NATIONAL ACADEMY OF SCIENCES

WALTER MONROE FITCH
1929–2011

A Biographical Memoir by
FRANCISCO J. AYALA

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Walter M. Fitch

WALTER MONROE FITCH

May 21, 1929–March 10, 2011

BY FRANCISCO J. AYALA

WALTER MONROE FITCH WAS born on May 21, 1929, in San Diego, California, where he attended primary and secondary school. He went to the University of California, Berkeley, where he received an A.B. in chemistry (1953) and a Ph.D. in comparative biochemistry (1958). After a series of postdoctoral appointments, in 1962 he joined the Department of Physiological Chemistry at the University of Wisconsin Medical School in Madison, where he was an assistant professor (September 1962-August 1967), associate professor (September 1967-August 1972), and professor (September 1972-September 1986). He was a visiting professor, Population Genetics Laboratory, University of Hawaii Honolulu (September 1973-July 1974); visiting professor, Department of Earth and Space Sciences, University of California, Los Angeles (August 1981-July 1982); and visiting professor, Department of Mathematics, University of Southern California, Los Angeles (January-June 1985).

In 1986 Walter returned to his native California as a professor in the Department of Biological Sciences at the University of Southern California, Los Angeles. Three years later he moved to the Department of Ecology and Evolutionary Biology at the University of California, Irvine (UCI), where he was a professor from 1989 until 2009 and professor emeritus until 2011.

In the second half of the first decade of the 2000s Walter's health deteriorated owing to various ailments, leading to his retirement in 2009, although he continued to come to his office and to write. He passed away peacefully in his sleep in the early morning of March 10, 2011. The family held a memorial service at UCI's University Club on April 8, 2011. UCI's School of Biological Sciences held a memorial on May 26, 2011, at the Beckman Center of the National Academies in Irvine. Walter Fitch is survived by his wife, Chung Cha, formerly Ziesel; two daughters; one son; two stepdaughters; and seven grandchildren.

Walter Fitch is acknowledged as the founder of the discipline of molecular phylogenetics, the reconstruction of evolutionary phylogeny using molecular data, which is now an enormously active field of research and publication, perhaps the most intensely used method of ascertaining the evolutionary history of living organisms and the one method that can incorporate all sorts of organisms, from bacteria and protozoa to plants and animals, using a single, all-encompassing trait, a chosen DNA sequence or protein molecule. Thus, Fitch also counts as one of the earlier pioneers of the now enormous field of molecular evolution, currently represented by scores of journals and treatises, thousands of scholarly papers, dozens of academic departments and hundreds of courses in universities and other institutions of higher learning, and thousands of research scientists.

Walter's early publications, up to 1964, are in biochemistry, such as three papers published in 1959 and 1960 in the *Journal of Biological Chemistry* concerning glycolytic enzyme activities in the liver of normal and diabetic rats, and three papers published in 1961 in the *Archives of Biochemistry and Biophysics* focused on glucose and dietary metabolism also in rats. All but one of these papers have Fitch as the first author but include I. L. Chaikoff, his postdoctoral mentor, as coauthor. After becoming an assistant professor at the University of Wisconsin, Fitch changed his research topics. First, there is a series of three papers with Fitch as sole author, on "Studies on a Cholinesterase of *Pseudomonas fluorescens* I, II, and III," published in *Biochemistry* and the *Journal of Biological Chemistry* in 1963 and 1964. Then there is a radical shift from biochemistry to molecular evolution, represented by five papers, four of them single authored, published between 1964 and 1966, on subjects such as nucleotide codon sequences, amino acid composition in phages, gene duplication, and evolutionary homology, three of them published in the *Journal of Molecular Biology,* one in *Virology,* and one in the *Proceedings of the National Academy of Sciences U. S. A.* The subject of molecular evolution would overwhelmingly remain his predominant research subject for the remaining 45 years of his life.

MOLECULAR PHYLOGENY

In January 1967 Walter M. Fitch and Emanuel Margoliash published "Construction of Phylogenetic Trees" in *Science,* a paper that may well be considered the founding document of molecular phylogenetics and one that would forever affect the way biologists reconstruct the phylogeny of living species. Based on the amino acid sequence of a small protein, cytochrome *C,* Fitch and Margoliash had, astonishingly, constructed a phylogenetic tree of 20 very diverse species, from yeast, through insects, fish, reptiles, birds, and mammals, to humans, a tree that was "remarkably like the classical phylogenetic tree that has been obtained from purely biological data" (Fitch and Margoliash, 1967, p. 279). The tree encompassed more than 1 billion years of evolution, from their last common ancestor to the 20 living species. The possibilities were astounding: organisms carry thousands of genes and proteins, every one recording the same evolutionary history. One and another and another gene or protein could be studied so as to achieve as much precision as wanted in a phylogeny. In order to determine the phylogeny Fitch and Margoliash formulated the minimal "mutation distance," an "analytical method [that] has general applicability" (Fitch and Margoliash, 1967, p. 279), subject to quantification and statistical analysis.

There were important antecedents. DNA, RNA, and proteins had been called "information macromolecules" (Vogel et al., 1963) because they convey evolutionary information in the linear sequence of their nucleotide or amino acid components, similarly as the sequence of letters in an English text conveys semantic information. Zuckerkandl and Pauling (1965), among others, had noticed that the number of component differences between homologous molecules obtained from different organisms seemed to be proportional to the time elapsed since the evolutionary divergence of the species, or in the case of paralogous genes—genes that arise by duplication—since the time a gene duplication may have occurred. In their investigation, focused primarily on different hemoglobin polypeptides from the same or different species, Zuckerkandl and Pauling had postulated that most nucleotide or amino acid replacements would be adaptively neutral and "*there may thus exist a molecular evolutionary clock*" (Zuckerkandl and Pauling, 1965, p. 148, their emphasis).

But the emergence of molecular phylogenies as a major field of study can be traced to the 1967 publication of Fitch and Margoliash's paper in *Science* mentioned above. Margoliash, a distinguished biochemist at the Abbott Laboratories in North Chicago, had obtained for several species the amino acid sequence of cytochrome *C*, a small protein involved in cell respiration, consisting of about 104 amino acids. In collaboration with Walter, Margoliash extended the sequences to a total of 20 extremely diverse species, as noted above. The reconstruction, using only one small protein, of the evolutionary history of a set of species that had shared their last common ancestor more than 1 billion years ago was a remarkable outcome. The paper introduced the method of "mutation distances" as an algorithm to reconstruct the evolutionary history of species, based on a distance matrix that included the number of amino acid differences among the aligned protein sequences of all pairs of the 20 species.

In the ensuing years and beyond, Walter would formulate additional concepts, computer algorithms, and statistically reliable methods of wide applicability in the investigation of molecular evolution. We owe to Walter useful concepts such as "covarions" (concomitantly variable codons), neutral mutation, rate of fixation of nucleotide replacements, orthologous versus paralogous genes, molecular convergence versus divergence, minimal mutation distance, parsimony, and much more. The *Science* paper and Walter's ensuing contributions largely account for the rapid expansion of molecular evolution studies, which now account for a sizeable parcel of evolutionary research, particularly concerning molecular phylogeny, rates of evolution and the molecular clock. A rush of publications followed that paper, for example, some notable contributions of Motoo Kimura: "Evolutionary Rate at the Molecular Level" (1968), "The Rate of Molecular Evolution Considered from the Standpoint of Population Genetics" (1969), and (with Tomoko Ohta) "Protein Polymorphism as a Phase of Molecular Evolution" (1971).

Walter's contributions to the conceptual and methodological development of molecular evolution extended throughout his career, with a bibliography consisting of more than 180 peer-reviewed papers. One long paper, published in 1970, chock-full of new ideas, precisely defined terms, algorithms, and specific methodologies, is “The Usefulness of Amino Acid and Nucleotide Sequences in Evolutionary Studies” (Fitch and Margoliash, 1970) In 1971 Walter published “Towards Defining the Course of Evolution: Minimum Change for a Specific Tree Topology” (Fitch, 1971), designated a Citation Classic by *Current Contents.*

MOLECULAR CLOCK

Paleontology, comparative anatomy, biogeography, and other traditional disciplines continue to be used in the reconstruction of phylogeny, and they have distinctive advantages for certain purposes, notably paleontology for the investigation of the morphology, distribution, and other characteristics of extinct species. But molecular evolutionary studies have three notable advantages over classical disciplines. One is *quantification*, because the molecular information is readily quantifiable. The number of units (nucleotides or amino acids) that are different is easily established when the sequence of units is known for a given macromolecule in different organisms. It is simply a matter of aligning the nucleotides or amino acids between two or more species and counting the differences. The second advantage is *universality*, because comparisons can be made between very different sorts of organisms. There is very little that paleontology or comparative anatomy can say when, for example, organisms as diverse as yeasts, pine trees, and human beings are compared, but there are numerous DNA and protein sequences that can be compared in all three. The third advantage is *multiplicity*. Each organism possesses thousands of genes and proteins, every one of which reflects the same evolutionary history. If the investigation of one particular gene or protein does not satisfactorily resolve the evolutionary relationships of a set of species, additional genes and proteins can be investigated until the matter has been settled.

A theory that emerged early in the field asserts that molecular evolution may be used as a molecular clock of evolution, a method to determine the time of past evolutionary events, including the times in remote history when two species or groups of species diverged from one another, or when a new species or group may have emerged. The underlying construct was the observation that some—perhaps a majority—nucleotides in DNA sequences or amino acids in proteins may not affect function and, thus, might not be subject to natural selection. Such nucleotides or amino acids are called "neutral" and, according to the molecular clock theory, are expected to have evolved at stochastically constant rates, that is, their probability of replacement remains constant through time. The number of neutral differences between two species could consequently be used as a molecular clock, just as radioactive decay is used to measure time, precisely because radioactive decay occurs, for a given particular element in the periodic table, at a stochastically constant rate.

Walter developed increasingly sophisticated methodologies to test the theory of the molecular clock, that is, the constancy of molecular evolution. Notable contributions include "An Examination of the Constancy of the Rate of Molecular Evolution" (Langley and Fitch, 1974) and "Molecular Evolutionary Clocks" (Fitch, 1976), "The Estimate of Total Nucleotide Substitutions from Pairwise Differences Is Biased" (Fitch, 1986a), and more recently "The Superoxide Dismutase Molecular Clock Revisited" (Fitch and Ayala, 1994a).

Walter demonstrated that the variance in the rate of molecular evolution was statistically larger than expected under the theory of the molecular clock and, thus, the underlying assumption of "neutral" replacements in DNA or proteins was not correct. However, he demonstrated that by combining the data from several genes or proteins, the average number of differences observed converged to the expected time since the divergence of the species investigated. Typical of Walter's approach to science was noticing that a particular theory could be used to reach valuable conclusions, even though the theory might not be precisely correct.

INFLUENZA AND VACCINES

In 1986 Fitch and collaborators published two papers, one in *Science* and the other in *Virology*, on the evolution of influenza viruses with the important inference that genes in influenza viruses evolved at largely uniform rates (Buonagurio et al., 1986a,b). The potential significance of this discovery was that the near-future evolution of influenza-causing viruses could be predicted, making possible the development of vaccines for the ensuing flu season.

For the last two decades of his life Fitch would apply his considerable evolutionary knowledge and skills to the same issue, namely, the investigation of the patterns of evolution of viruses of health import, particularly the influenza viruses. This work became all-important in the development of flu vaccines. The investigation of the numerous virus strains that evolve during each flu season allowed Walter and his collaborators to predict which strain or strains of the virus would become dominant during the ensuing flu season and, thus, the ones to use in developing the flu vaccine. Notable investigations, in addition to the two mentioned above, include "Positive Darwinian Evolution in Human Influenza A Viruses" published in the *Proceedings of the National Academy of Sciences U. S. A.* (Fitch et al., 1991) and "The Variety of Human Virus Evolution," in *Molecular Phylogenetics and Evolution* (Fitch, 1996).

Particularly significant for the development of flu vaccines were several papers coauthored with Robin M. Bush and others, such as a paper published in *Science* in 1999, "Predicting the Evolution of Human Influenza A" (Bush et al., 1999) and

"Effects of Passage History and Sampling Bias in Phylogenetic Reconstruction of Human Influenza A Evolution" published in the *Proceedings of the National Academy of Sciences U. S. A.* (Bush et al., 2000). An important collaborator in these papers was Nancy J. Cox, from the Centers for Disease Control and Prevention in Atlanta, the source of the influenza virus strains and sequences used in the phylogeny reconstruction. Two of Fitch's last research papers, published with different coauthors, concerned virus evolution, "Different Epidemic Potentials of the HIV-1B and C Subtypes" in the *Journal of Molecular Evolution* (Salemi et al., 2005) and the influenza virus again, "A Statistical Phylogeny of Influenza A HSN1" in the *Proceedings of the National Academy of Sciences U. S. A.* (Wallace et al., 2007).

EVOLUTION: THEORY AND EXPERIMENTS

The last two decades of Fitch's research career, coinciding with his move from Wisconsin to California, were extremely productive, counting 80 publications out of his total output of 180. In addition to his research on the evolution of the flu and other viruses, Fitch published extensively on phylogenetic issues, developing new algorithms or enhancing previous ones. Examples are four papers published in 1986: "The Estimate of Total Nucleotide Substitutions from Pairwise Differences Is Biased" (Fitch, 1986a); "Unresolved Problems in DNA Sequence Analysis" (Fitch, 1986b); "Detecting Internally Repeated Sequences and Inferring the History of Duplication" (Fitch et al., 1986); "An Estimation of the Number of Invariable Sites is Necessary for the Accurate Estimation of the Number of Nucleotide Substitutions since a Common Ancestor" (Fitch, 1986c). Notable analytical contributions to phylogeny also include, among others, Shoemaker and Fitch (1989), Williams and Fitch (1989), Fitch (1992, 1995, 2000), McClure et al. (1994), Miyamoto and Fitch (1995a,b), and Finkelstein et al. (1998).

Fitch's last two decades also include research publications on a number of molecular evolutionary subjects, including several with William R. Atchley on the phylogeny of inbred strains of mice (Fitch and Atchley, 1987; Atchley and Fitch, 1991, 1993) and other topics (Atchley et al., 1994, 2000; Atchley and Fitch, 1995). During these two prolific decades, Fitch published on issues such as the origin of the genetic code: "The Evolution of Life: An Overview of the General Problems and a Specific Study of the Origin of the Genetic Code" (Fitch and Upper, 1988a) and "The Phylogeny of tRNA Sequences Provides Evidence for Ambiguity Reduction in the Origin of the Genetic Code" (Fitch and Upper, 1988b).

ROOTING FOR EVOLUTION AND THE COMMUNITY OF SCIENTISTS

In 1989 shortly after his joining the Department of Ecology and Evolutionary Biology at the University of California in Irvine (UCI), Walter and I embarked on the planning of several colloquia, sponsored by the National Academy of Sciences, intended to commemorate significant anniversaries of four major books in the formulation of the modern theory of evolution. Our purpose was to update the knowledge concerning the topics broached by the four classics. In addition, we sought to enhance the visibility of evolutionary studies among the members of the National Academy of Sciences and the scientific community at large. The colloquia were held at the Arnold and Mabel Beckman Center of the National Academies, which is adjacent to the UCI Campus. The colloquium papers were published in the *Proceedings of the National Academy of Sciences U. S. A.* (also published as separate books by the National Academy Press). The four colloquia were "Tempo and Mode in Evolution" (January 27-29, 1994) commemorating the 50th anniversary of G. G. Simpson's book with the same title (Fitch and Ayala, 1994b); "Genetics and the Origin of Species" (January 30-February 1, 1997) on the 60th anniversary of Theodosius Dobzhansky's classic book with the same title (Ayala and Fitch, 1997); "Variation and Evolution in Plants and Microorganisms" (January 27-29, 2000) on the 50th anniversary of G. L. Stebbins's *Variation and Evolution in Plants* (Ayala et al., 2000); and December 16-18, 2004, just a few months before Ernst Mayr passed away, at 100 years of age, and 62 years after publication of his classic book with the same title, "Systematics and the Origin of Species" (Hey et al., 2005).

The contributions of Walter M. Fitch to science go beyond his research and scientific publications and include a major role in the development of the molecular evolution community of scientists. In 1983 Fitch became the first editor in chief of the newly founded journal *Molecular Biology and Evolution,* one of the most visible and important journals dedicated to molecular evolution. Fitch was editor in chief for its first 10 years, from December 1983 (volume 1, number 1) through July 1993 (volume 10, number 4). In the "Introductory Statement" explaining the scope and justification of a new journal, Walter called attention to the journal's title, which included *and*, not *or*, "that is, a paper must contain material about macromolecules *and* about their evolutionary implications." *Molecular Biology and Evolution*'s record of significant publications starts with the very first issue, which included papers by Nobel Laureate M. F. Perutz, "Species Adaptation in a Protein Molecule," and by distinguished evolutionists, such as John C. Avise, Howard Ochman, Robert K. Selander, Motoo Kimura, Wen-Hsiung Li, Takashi Gojobori, Barry G. Hall (who would become editor starting in September 1993), and by Fitch himself ("Evolution of Antibiotic Resistance Genes: The DNA Sequence of a Kanamycin Resistance Gene from *Staphylococcus aureus*," in collaboration with Gary S. Gray).

Walter Fitch was the first president of the Society for Molecular Biology and Evolution. Established in January 1993, the society has met annually ever since. One feature at the annual meeting is the Walter M. Fitch Symposium, a forum for young investigators. The Walter M. Fitch Award was established to honor the best presentation at the symposium.

Fitch was a longtime member of the National Center for Science Education (NCSE), dedicated to defending the teaching of evolution in public schools. He participated at various times in the center's activities. He was a member of the working group that wrote *Evolution, Science, and Society: Evolutionary Biology and the National Research Agenda* (National Science Foundation, 1998) and contributed "Evolution is a Fact" to *Evolutionary Science and Society: Educating a New Generation* (Fitch, 2005). In 2002 he delivered the plenary address at the meeting of the Southern California Academy of Sciences on "Creation Science: An Oxymoron." He occasionally engaged in public debates with creationists. At the University of California, Irvine, he taught for years a course for nonbiology majors on "Creation and Evolution." At the time of his death he was finishing the book *Logic, Rhetoric, and Science: And Why Creationism Fails at All Three,* which is expected to be published in 2012 by the University of California Press.

After his election to the National Academy of Sciences in 1989, he repeatedly served on the Class II Membership committee as either representative of Section 27, "Population, Biology, Evolution, and Ecology," for each of four years, 1995-1998, or a member-at-large, 1993 and 1994. He was chair of Section 27, 1995-1998.

RECOGNITION AND HONORS

Walter Fitch received distinguished honors throughout his career, including election to the three most honorific societies for scientists in the United States: the National Academy of Sciences in 1989; the American Academy of Arts and Sciences in 1991; and the American Philosophical Society in 2000. Fitch was elected a foreign member of the Linnean Society (London) in 1994, and received a doctor *honoris causa* degree from North Carolina State University in 2001. Other honors include Marker Lecturer, Pennsylvania State University, 1996; Wilhelmine E. Key Invitational Lecture, American Genetic Association, 1999; and the Outstanding Scientist Award, Center for the Study of Evolution and the Origin of Life, University of California, Los Angeles, 2001.

In 2005 Walter Fitch was awarded the UCI Medal, the greatest distinction awarded by the University of California. UCI also recognized him with the Distinguished Faculty Award for Research in 1998. The Walter M. Fitch Symposium held yearly since 1993 at the annual meeting of the Society for Molecular Biology and Evolution, and the Walter M. Fitch Award presented each year are two ways that the society seeks to honor him.

PERSONAL REMINISCENCES

Walter and I first met in late June 1969. Theodosius Dobzhansky, the eminent evolutionist, and I were driving across the country from New York to California to the Mather Station of the Carnegie Institution near the entrance to Yosemite National Park, where we would do field research with *Drosophila* flies in the Sierra Nevada mountains. One stop along the way was Madison, where we wanted to visit with two or three scientists at the University of Wisconsin. One of them was Fitch.

Walter Fitch and Emanuel Margoliash had published in 1967 in *Science,* as mentioned above, "Construction of Phylogenetic Trees," a paper that—as Dobzhansky had told me when all excited he walked into my lab at Rockefeller University the morning he received the January 20, 1967, issue of *Science*—"would impact forever the way in which we reconstruct the phylogenies of living species."

More recently Fitch and Margoliash had written, at Dobzhansky's invitation, a long paper, "The Usefulness of Amino Acid and Nucleotide Sequences in Evolutionary Studies" (1970), still in press at the time of our visit, where they belabored their methods and a variety of useful concepts, such as "covarions" (concomitantly variable codons), neutral mutations, rate of fixation of nucleotide replacements, convergence versus divergence, and more. We wanted to meet Walter, this incisive evolutionist genius, as we saw him, then an assistant professor in the Department of Physiological Chemistry at the University of Wisconsin-Madison.

In 1975 I organized a symposium entitled "Molecular Study of Biological Evolution," sponsored by the Society for the Study of Evolution and the American Society of Naturalists, held at the University of California, Davis, on June 17 and 18. The papers were published as chapters in a book, *Molecular Evolution* (Ayala, 1976), eventually reprinted in English and translated into foreign languages. The early chapters dealt with molecular variation *in* populations; chapters 6 to 13 with variation *between* populations. Walter authored chapter 10, "Molecular Evolutionary Clocks" (Fitch, 1976, pp. 160-178), where with his distinctive analytical acumen Fitch introduced to the field of molecular evolution concepts such as measurability, reliability, reciprocity, and regularity. Walter stayed in Davis for several days, attending talks, while we also shared meals, talked a lot with each other, and developed what would become a lasting friendship.

Over the next decade Walter and I frequently met at scientific meetings and other events in the United States and abroad. In 1986 Walter moved from the University of Wisconsin to the University of Southern California in Los Angeles. In the fall of 1987 I moved from Davis to the relatively new campus of the University of California in Irvine, some 45 miles from USC. Shortly thereafter, in 1988, Walter invited me to give a seminar at USC, and I used the occasion to begin the process of persuading Walter to move to UCI. Over the next several months he repeatedly visited UCI, where he was appointed professor in the Department of Ecology and Evolutionary Biology, starting on September 1, 1989, a position he held until his retirement in June 2009.

Other important events in Walter's life happened in 1989. In April he was elected to the National Academy of Sciences of the U.S.A. On September 9 he married Chung Cha (formerly Ziesel) in a private ceremony on the front patio of the fairly new Beckman Center of the NAS, at the edge of the UCI campus. Hana, my wife, and I were the witnesses. We had known Chung Cha for more than a year. She already was, as she continues to be, our intimate and cherished friend.

At UCI Walter taught and his scientific accomplishments continued to blossom in number and significance, as earlier documented. Walter and I published several joint papers on topics of molecular evolution, particularly the theory of the molecular clock of evolution. At UCI, Walter was chair of the Department of Ecology and Evolutionary Biology from July 1990 to June 1995.

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