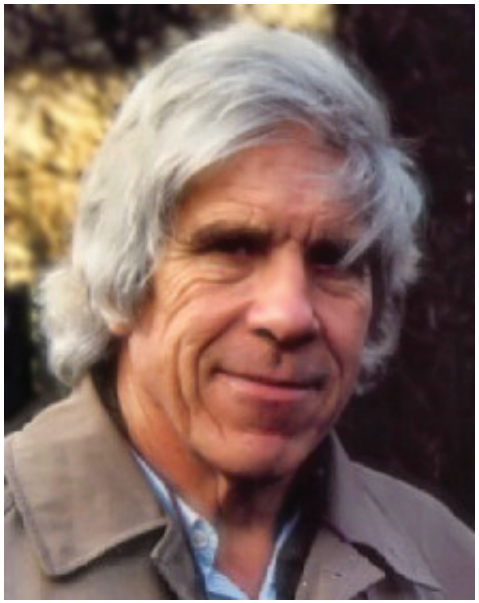
If mammal head is derived character & fossil is 200 Mill. Years old then bird-mammal split must have been at least 200 million years old. This is a constraint on a divergence time.

Christian Anfinsen

Ernst Mayr

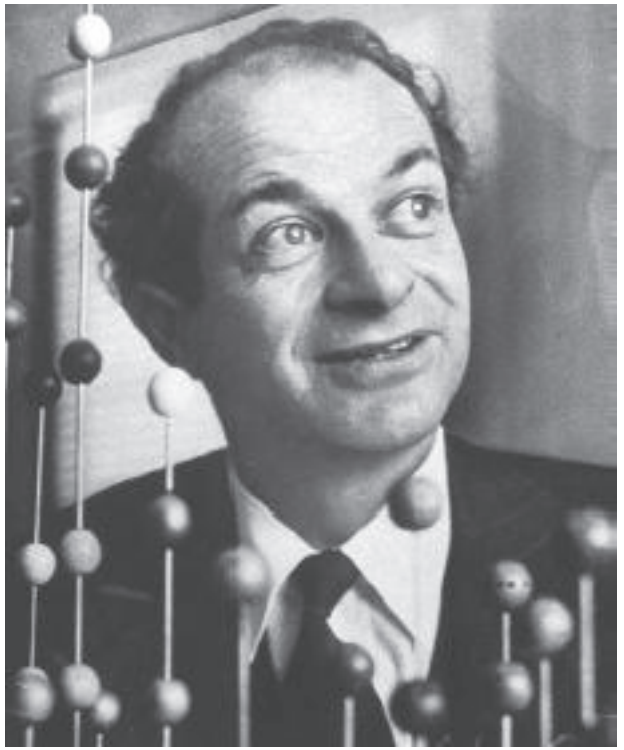


Linus Pauling

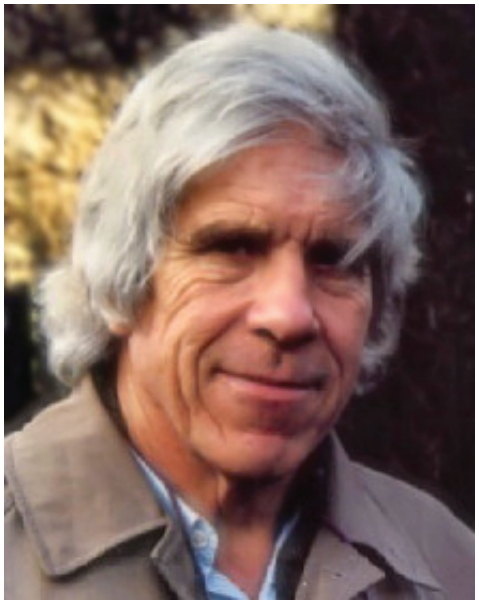


Christian Anfinsen

Ernst Mayr



Linus Pauling



W.D. Hamilton

Hamilton's rule: $C < r \times B$

[fitness cost C is "worth it" if it is less than product of "genetic relatedness to beneficiary of action" and "fitness benefit of beneficiary of action"]

Altruism

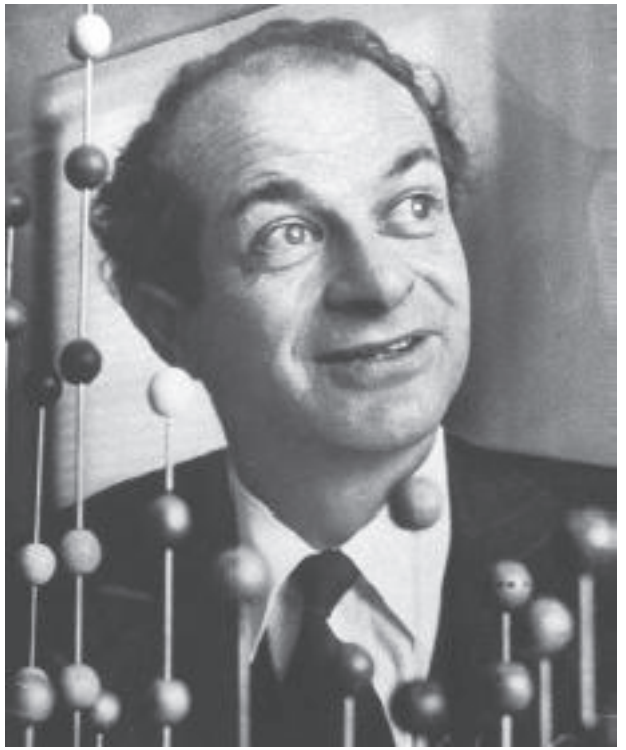
Sex Ratios & Evolution

Most prominent scientific proponent of Oral Polio Vaccine hypothesis

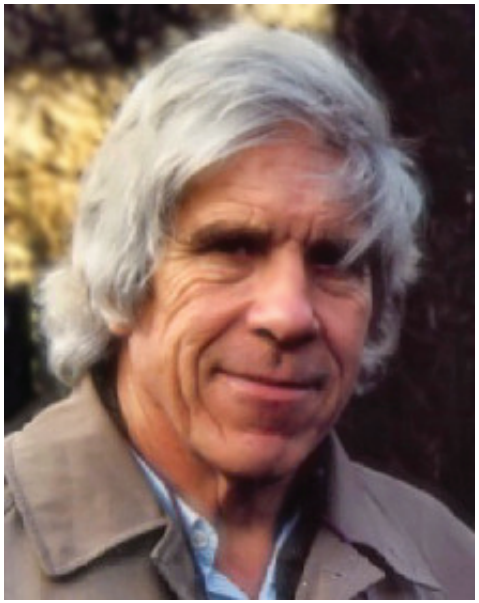
images courtesy of wikipedia.

Christian Anfinsen

Ernst Mayr



Linus Pauling

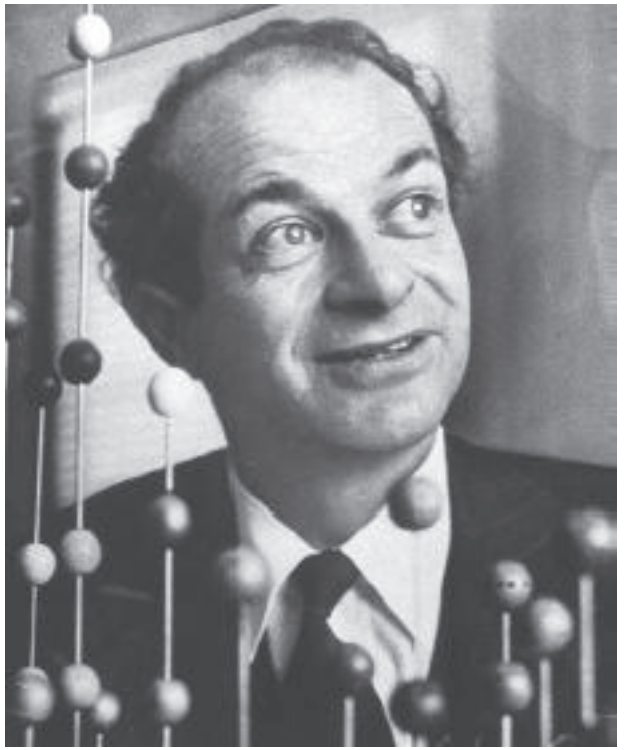


W.D. Hamilton

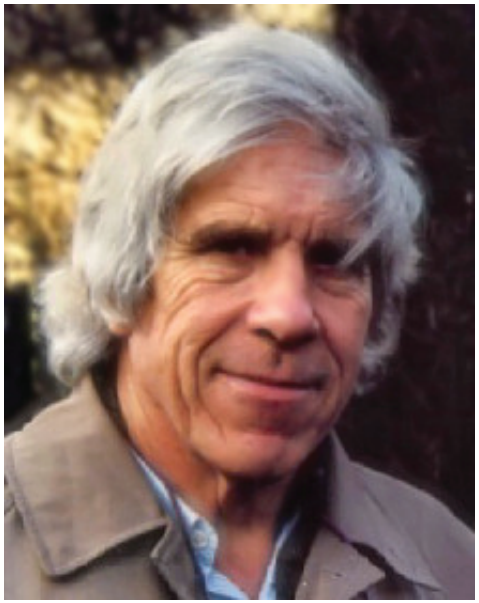
Lower right image from N.Y. Times
All other images courtesy of wikipedia.

Christian Anfinsen

Ernst Mayr



Linus Pauling



W.D. Hamilton

Arno Motulsky

Jeff Thorne's Human Genetics" teacher!

"father of pharmacogenomics"

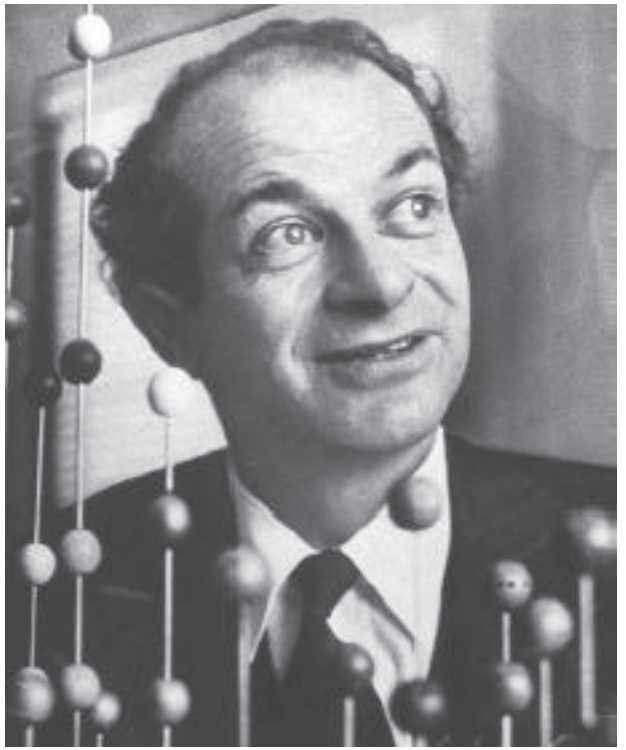
Had 1959 HIV sample in lab freezer!

Was stuck on S.S. St. Louis

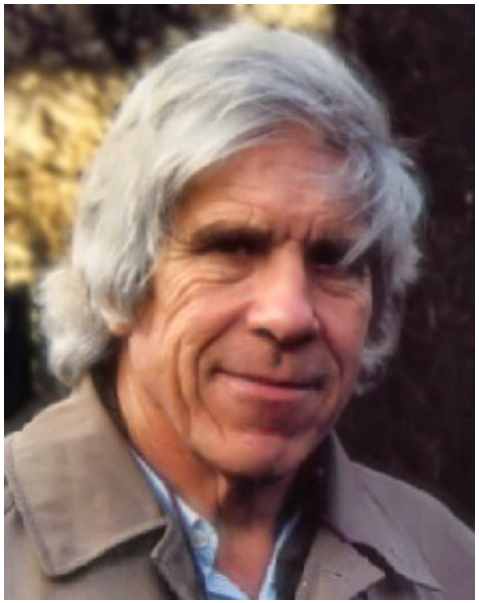
Lower right image from N.Y. Times
All other images courtesy of wikipedia.

Christian Anfinsen

Ernst Mayr



Linus Pauling



W.D. Hamilton

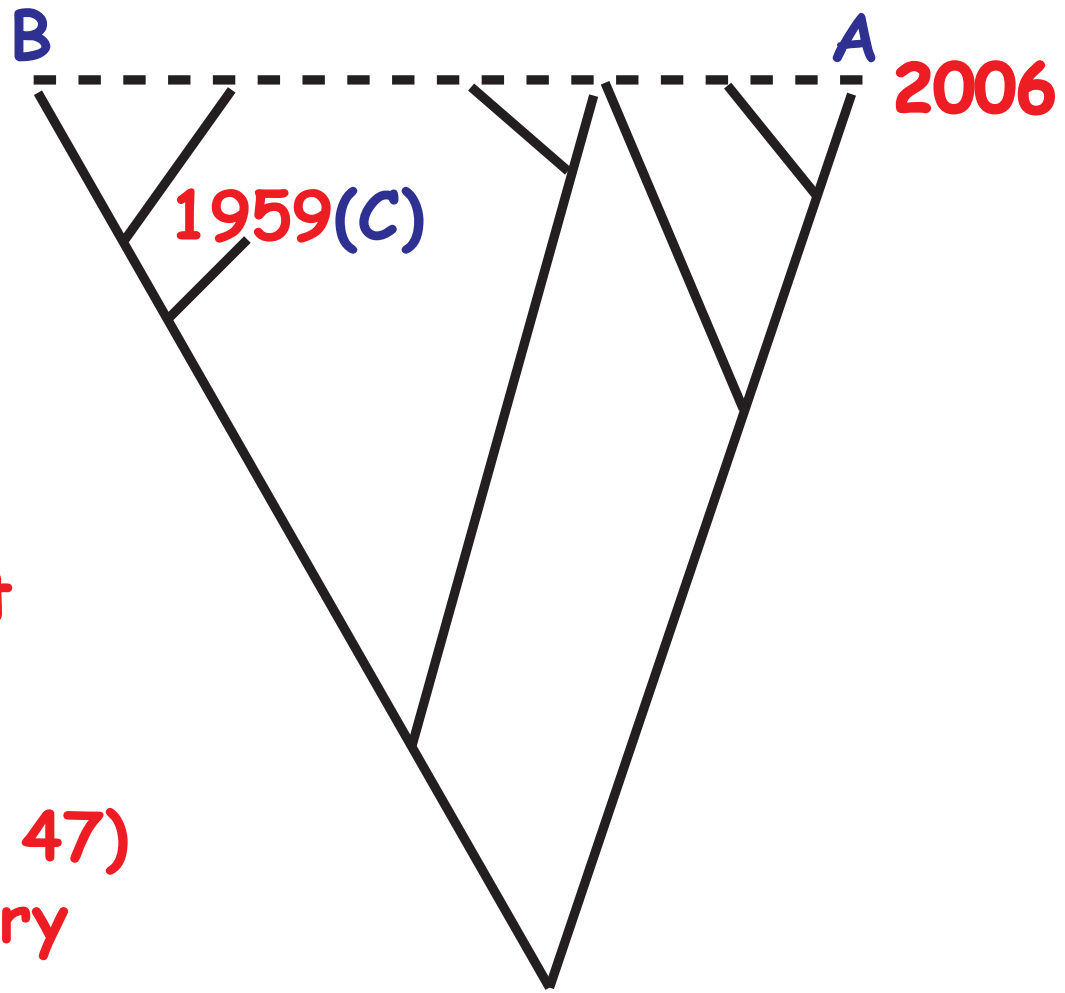
Arno Motulsky

Lower right image from N.Y. Times
All other images courtesy of wikipedia.

Can separate rates and times for quickly evolving (e.g., viral) lineages but cannot for slow lineages.

(2006-1959) =
47 missing years
of evolution

Sequence C should be 47 years closer to Sequence A than Sequence B is to Sequence A. The amount by which C is closer to A than B is closer to A can be used (after dividing by 47) to estimate the evolutionary rate per year.



Serially Sampled Data

Korber et al.2000.Timing the Ancestor of the HIV-1 Pandemic Strains. Science 288:1789

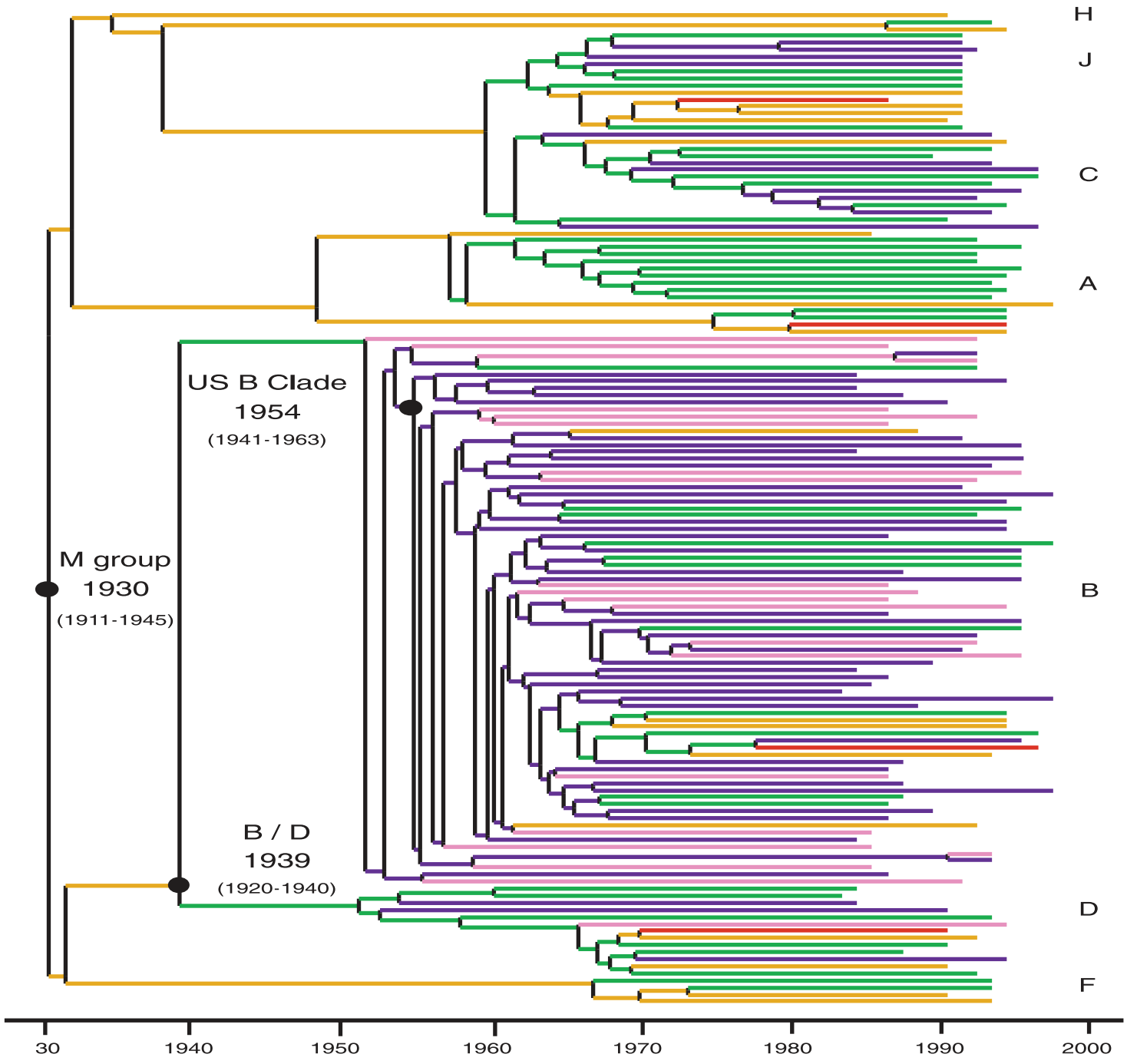


Table 1 from:

Polio vaccine samples not linked to AIDS

Philippe Blancou, Jean-Pierre Vartanian, Cindy Christopherson, Nicole Chenciner, Claudio Basilico, Shirley Kwok and Simon Wain-Hobson

Nature 410, 1045-1046(26 April 2001)

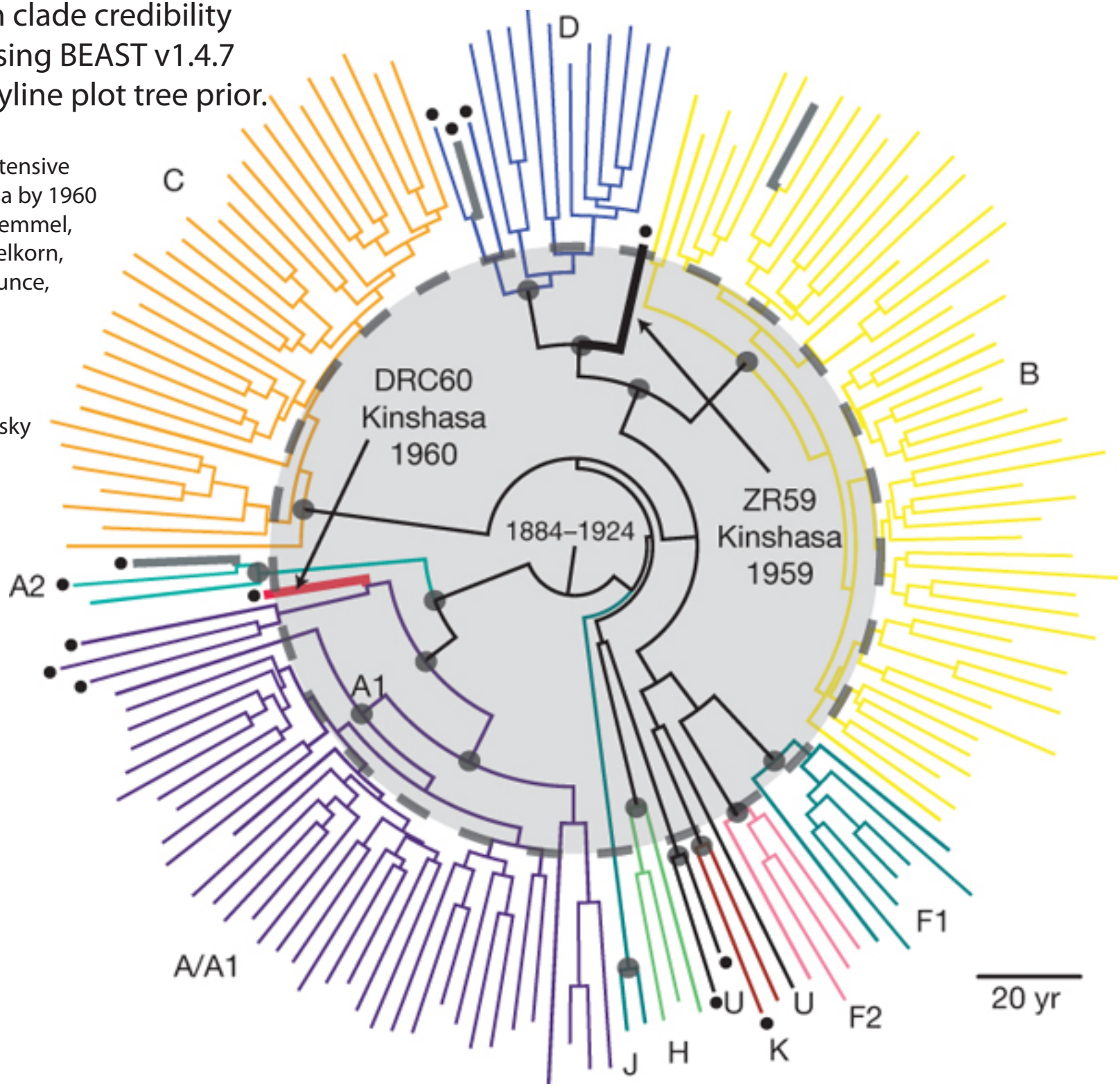
Table 1 Oral poliovirus vaccine samples tested

Wistar samples		SIV_{CPZ}/HIV-1	Polio
CHAT pool 13	75,000 vaccinated in Léopoldville	–	+
CHAT pool 16 A-5	Closest passage to pool 13 available	–	+
CHAT pool 23 7.7. logs	Possibly used in other large trials; protocol on file	–	+
W Ch 24 57C-40 137-71	Possibly used in other large trials	–	+
W Ch 25	Late-passage virus	–	+
CDC samples			
CHAT pool 13	Monkey-kidney passage of CHAT pool 13 (29 Aug 1960)	–	+
CHAT type I Wy4B-5	Obtained from Wistar, made at Wyeth	–	+
CHAT 1FL	Late passage of CHAT 13 in human FL cells (15 Oct 1979)	–	+

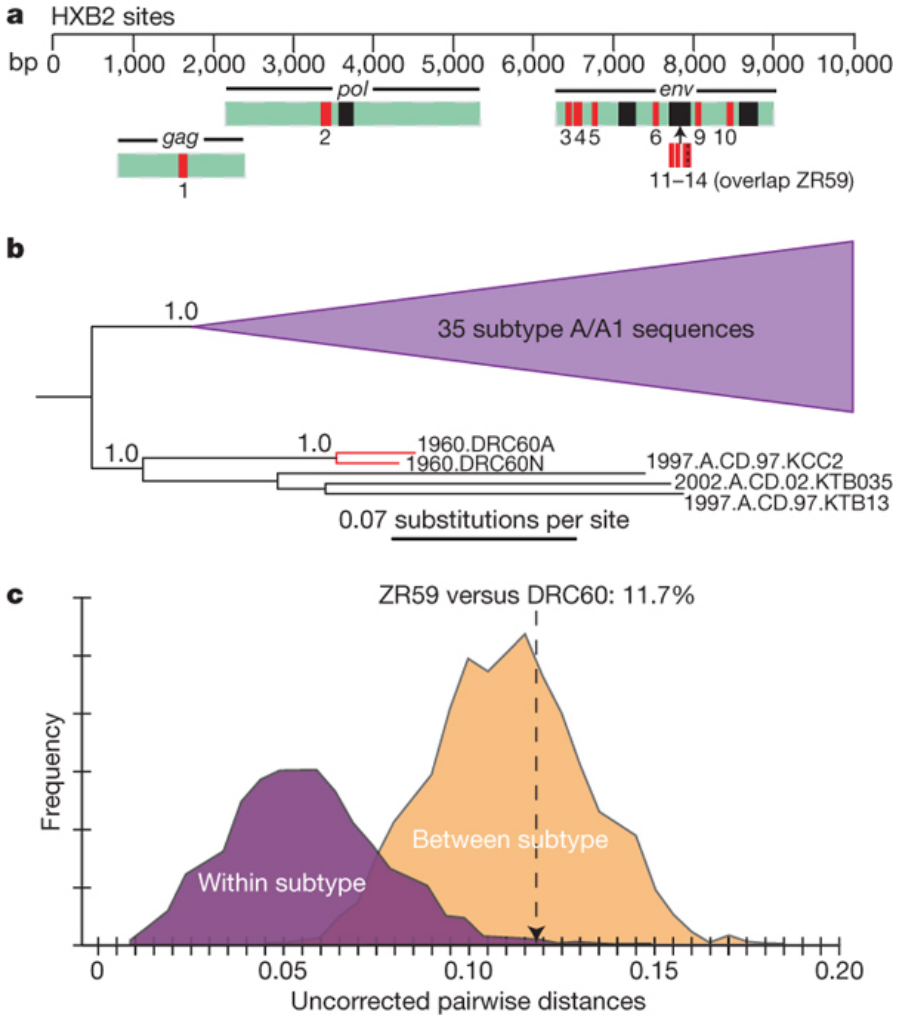
SIV_{CPZ} is the isogenic chimpanzee counterpart of HIV-1 strains. For detection of SIV_{CPZ}/HIV-1 sequences, we used four primer pairs and two for poliovirus. A committee set up by the Wistar Institute identified frozen OPV samples that had been used in Central Africa or had been prepared during that era. Samples and controls were coded and hand-delivered to Roche Molecular Systems and the Institut Pasteur, each ignorant of the other's identity. Choice of amplification primers was left to the individual investigators to increase the chances of detection by at least one group. Small fragments were amplified in case there had been degradation of nucleic acids, particularly RNA, after being frozen for 40 years. Samples were also tested for poliovirus sequences (because if an OPV sample tested negative, then a negative result for SIV/HIV-1 and mtDNA would be meaningless). Infectious poliovirus was recovered for CHAT pool 16 and all three CDC-held samples (V. Racaniello, personal communication). A recent sample of Sabin-1 poliovirus grown on a rhesus monkey kidney cell line[11] was included as a positive control. mtDNA from four animals and a titration of HIV-1 isolate VQA, SIV_{CPZ} Gab1, HIV-2 NIH-Z stocks served as controls.

FIGURE 2. Maximum clade credibility topology inferred using BEAST v1.4.7 under a Bayesian skyline plot tree prior.

From: Direct evidence of extensive diversity of HIV-1 in Kinshasa by 1960
Michael Worobey, Marlea Gemmel, Dirk E. Teuwen, Tamara Haselkorn, Kevin Kunstman, Michael Bunce, Jean-Jacques Muyembe, Jean-Marie M. Kabongo, Raphaël M. Kalengayi, Eric Van Marck, M. Thomas P. Gilbert & Steven M. Wolinsky
Nature 455, 661-664.



Fragments amplified from DRC60, and the results of the phylogenetic and sequence analyses (Figure 1)



M Worobey *et al. Nature* **455**, 661-664 (2008) doi:10.1038/nature07390