Morris Goodman

1925–2010

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
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NATIONAL ACADEMY OF SCIENCES

MORRIS **GOODMAN**

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By Lawrence I. Grossman and Derek E. Wildman

Morris Goodman shook anthropology by first proposing, based on immunological and then later genomic data, that humans and chimpanzees form sister phylogenetic groups. He was a major figure in biological anthropology and molecular evolution for more than half a century, and he died in Oak Park, Michigan, on November 14, 2010, at age eighty-five. He worked to the end, leaving behind a briefcase with the unfinished manuscripts he was writing.

Morris (as he was known to almost all) was born in 1925 and grew up in a working class family in Milwaukee, Wisconsin, in the period between the two great wars that included the Great Depression. Like others of his generation, this experience left a lasting impression on him. As he later told an interviewer, "We were strong believers in Franklin Roosevelt and the New Deal and during my high school years…I became interested in how societies have evolved over human history…I would say it was first this interest in the social situation we were in that made me very receptive to the concept of biological evolution."

He entered the University of Wisconsin in the fall of 1942 and during his first year enlisted in the Army Air Force. At the completion of his first academic year he was called up and entered the 8th Air Force, originally wanting to be a pilot but, as he later recalled, because the navigational systems had been upgraded and he did best in his group at operating them, he was asked instead to be the navigator of a B-17. Remembering a particular mission over Berlin, he said, "The plane was hit by flak. So we dropped out of formation and headed for Poland because the Russians had already moved past Poland. But it developed that the flak hadn't that much disabled the plane so the pilot figured we could get back to our base in England. What's memorable is that the navigation depended on my instructions to get back."

The immunology years and redefining hominidae

In 1945, when the war in Europe ended, Morris was sent back to the United States, first to Houston, where he met his future wife, Selma, whom he married in 1946. He also returned that year to the University of Wisconsin, majoring in zoology and minoring in biochemistry. He completed a masters degree and a PhD, working with Harold Wolfe, an immunologist interested in comparative serology. He worked on antigen-antibody serology with chicken antibodies and studied the physical-chemical factors that affected the reaction, producing a thesis titled, "The Effects of Physical Factors on the Avian Precipitin Reaction." That the reaction was affected by factors like salt concentration, he later said, "apparently has to do with the physical/chemical properties of the bird immunoglobulins. So, that got me into the literature on protein chemistry and so broadened my interests."

With a fresh PhD in hand, Morris went on to the California Institute of Technology (Caltech) as a National Institutes of Health postdoctoral fellow. There, his sponsors were Ray Owen, who had come from the University of Wisconsin not too much earlier, and Dan Campbell, an immunochemist working in the Division of Chemistry and Chemical Engineering. Morris wound up doing a project with Campbell on antigenic differences between adult, fetal, and sickle cell hemoglobins. He and Campbell published a paper in 1953 on the antigenic differences between fetal and adult hemoglobin and also between adult normal and sickle hemoglobin. This attracted a bit of attention, because it had only been a few years since his colleagues (just down the hall) Linus Pauling, Harvey Itano, and collaborators had published their classic paper in Science, "Sickle Cell Anemia, a Molecular Disease" (Pauling et al., 1949) that was to start a period of considerable interest in the hemoglobins.

Morris continued to work on globin genes for the rest of his life. Despite the recognition of his work with Campbell, Goodman left Caltech after a year and moved first to the University of Illinois in Chicago, and then, several years later, to the Wayne State University School of Medicine, where he spent the next fifty-three years. One of the basic tools he learned in immunology was the precipitin reaction, in which antigen and antibody allowed to diffuse toward each other would form a precipitate upon meeting, such that the precipitate from a homologous pair could be differentiated from a heterologous pair by analysis of the shape of the precipitin line.

It was in Detroit that his interest in evolution developed. Morris and his friend and colleague at the Veterans Hospital in Chicago, Morris Wilson, began to contemplate

how proteins expressed in serum may differ developmentally and evolutionarily between species. With the help of George Rabb at the Chicago Zoological Park, also known as the Brookfield Zoo, they obtained a panel of primate sera and used these samples to examine albumin and gamma globulin (now called 7S immunoglobulin) across primate species. Speaking about the technique they used, Morris said:

> *I think the importance is that we could visualize reactions due to individual proteins. Often, of course, because we could make our anti-serum just to a purified protein, but even if you made your anti-serum to a mixture of proteins you would get separate precipitin lines in the gel. Each line would represent a subset of the mixture of proteins, but not a single protein. So, the nature of the method allows you to get more accurate results. See, if two species were very similar to each other, you would end up getting these reactions of identity. The two precipitin lines would merge with each other. But if one species had diverged away from the species to which you had made the anti-serum (we call that the homologous species), then you would get a spur. The original work of Nuttall was much cruder. But more important than that is he didn't really relate it to current knowledge. It wasn't known in his day how genes encoded proteins and things like that, but I could go from these immunological reactions and deduce genetic relationships and generalize from it. So, I felt much more confident in making the proposal [about primate relationships] that I did, and, of course, with that a fair body of data to back us up. I think it was a time when the knowledge had accumulated and it was right to put it together and draw some conclusions from it.*

Seeing the biological interpretation of this simple immunological reaction allowed Morris to start a fundamental appraisal of the then-current state of classification of organisms. Soon after starting this work, he began to publish the primate sera data. Initial results for the serological data suggested that humans, chimpanzees, and gorillas had diverged only slightly from one another, with the surprising result that chimpanzees were actually more closely related to humans than either was to gorillas. These results were first presented at a conference on biochemical anthropology that Stanley Garn had organized in Yellow Springs, Ohio, in 1961.

The following year at the New York Academy of Sciences, Morris proposed that chimps and gorillas should be removed from the Pongidae and placed with humans in the family

Hominidae. His proposal and the data behind it caused him to be invited afterwards to a meeting sponsored by the Wenner-Gren Foundation for Anthropological Research. This meeting was attended by two interesting groups: the established leaders of the neo-Darwinian synthesis, George Gaylord Simpson, Ernst Mayr, and Theodosius Dobzhansky; and also Emile Zuckerkandl, Morris Goodman, and Harold Klinger, who perhaps represented the field that Zuckerkandl named: molecular anthropology.

Morris realized at such meetings that classification was not, as he had thought, cut and dried; but rather, it was controversial and surprisingly subjective. Given the relative clarity of the immunological data he was deriving, he was able to say, "I know enough about science and what we want out of the classification, or what we should want, to feel uninhibited in proposing certain revisions where I have some knowledge."

Hemoglobins

Although he continued to use immunological data from his first publication (Wolfe et al., 1950) for more than thirty years, he had already started to switch to protein sequencing ten years earlier. In a longer temporal view of Morris's contributions, he, in part, reflects the history of biology for the period in which he found himself. When DNA sequencing became available, he was right there, as well. The underlying theme has not been technology, however, but rather, its use to probe fundamental questions at their next level of accessibility.

The protein chosen first for sequencing was hemoglobin. Using it, Morris said, "I think we were the first to get hard evidence of Darwinian evolution." He could do so because Perutz had analyzed the three-dimensional structure of hemoglobin and developed an idea of the function of each part of the molecule. Morris focused on the positions involved in what is called the Bohr effect—the cooperation between the subunits responsible for unloading oxygen in the tissues. Since globin protein sequences were already available for a broad range of taxa, it was possible to reconstruct ancestral sequences at the nodes of the tree.

We found that the sites concerned with cooperativity showed a big burst of change with the emergence of the jawed vertebrates and kept going on this change until the amniotes emerged. Then these sites became very slow evolving, even more conserved than the heme binding sites. That's what we emphasized in the paper (Barnabas et al. 1972; Goodman et al. 1971; Goodman et al. 1974). I think that I was one of the first to use the concept of using this three dimensional structural data to compare for a protein—or

a protein family—the changes in certain sites both early and then later in evolution and to draw some conclusions as to whether we thought they were neutrally evolving, or under stabilizing selection, or at some stage under positive selection. I think that was one of the first papers to show that this could be done in a meaningful way. Now it's rather commonly done.

Hemoglobin was not only the vehicle for first showing Darwinian evolution. Later, working now at the DNA level, it was also the vehicle for showing adaptive evolution (Bailey et al. 1992; Bailey et al. 1991; Koop et al. 1986). Recalling this, Morris said, "Using nucleotide sequences of the globins, not just the amino acid sequences, and comparing the non-synonymous changes to synonymous…we provided some evidence that when there was a big burst of non-synonymous change [nucleotide change that changes an amino acid] that seemed greater than what you'd expect in a neutral state, then you might draw the conclusion that positive selection was going on."

The hominoid slowdown

The questions addressed here were ones that occupied Morris for much of his career—the rate of the molecular clock and neutral evolution versus adaptive positive selection. Morris first got hints of an apparent slowdown in hominoid evolution early in his career, from serological comparisons of proteins. As he remembered, "I never liked the idea too much of a universal molecular clock." In 1961, Morris first proposed that rates of molecular evolution were slower in hominoid primates compared to other mammals. This proposal was elaborated in other studies published by Goodman in 1962 and 1963 (Goodman, 1962a, b, 1963a, b). This concept has come to be known as the hominoid slowdown. Hominoids are the group of primates that include humans, chimpanzees, bonobos, orangutans, gibbons/siamangs, and their extinct relatives.

In 1971, Morris published a notable paper in *Nature*, "Molecular evolution in the descent of man" (Goodman et al. 1971), that was opposed to the idea of a universal clock. Years later he and others attributed decreasing mutation rates to both lengthened generation times and the evolution of more efficient DNA repair mechanisms in hominoids. Whatever the cause, however, the existence of such a slowdown in what had been considered to be a "universal molecular clock" raised the pragmatic question of how to determine evolution rates across lineages. Here, Morris proposed what he called a "local molecular clock" to account for this variation, and he further proposed that it be calibrated or "set" by using well-calibrated fossils. In this way, he and his colleagues, and later others, could show that apes have slower rates of evolution than Old World

monkeys. The concept of "local" or "relaxed" molecular clocks is now part of the toolkit used by others to estimate rates of species evolution and divergence.

In presenting the original immunological data supporting the hominoid slowdown in molecular evolution—wherein Morris conducted a series of experiments that demonstrated no antigenic divergence among homologous human, chimpanzee, bonobo, and gorilla proteins, and little antigenic divergence among homologous proteins from these four species with those of orangutans and gibbons—Morris noted that similar observations had been made by Nuttall in the early twentieth century (Nuttall 1904). However, Morris extended this work greatly by grasping the phylogenetic implications of it. He noted that lack of antigenic divergence among taxa likely reflected a great deal of similarity in the amino acid sequences that formed the building blocks of the protein polypeptides. This conclusion was indirect, because the underlying amino acid sequences for the proteins were unknown at the time. Moreover, Morris observed that antigenic divergences were greater within platyrrhine and strepsirrhine primates, as well as within bovids, than was observed within hominoids. These observations led Morris to infer that humans, the two chimpanzee species, and gorillas must be more closely related to each other than they were to other hominoids such as orangutans and gibbons.

Morris proposed two primary reasons for a slowdown in hominoid molecular evolution. The first was that hominoids have slower rates of reproduction than non-hominoids (Goodman 1962a, b). Therefore, in the same amount of evolutionary time, hominoids had fewer opportunities to introduce new mutations than the number of opportunities afforded to faster-reproducing taxa, such as lemurs. This phenomenon has subsequently been described at the nucleotide sequence level as the generation time effect (Wu and Li, 1985).

The second reason Morris proposed was that rates of molecular evolution were slower in hominoids relative to other taxa due to maternal immunization to fetal antigens. Because the placenta is a semi-allograft (Medawar 1953), the maternal immune system likely recognizes paternally derived alleles expressed in the placenta that differ from the maternal alleles as non-self. Therefore, Morris speculated, there is strong selection pressure against the expression of these non-self alleles early in gestation. He suggested that natural selection might be maintaining homozygous alleles in hominoids as a means for preventing maternal rejection of the developing fetus (Goodman 1963c).

Morris's pioneering work on serum protein evolution constituted a shift in the prevailing paradigm regarding human evolution. It broke down the divide between humans and

the "great apes" (i.e., chimpanzees, gorillas, orangutans) by demonstrating that humans had more affinity to some great apes than to others and that chimpanzees and gorillas are more similar to humans than they are to orangutans. In later years, Morris elaborated his view on human classification by going so far as to classify humans and chimpanzees as separate subgenera in the genus Homo (Goodman et al. 1998, Wildman et al. 2003). Moreover, the hominoid slowdown presented a paradox, because it showed that molecular evolution is slow in the group of primates that exhibit rapid morphological evolution, the most dramatic example of which includes the emergence of the enlarged human neocortex and the remodeling of the human pelvis.

In order to move research on the hominoid slowdown beyond the level of immunological divergence, Morris subsequently undertook a series of studies based on the sequences of amino acids, and later, the sequence of nucleotides. These studies confirmed the existence of a rate slowdown in hominoids relative to other primates and mammals. One of Morris's important achievements in this area relates to the evolution of non-coding DNA sequences. A problem with the hominoid slowdown was the principle of Darwinian natural selection. Because many serum proteins perform important functions, there is likely selection pressure against novel mutations. Therefore, it is reasonable to speculate that the hominoid slowdown was partly due to increased selection pressure, rather than extrinsic factors such as reduced rates of reproduction and the evolution of better DNA repair mechanisms. Morris reasoned that relative to amino acid or protein-coding DNA sequences, non-coding DNA would be relatively free from the constraints of natural selection. Indeed, emerging work in the 1970s and through the 1990s demonstrated that non-coding DNA evolves at a more rapid rate than does the more functionally constrained coding sequence. Morris felt a strong test of the hominoid slowdown idea would lie in the examination of evolutionary rates of non-coding DNA. Using multiple sequence alignments from the orthologous sequences in the flanking region of beta hemoglobin gene cluster in a wide range of mammals, Morris and his colleagues calculated rates of nucleotide substitution (Bailey et al. 1992; Bailey et al. 1991). These studies clearly demonstrated a rate slowdown in the nucleotide substitution rates of hominoid non-coding DNA compared to other species. This finding was subsequently confirmed on a genome-wide scale (Elango et al. 2006). The mechanisms underpinning the hominoid slowdown are today considered to be the interaction of many parameters, including generation time, effective population size, longevity, and enhanced DNA repair in hominoids. That Morris observed these phenomena before the advent of amino acid

and DNA sequencing technologies speaks to his brilliance as a scientist, and his pursuits of these studies over the span of five decades points to his perseverance.

Adaptive evolution

Starting with his work on hemoglobin, Morris was able to observe the relation of evolutionary change to function. He observed the improvements in function produced by change, and thereafter, the preservation of those improvements. This led Morris and his colleagues to the idea of adaptive evolution and then to development of methods for detecting adaptive evolution on DNA sequences, including 1) the ratio of nonsynonymous and synonymous substitutions for branches in a phylogeny, 2) amino acid substitution rates, and 3) the distributions of substitutions in functionally different regions of the hemoglobin molecule. They suggested that positive selection of adaptive sites is often followed by the fixation of adaptive substitutions and maintenance of these sites via purifying selection.

A phylogenomic approach to human evolution

The last period in Morris's career, encompassing more than twenty years, started with work on the adaptive evolution of the mitochondrial electron transport chain following the observation (Lomax et al., 1992) that a nuclear DNA gene encoding a subunit of cytochrome c oxidase, the terminal complex of the chain, had evolved relatively rapidly on the lineage leading to humans compared with the lineage of other mammals. An observation like that leads to a multitude of questions, and addressing some of them led to a preoccupation and collaboration that lasted the remainder of Morris's life.

Morris's approach was to consider the problem in a phylogenetic framework and ask whether the observation made in humans was unique to humans. When the accelerated rate of evolution was traced to the stem of the anthropoids, he went on to other subunit genes for cytochrome oxidase, and when most of them turned out to share the property of an accelerated evolution rate earlier in primate evolution, he went on to genes in other respiratory complexes. He could, in this way (with primary collaborators Timothy R. Schmidt and the present authors), develop a picture of the electron transport chain undergoing accelerated evolution in anthropoid primates that, in a number of instances, showed the properties of adaptive evolution.

It was almost immediately clear to Morris that evolution was being driven by the unprecedented expansion of the neocortex—the most energetically expensive tissue relative to its weight. Yet the question of how the evolutionary changes helped support a larger

neocortex remains elusive. In a demonstration of Morris's deft response to obstacles, he turned the obstacle into a way forward by going from phylogenetics to phylogenomics. In a series of papers with primary collaborators Kirstin Sterner and the present authors, he showed that an unbiased search of brain expressed genes in anthropoid ancestry for those showing the highest positive selection found the categories mitochondrial and oxidative metabolism.

A summing up

The questions Morris addressed, which were driven largely by his abiding interest in primate phylogeny encompassed, therefore, the forces that move evolution forward—the roles of positive selection, of purifying selection, of neutral change—can be addressed now in the age of high throughput genomic sequencing, with which he overlapped, by an increasing number of genes and genomes.

He was a founder of molecular evolution and an important figure in the research field for nearly fifty years. Among his key contributions are the close affinity of human, chimpanzee, and gorilla; the detection of Darwinian evolution by analyzing DNA sequences; the concept of the Hominoid slowdown and local molecular clocks; the contribution of phylogenetic algorithms and theory; the introduction of genomic methods to identify regulatory sequences; the introduction of comparative methods to identify human specific features; and a relatively mature primate phylogeny. Nevertheless, thinking in an evolutionary framework gave Morris a holistic (or sobering) view of the human species, causing him once to observe that "if you have an evolutionary perspective, you can well imagine that we may become extinct and that there is nothing sacred about us surviving forever."

In addition to a lengthy list of key contributions, Morris left behind a lengthy list of students and collaborators to continue practicing his comparative approach to the molecular underpinnings of human ancestry. Morris was open, welcoming, and inclusive, attracting what has turned out to be nearly two dozen graduate and postdoctoral students, of whom many have gone on to notable careers. Even beyond that, he has managed to collaborate with a surprising number of his colleagues at Wayne State University, drawing them into his sphere by calling upon their expertise and applying it to questions of human origin. During the hemoglobin years, the protein chemists and physiologists Robert Johnson and Daniel Walz were among them, as well as nearby colleagues Deborah Gumucio and (for a time) Francis Collins. In the mitochondrial and neuroscience years, Maik Hüttemann, Gregory Kapatos, Monica Uddin, and Leonard

Lipovich from Wayne State were drawn in, again along with workers at other institutions, primarily Chet Sherwood, Christopher Kuzawa, and Patrick Hof, among others.

In 1991, Morris founded the journal Molecular Phylogenetics and Evolution and served as its editor-in-chief until his death. Under his leadership it became a thriving journal and a leader in featuring studies of phylogenetics and evolution. He received a number of the highest awards Wayne State University bestows, including, in 2000, the Distinguished Service Award from the Board of Governors. It was also in this period that external recognition increasingly came to him. In 1996 he was elected a fellow of the American Association for the Advancement of Science, in 2002 Morris was awarded the American Association of Physical Anthropologists' Charles Darwin Lifetime Achievement Award, and the same year he was elected to membership in the U.S. National Academy of Sciences.

Morris was pre-deceased by his wife of sixty-one years, Selma Goodman, and is survived by three children—Louise, Julia, and David—and a grandson.

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