

Paradox and Persuasion: Negotiating the Place of Molecular Evolution within Evolutionary Biology

MICHAEL R. DIETRICH

*History and Philosophy of Science Program
University of California, Davis
Davis, California 95616*

Introduction

Spurred on by tremendous advances in the 1950s, molecular biologists of the early 1960s developed a confidence in their emerging field that bordered on imperialistic zeal.¹ To evolutionary biologist Theodosius Dobzhansky, molecular biology had become a “glamour field”, attracting old and young alike, and gave currency to the notion that “the only worthwhile biology is molecular biology”.² Only twenty years earlier, evolutionary biologists had celebrated their own achievement of a modern synthesis unifying diverse interests in paleontology, genetics, systematics, zoology, and botany.³ However, as molecular biologists began to ride roughshod over the achievements of the evolutionary synthesis, its principal architects, Theodosius Dobzhansky, Ernst Mayr, and G. G. Simpson, began an unprecedented counterattack on the place of molecular biology. Dobzhansky, Mayr, and Simpson did not want to put an end to molecular biology but were trying to articulate a relationship between molecular biology and organismal biology that allowed the two to be integrated instead of the one being reduced to the other.⁴ They did this primarily by making distinctions between “ultimate” and “proximate” explanation, “Cartesian” and “Darwinian” science, and causation at the molecular and organismal levels.

As these distinctions were being offered, the field of molecular evolution was also coming into its own. Before the discovery of the structure of DNA by

¹ E. O. Wilson, *Naturalist* (Washington, D.C.: Island Press, 1994), 218–237.

² Theodosius Dobzhansky, “Biology, Molecular and Organismic”, *Amer. Zool.*, 4 (1964), 443–452; quotation, 443.

³ Vassiliki B. Smocovitis, “Unifying Biology: The Evolutionary Synthesis and Evolutionary Biology”, *J. Hist. Biol.*, 25 (1992), 1–65; Smocovitis, *Unifying Biology: The Evolutionary Synthesis and Evolutionary Biology* (Princeton: Princeton University Press, 1996).

⁴ John Beatty, “Evolutionary Anti-reductionism: Historical Reflections”, *Biol. Phil.*, 5 (1990), 199–210.

James Watson and Francis Crick in 1953, Marcel Florkin had revived interest in molecular evolution and the use of molecular characters in phylogeny reconstruction.⁵ While comparisons of crystallographic features of large molecules such as starch had been used as data for systematics as early as 1907,⁶ during the 1950s new techniques in immunology and biochemistry made the use of molecular features much more attractive. These technological innovations allowed researchers to measure immunological similarity between molecules and to compare the amino-acid sequences of some proteins with greater ease and precision. From an evolutionary perspective one of the most important features of these innovations was that they allowed researchers to identify degrees of similarity and difference between the same molecules in different species as well as similarities and difference between similar molecules in the same species. These measures of similarity could then be used to reconstruct phylogenies for the different species or the different molecules within a species.

Dobzhansky, Mayr, and Simpson attended many of the early conferences on molecular evolution and were influential in the direction of its development and in the type of relationship posited between molecular evolution and organismal evolution. Although Simpson was more oppositional than Dobzhansky and Mayr, they all employed similar strategies for negotiating the place of molecular biology and molecular evolution. In the case of molecular evolution, for instance, they argued for the causal distinctiveness of organismal evolution and molecular evolution, that is, natural selection acted only on the organismal level. From the perspective of the architects of the synthesis, this distinction called for the integration of molecular evolution with evolutionary biology. I will argue that in response to this distinction and to the perception of opposition between molecular and organismal biology expressed most notably by Simpson, some molecular evolutionists began to articulate their position relative to evolutionary biology as a whole by invoking a molecular/morphological paradox and its resolutions.

The molecular/morphological paradox drew upon the growing belief among molecular evolutionists in the 1960s that the rate of evolution on the molecular level was constant; that there was a molecular clock. Because the rate of evolution at the organismic level was thought to be highly variable, the constancy at the molecular level was dubbed paradoxical. The paradox was resolved, at least initially, by removing natural selection as the predominant

⁵ Marcel Florkin, *Biochemical Evolution* (New York: Academic Press, 1949).

⁶ E. T. Reichert had pioneered the use of molecular characters in phylogeny reconstruction beginning in 1907, but Reichert inspired few followers until the 1950s. See especially, Reichert and A. P. Brown, *The Differentiation and Specificity of Corresponding Proteins and Other Vital Substances in Relation to Biological Classification and Organic Evolution: The Crystallography of Hemoglobins* (Washington, D.C.: Carnegie Institution, 1909).

cause of evolution at the molecular level. During the early 1970s proponents of the molecular clock, especially Allan Wilson, often invoked the molecular/morphological paradox and always had a resolution ready at hand.⁷ It is in my contention that the paradox became a tool of persuasion; it was always offered by molecular evolutionists *with a resolution* and so seemed to resolve tensions between the study of evolution at the molecular and morphological levels. The appeal of this paradox and its resolution was fostered, I argue, partly by the way Dobzhansky, Mayr, and Simpson guided the articulation of the relationship both between molecular biology and evolutionary biology and between molecular evolution and organismal evolution. As a result of the way these relationships were articulated, particular resolutions of the molecular/morphological paradox became powerful tools of advocacy for the contributions of molecular evolution. On a more general level, the molecular/morphological paradox and its initial resolution is emblematic of the persuasive power of “paradox” and its resolution in scientific controversies. Paradoxes and resolutions, such as this one or the developmental paradox⁸ act as devices for the advocacy of new fields of research by articulating relationships among existing fields that are divisive yet reconciliatory.

The Evolutionary Synthesis and the Molecular Biology “Bandwagon”⁹

In the 1940s evolutionary biology came into its own as a field. The evolutionary synthesis had brought together geneticists, systematists, paleontologists, botanists, and zoologists to create a new field called evolutionary

⁷ Allan Wilson, “Protein Structure and the Role of Evolution”, Molecular Biology Seminar, February 14, 1968, 4, Allan Wilson Papers, Bancroft Library, University of California, Berkeley (hereafter AWP); Allan Wilson, Seminar Notes, May 19, 1970, Vancouver, AWP; D. G. Wallace, L. R. Maxson, and Allan Wilson, “Albumin Evolution in Frogs: A Test of the Evolutionary Clock Hypothesis”, *Proc. Nat. Acad. Sci.*, 68 (1971), 3127–3129, at 3129; Allan Wilson, “Selectively Neutral Changes in Protein Evolution”, unpublished MS, 1973, 18, AWP; Allan Wilson, “Is Protein Evolution at the Basis of Organismal Evolution?” Biosystematists Group, February 11, 1975, Berkeley, Calif., AWP; Allan Wilson, Linda Maxson, and Vincent Sarich, “Two Types of Molecular Evolution: Evidence from Studies of Interspecific Hybridization”, *Proc. Nat. Acad. Sci.*, 71 (1974), 2834–2847; Allan Wilson, Vincent Sarich, and Linda Maxson, “The Importance of Gene Rearrangement in Evolution: Evidence from Studies on Rates of Chromosomal, Protein, and Anatomical Evolution”, *Proc. Nat. Acad. Sci.*, 71 (1974), 3028–3030. See also Mary-Claire King and Allan Wilson, “Evolution at Two Levels in Humans and Chimpanzees”, *Science*, 188 (1975), 107–116.

⁸ Jan Sapp discusses the developmental paradox used to articulate a relationship between genetics and embryology: “Concepts of Organization: The Leverage of the Ciliate Protozoa”, in *A Conceptual History of Modern Embryology*, ed. Scott Gilbert (Baltimore: Johns Hopkins University press, 1991), 229–258.

⁹ The term “bandwagon” was used by Ernst Mayr in “The New versus the Classical in Science” (editorial), *Science*, 141 (1963), 763. See also Beatty’s discussion in “Evolutionary Anti-reductionism” (above, n. 4).

biology.¹⁰ Marked by the founding of the Society for the Study of Evolution and the inception of the journal *Evolution* in 1947, this new field had a culture that celebrated unification and the unifying power of the synthesis.¹¹ Although there was not a single theory with which all members of the synthesis community fully agreed, there was certainly an evolutionary constriction as proposed mechanisms of evolution such as saltation, orthogenesis, and the inheritance of acquired characteristics were ruled out.¹² Similarly, great efforts were made to integrate previously divergent areas such as paleontology and genetics. The Committee on Common Problems of Genetics, Paleontology, and Systematics met during the early 1940s and circulated its mimeographed bulletins in an effort to create discussion and better integrate these fields.¹³ By the time of the committee's culminating conference at Princeton in 1947, H. J. Muller felt confident in claiming that the evolutionary biology community was reaching a common point of view.¹⁴

In the wake of the Princeton conference, evolutionary biologists involved in the synthesis increased their commitment to natural selection. Throughout the 1950s population geneticists Sewall Wright and R. A. Fisher actively debated the role of random genetic drift in evolution with the eventual conclusion that natural selection was the most important agent of evolutionary change (panselectionism).¹⁵ Dobzhansky also moved away from drift and toward panselectionism as he struggled to explain patterns of chromosomal change in his landmark "Genetics of Natural Populations" series.¹⁶ This increasing

¹⁰ Ernst Mayr and William Provine, eds., *The Evolutionary Synthesis* (Cambridge: Harvard University Press, 1980); Smocovitis, "Unifying Biology" (above, n. 3); Smocovitis, *Unifying Biology* (above, n. 3); Vassiliki B. Smocovitis, "Organizing Evolution: Founding the Society for the Study of Evolution", *J. Hist. Biol.*, 27 (1994), 241–309; J. Cain, "Common Problems and Cooperative Solutions: Organizational Activity in Evolutionary Studies", *Isis*, 84 (1993), 1–25; J. Cain, "Ernst Mayr as Community Architect", *Biol. Phil.*, 9 (1994), 387–427.

¹¹ Smocovitis, "Unifying Biology" (above, n. 3).

¹² William B. Provine, "Progress in Evolution and the Meaning of Life", in *Evolutionary Progress*, ed. M. Nitecki (Chicago: University of Chicago Press, 1988), 61; Michael R. Dietrich, "Richard Goldschmidt's 'Heresies' and the Evolutionary Synthesis", *J. Hist. Biol.*, 28 (1995): 431–461.

¹³ Cain, "Common Problems" (above, n. 10).

¹⁴ H. J. Muller, "Redintegration of the Symposium on Genetics, Paleontology, and Evolution", in *Genetics, Paleontology and Evolution*, ed. Glenn Jepson, G. G. Simpson, and Ernst Mayr (Princeton: Princeton University Press, 1949) 421–445, at 422.

¹⁵ A detailed account of the debates between Wright and Fisher can be found in William Provine, *Sewall Wright and Evolutionary Biology* (Chicago: Chicago University Press, 1986). See especially chap. 8, 9, 12.

¹⁶ John Beatty, "Dobzhansky and Drift: Facts, Values, and Chance in Evolutionary Biology", in *The Probabilistic Revolution*, Vol. 2, ed. L. Kruger, G. Gigerenzer, and M. Morgan (Cambridge: MIT Press, 1987), 271–311; John Beatty, "Weighing the Risks: Stalemate in the Classical/Balance Controversy", *J. Hist. Biol.*, 20 (1987), 289–319; Richard Lewontin, "Introduction: The Scientific Work of Theodosius Dobzhansky", in *Dobzhansky's Genetics of*

emphasis on natural selection to the exclusion of other agents of evolution represents what Stephen Jay Gould calls the hardening of the synthesis.¹⁷

While the evolutionary synthesis hardened in the 1950s and 1960s, molecular biology was also developing into a field of its own that was often perceived to be in direct competition or conflict with evolutionary biology.¹⁸ E. O. Wilson reports that at Harvard in the early 1960s the brash attitude of James Watson helped polarize the department into those working on the “cutting edge” of biology in molecular biology and those languishing with the concerns of “classical” biology such as evolution and systematics. According to Wilson, the atmosphere was “stifling.”¹⁹ The nonmolecular biologists (known as organismal biologists) were, in Wilson’s words, “forced by the threat [of molecular biology] to rethink our intellectual legitimacy.”²⁰

Evolutionary biologists, at Harvard and elsewhere, responded by defending evolution’s importance for biology and offering a variety of philosophical arguments concerning causation, reduction, and levels of biological organization. The tension between molecular and evolutionary biology began to surface in a public exchange between George Wald, Ernst Mayr, and others over the importance of molecular biology,²¹ and in Ernst Mayr’s 1959 survey of the status of genetics and evolutionary biology. After reviewing the first hundred years of evolutionary biology, boiling down the modern synthesis to two postulates, and surveying future prospects, Mayr ended with an admonition:

We live in an age that places great value on molecular biology. Let me emphasize the equal importance of evolutionary biology. The very survival of man on this globe may depend on a correct understanding of the evolutionary forces and their application to man. The meaning of race, the impact of mutation, whether spontaneous or radiation-induced, of hybridization, of competition, – all these evolutionary phenomena are of the utmost importance for the human species.²²

Natural Populations I–XLIII, ed. R. C. Lewontin, J. A. Moore, W. B. Provine, and B. Wallace (New York: Columbia University Press, 1981), 93–115.

¹⁷ Stephen Jay Gould, “The Hardening of the Modern Synthesis”, in *Dimensions of Darwinism*, ed. Marjorie Grene (Cambridge: Cambridge University Press, 1983), 71–93.

¹⁸ Pnina Abir-Am, “The Politics of Macromolecules: Molecular Biologists, Biochemists, and Rhetoric”, *Osiris*, 7 (1992), 164–191; Smocovitis, *Unifying Biology* (above, n. 3), 174–178.

¹⁹ Wilson, *Naturalist* (above, n. 1), 225.

²⁰ *Ibid.*, 228. Angela Creager describes similar disciplinary tensions at the University of California, Berkeley, in the 1960s between biochemists and self-identified molecular biologists. See Angela Creager, “Wendell Stanley’s Dream of a Free-Standing Biochemistry Department at the University of California, Berkeley”, *J. Hist. Biol.*, 29 (1996), 331–360.

²¹ Smocovitis, *Unifying Biology* (above, n. 3), 1974; Ernst Mayr to Michael Dietrich, personal communication, November 19, 1996.

²² Ernst Mayr, “Where Are We?” *Cold Spr. Harbor Symp. Quant. Biol.*, 24 (1959), 13.

With the Cold War controversy over the genetic effects of radiation raging between Theodosius Dobzhansky and H. J. Muller,²³ Mayr's words probably struck a responsive chord. They are doubly significant given the tensions developing in Mayr's own Harvard Biology Department between molecular and organismal biologists.

Mayr was not alone. In 1961, Dobzhansky took the occasion of his review of Simpson's *Principles of Animal Taxonomy* to assert that although molecular biology was "exciting and thought-provoking", some of it was "intellectually shallow". Molecular biology may have been making "spectacular progress", but, like Mayr, Dobzhansky argued that the "non-molecular aspects of biology happen to be the ones chiefly relevant to understanding man and his place in the universe, to problems of anthropology, sociology, and psychology, in short – to humanism."²⁴ Contentious as these statements may seem, they were only the initial salvo. The issue of the impact of molecular biology was brought to a head for the architects of the synthesis when they began to negotiate the place of the study of molecular evolution in 1962.

Evolution Goes Molecular

In the 1950s and 1960s as interest in molecular biology grew, so did interest in molecular evolution. Marcel Florkin's efforts to promote molecular systematics were joined by others doing similar comparative research as well as research on the evolution of the genetic code and rates of evolution.²⁵ The rise of molecular systematics was strongly tied to technological innovations in immunology and biochemistry that allowed careful comparison of similarities and differences between molecules.

The use of immunological features originated with G. H. F. Nuttall in 1904.²⁶ Nuttall's technique was refined by A. Boyden beginning in 1954, and Boyden's work, in turn, helped form the foundation for serological comparisons in the 1960s by Curtis Williams and Morris Goodman among others.²⁷

²³ See Beatty, "Weighing the Risks" (above, n. 16).

²⁴ Theodosius Dobzhansky, "Taxonomy, Molecular Biology, and the Peck Order", *Evolution*, 15 (1961), 263.

²⁵ Florkin, *Biochemical Evolution* (above, n. 5); Christian Anfinsen, *The Molecular Basis of Evolution* (New York: Wiley, 1959).

²⁶ G. H. F. Nuttall, *Blood Immunity and Relationship* (New York: Cambridge University Press, 1904).

²⁷ A. Boyden, "The Measurement and Significance of Serological Correspondence among Proteins", in *Serological Approaches to Studies of Protein Structure and Metabolism*, ed. W. Cole (New Brunswick: Rutgers University Press, 1954); C. A. Williams and C. T. Wemyss, "Experimental and Evolutionary Significance of Similarities among Serum Protein Antigens of Man and the Lower Primates", *Ann. N. Y. Acad. Sci.*, 94 (1961), 77–92; Morris Goodman,

Williams and Goodman were both concerned with primate evolution and used immunological comparisons as a way of reconstructing the evolutionary phylogeny of the primates.²⁸

More wide ranging comparisons were being done in the early 1960s as a result of breakthroughs in protein sequencing. In 1961, Emil Smith, Emmanuel Margoliash, Gunther Kreil, and Hans Tuppy announced that they had determined the amino acid sequence of cytochrome c by analyzing fragments created by different enzymes (enzymes that cut protein molecules).²⁹ By 1963, Margoliash was comparing amino acid sequences of cytochrome c molecules from horses, humans, pigs, rabbits, chicken, tuna, and baker's yeast.³⁰ The similarities and differences in these sequences could then be used to infer phylogenetic relationships and, as Emilé Zuckerkandl and Linus Pauling had claimed in 1962, they could be used to infer the time of divergence from a common ancestor.³¹ Zuckerkandl and Pauling pioneered the use of sequence comparisons to infer evolutionary relationships with data from hemoglobin sequences. Like Williams and Goodman, Zuckerkandl and Pauling were concerned with primate phylogeny.

Architects of the evolutionary synthesis, such as Mayr and Simpson, were eager to follow the developments of molecular evolutionists, but as they began to attend conferences in the early 1960s, they did not always like what they heard.³² Zuckerkandl and Pauling, in particular, had suggested that molecules did not evolve the same way that morphological features did when they proposed that the rate of change in amino acid sequence may be constant.³³ The opportunity to address these differences came in 1962.

In the summer of 1962, the Wenner-Gren Foundation sponsored a conference of eighteen scientists to discuss classification and human evolution at its European conference center, Burg Wartenstein. Among the participants were

"On the Emergence of Intraspecific Differences in the Protein Antigens of Human Beings", *Amer. Nat.*, 94 (1960), 153–166.

²⁸The evolution of primates and especially the phylogenetic relationships among apes and humans was a central concern for many molecular evolutionists. Williams and Goodman, as well as Allan Wilson and Vincent Sarich, were central players in the development of molecular anthropology and its main controversies, as we shall see below.

²⁹E. Margoliash et al., "Amino-Acid Sequence of Horse Heart Cytochrome c: The Complete Amino-Acid Sequence", *Nature*, 192 (1961), 1125–1127.

³⁰E. Margoliash, "Primary Structure and Evolution of Cytochrome c", *Proc. Nat. Acad. Sci.*, 50 (1963), 672–679.

³¹Emilé Zuckerkandl and Linus Pauling, "Molecular Disease, Evolution, and Genic Heterogeneity", in *Horizons in Biochemistry*, ed. M. Kasha and B. Pullman (New York: Academic Press, 1962), 189–225.

³²The importance of molecular evolution is noted in a letter from G. G. Simpson to Ernst Mayr, January 6, 1964. Simpson Papers, American Philosophical Society Library, Philadelphia.

³³Zuckerkandl and Pauling, "Molecular Disease", *Evolution, and Genic Heterogeneity*" (above, n. 3), 200–204.

G. G. Simpson, Ernst Mayr, Theodosius Dobzhansky, Morris Goodman, and Emilé Zuckerkandl. Goodman and Zuckerkandl, among others, were slated to present on molecular approaches to primate classification and evolution. Significantly, a “restricted committee” met during the course of the conference to discuss “the potentialities of the molecular approach to anthropology and the study of evolution.”³⁴ The committee included Bernard Campbell, Dobzhansky, Goodman, G. Harrison, H. Klinger, Mayr, Simpson, and Zuckerkandl. Although no transcripts of the discussion in the committee or at the larger conference remain, Zuckerkandl included a lengthy discussion of the specific contributions of the members of the restricted committee in his published paper for the conference proceedings.

Zuckerkandl, an Austrian biochemist who had been trained in France, had moved to the California Institute of Technology in 1959 to work with Linus Pauling. Zuckerkandl’s earlier work had been on hemocyanins and physiological uses of copper. Pauling, who was actively working on hemoglobins and what he called molecular diseases, for example, sickle cell disease, was intrigued and asked Zuckerkandl to collaborate with one of his graduate students, Richard T. Jones, on the evolution of primate hemoglobins.³⁵ In the course of this comparative work, Zuckerkandl used differences in hemoglobins from various species as a way of estimating the time back to a common ancestor. A crucial component of this method was the claim that, in Zuckerkandl and Pauling’s words, “the evolutionarily effective mutation rate, i.e., the rate of the mutations that have not been eliminated by natural selection, fluctuated during the time of evolution of hemoglobin around a mean without showing a predominant trend to increase or decrease”.³⁶ In other words, the rate of mutation was roughly constant. Comparisons of alpha and beta hemoglobins from gorillas and humans allowed Zuckerkandl and Pauling to estimate a time of divergence of eleven million years, which was at the “lower limit of the range estimated on paleontological grounds”.³⁷ Since the paper making this claim was to be published in a volume dedicated to Albert Szent-Györgi, Pauling encouraged Zuckerkandl to write something “outrageous”.³⁸ Zuckerkandl’s use of molecular data was certainly daring, but in 1962 he was

³⁴ Emilé Zuckerkandl, “Perspectives in Molecular Anthropology”, in *Classification and Human Evolutions*, ed. S. Washburn (Chicago: Aldine, 1963), 254.

³⁵ Emilé Zuckerkandl, “On the Molecular Evolutionary Clock”, *J. Mol. Evol.*, 26 (1987), 34–46, see 34.

³⁶ Zuckerkandl and Pauling, “Molecular Disease, Evolution, and Genic Heterogeneity” (above, n. 31), 201.

³⁷ *Ibid.*, 202.

³⁸ Interview with Emilé Zuckerkandl, March 10, 1994, Palo Alto, California. Also, Emilé Zuckerkandl to Michael Dietrich, personal communication, November 23, 1996, 2.

still cautions and was careful to detail the possible sources of error involved in using molecular comparisons and constant-rate assumptions.³⁹

Zuckerkindl's paper for the Wenner-Gren conference was divided into two sections: in the first, he discussed the results of his collaboration with Pauling concerning the evolution of hemoglobins in primates; in the second, he turned to the disadvantages and advantages of the molecular approach. Of the five difficulties for the molecular approach that Zuckerkindl presented, only three represented limitations on the applicability of the molecular approach, for example, the lack of information on molecular structures and difficulties in the interpretation of amino acid sequence differences. The remaining difficulties were more serious objections to molecular evolution itself. Zuckerkindl conceded that "protein analysis tells us nothing about the openness or closedness of a given gene pool", and so did not address the question of species boundaries or the process of speciation. A more "fundamental restriction" of protein analysis, according to Zuckerkindl, lay in the fact that molecular studies "do not lead to elucidation of the causality of evolutionary trends". Molecules can make proposals but the causal action of natural selection acts at higher levels because, in Zuckerkindl's words, "natural selection acts on functional characters and functions are carried out by coordinated wholes".⁴⁰ In effect, the causally significant level for evolution by natural selection was agreed to be that of the organism.

Zuckerkindl's discussion of these difficulties represents part of the process of negotiation of molecular biology's place within evolutionary biology. This process of negotiation was even more pronounced when Zuckerkindl discussed the advantages of the molecular approach with reference to the comments of the restricted committee participants.

A major issue for the restricted committee, especially for Dobzhansky and Mayr, was the importance of polygenic effects in evolution. All morphological characters were thought to be polygenic, that is, effected by multiple genes. At the molecular level, the primary structure of a protein, its amino acid sequence, was not thought to be polygenic. Proteins were, thus, "a 'cleaner' material for phyletic investigations than morphological characters."⁴¹ Molecular characteristics, which were usually primary protein structures but sometimes included tertiary protein structures,⁴² were also thought to be "cleaner"

³⁹Zuckerkindl and Pauling, "Molecular Disease, Evolution, and Genic Heterogeneity" (above, n. 3), 204.

⁴⁰Zuckerkindl, "Perspectives in Molecular Anthropology" (above, n. 34), 258.

⁴¹Ibid., 260.

⁴²"Tertiary protein structure" refers to the three-dimensional folded structure of a molecule. Tertiary structures were recognized to be extremely important for interactions between molecules, including the creation of active sites within enzymes. "Primary protein structure" refers to the linear order of amino acids composing the protein.

in that the “almost hopelessly complex interweaving of causes and effects” acknowledged to produce morphological characters was “relatively disentangled at the molecular level”.⁴³ Primary protein structure was thought to be “immune” from environmental effects that could alter characteristics and as a result, according to Adolph Schultz, raised serious difficulty for the phyletic classification of hominids. The situation was summed up by G. A. Harrison and reported by Zuckerkandl as follows: “The further way we get in the series of integrated biological levels from the gene level, the more disturbance is caused by environmental effects with respect to the unambiguous expression of the structure of a given gene”.⁴⁴ In effect, Zuckerkandl was admitting, on the one hand, that natural selection acted at higher levels and that this action was entangled in a very complex web of causal relations. On the other hand, protein structures were thought to be phenotypic characteristics and hence data for systematists. Moreover, according to Zuckerkandl, protein structures may have been better data for systematists since they were “cleaner” and less arbitrary in the definition. Zuckerkandl was negotiating a trade-off: the molecular level provided clear advantages for systematics and the reconstruction of hominid phylogeny, but it did not address the process of speciation or the causal process of natural selection.

That said, there is also evidence that Zuckerkandl was not completely comfortable with this trade-off – it gave away too much. In the restricted committee meeting, Adolph Schultz pointed out that “many anatomical differences between man and the anthropoid apes can be reduced to a matter of differential growth rates”.⁴⁵ According to Zuckerkandl, analysis of protein structure could possibly distinguish between “structural genes and genes involved in establishing chromosomal characteristics that preside over the temporal and perhaps quantitative regulation of the activity of structural genes. . . .” In other words, molecular analysis ought to be able to detect genes that regulate rates of expression in structural genes and so rates of growth at higher levels. Although this possibility was admittedly sketchy, Zuckerkandl thought that it could “allow one in principle to establish the degree to which quantitative changes in characters are associated with mutations in structural genes”.⁴⁶ Protein analysis might then provide important insight into evolutionarily significant differences in gene action.

After the conference, Zuckerkandl rewrote his presentation, resulting in the published paper with the account of the comments in the restricted meeting. In retrospect, Zuckerkandl remembers that Mayr, Dobzhansky, and Simpson

⁴³ Zuckerkandl, “Perspectives in Molecular Anthropology” (above, n. 34), 260–261.

⁴⁴ *Ibid.*, 267.

⁴⁵ *Ibid.*, 265.

⁴⁶ *Ibid.*, 266.

may have had “allergic reactions” to molecular evolution, especially the molecular clock, but Mayr and Dobzhansky remained open minded about what the molecular level might contribute. According to Zuckerkandl, all three were “irritated” by molecular biologists more generally.⁴⁷

After this conference, Mayr, Dobzhansky, and Simpson began to write extensively against the imperialistic efforts of molecular biology. These attacks, which will be discussed below, could be the result of the increasing prominence of molecular biology, but I find it to be a striking coincidence that some of their most pointed attacks on molecular biology come after this 1962 conference. It is certainly clear that both Mayr and Simpson were concerned about the course of the molecular evolutionists and made a point of coordinating with each other about which of them would attend the next major conferences on molecular evolution 1964.⁴⁸

The Widening Gulf

In 1963, Mayr and Dobzhansky began to take a more public course concerning molecular biology with articles in *Science* bolstering organismal biology. Although molecular biology was not mentioned by name, Ernst Mayr’s editorial “The New versus the Classical in Science” was clearly aimed at the new “glamour fields” in science. According to Mayr, there was a rampant “bandwagon tendency in American science” that was producing “unconcealed contempt” for classical science and a reduction in funds for those fields. For Mayr, “the general well-being of American science and the attainment of a healthier balance between classical and frontier fields” depended on “more financial and moral support for the classical areas”.⁴⁹ The new did not displace the classical, according to Mayr, it supplemented it. Nevertheless, as Dobzhansky’s article later that year made even clearer, organismal biology was not perceived as keeping up with the Watsons.⁵⁰

Dobzhansky’s article, while ostensibly a review of evolutionary genetics, was part of a public relations effort, as indicated by the subtitle “Active and Intellectually Stimulating Research Is Going on in Organismic as well as Molecular Genetics”.⁵¹ Using the same type of appeal that he had in 1961,

⁴⁷ Emilé Zuckerkandl to Michael Dietrich, personal communication, November 23, 1996.

⁴⁸ G. G. Simpson to Ernst Mayr, January 6, 1964, Simpson Papers, American Philosophical Society Library, Philadelphia.

⁴⁹ Ernst Mayr, “The New versus the Classical in Science”, *Science*, 141 (1963), 763.

⁵⁰ In his account of the “Molecular Wars” at Harvard, E. O. Wilson depicts James Watson, codiscoverer of the structure of DNA, as the epitome of the molecular biologist with an attitude. In his words, Watson was “the Caligula of biology” (Wilson, *Naturalist* (above, n. 1), 219).

⁵¹ Theodosius Dobzhansky, “Evolutionary and Population Genetics”, *Science*, 142 (1963), 1131–1135.

Dobzhansky argued for the significance of biology to humanity: “Man is an organism, not a molecule, although some diseases which afflict his flesh are molecular diseases”.⁵² This jab at Pauling and Zuckerkandl’s work on molecular diseases was made sharper when Dobzhansky took up the topic of differences in the sequences of hemoglobin chains. Although they did discover these differences, Dobzhansky points out that when it comes to interpreting differences, biochemical geneticists “have not so far been helpful . . . ; they have, rather, made the puzzle more puzzling”.⁵³ Nevertheless, Dobzhansky would go on to characterize genetics, “both molecular and organismic”, as “in a period of rapid development” with “promises to lead to a better understanding of life and to a better understanding of man”.⁵⁴

This active promotion of evolution and organismal biology continued when the first major conferences on molecular evolution were held at Bruges and at Rutgers in 1964. As the proceedings of both of these conferences indicate, by 1964 the study of molecular evolution was well under way.⁵⁵ G. G. Simpson and Ernst Mayr participated in these conferences; Simpson had a paper read at Bruges and Mayr went to Rutgers. At each of these conferences, Simpson and Mayr promoted the power of natural selection and the model of evolution at the organismal level, although Simpson was certainly much more confrontational and vociferous than Mayr.⁵⁶

Marcel Florin had arranged for part of the 1964 annual colloquium on the protides of the biological fluids held in Bruges, to concern problems of phylogeny. Simpson was invited to participate and, although he was not able to attend, he wrote an important paper regarding organismic and molecular evolution which was read by Curtis Williams.⁵⁷ Simpson was trying to ease the “confrontation of molecular and organismal data” and argue against the idea that molecules, specifically serum proteins and cytochromes, “have evolved by some sort of internal constant-rate mutational process and not in

⁵² Ibid., 1131.

⁵³ Ibid., 1134.

⁵⁴ Ibid., 1135.

⁵⁵ Interview with Thomas Jukes, July 28, 1992, Berkeley. The Conference on Evolving Genes and Proteins was held at the Institute of Microbiology at Rutgers on September 17–18, 1964; the Colloquium on the Evolution of Blood Proteins was held in Bruges, Belgium, during the summer of 1964. The conference proceedings were published as *Evolving Genes and Proteins*, ed. V. Broysen and H. Vogel (New York: Academic Press, 1965); the colloquium proceedings, as *Protides of the Biological Fluids*, ed. H. Peeters (Amsterdam: Elsevier, 1964).

⁵⁶ George G. Simpsom’s comments from the 1964 colloquium in Bruges are published as “Organisms and Molecules in Evolution”, *Science*, 146 (1964), 1535–1538, and in *Protides of the Biological Fluids* (above, n. 55), 29–35. Ernst Mayr’s comments from the 1964 conference at Rutgers are published in the discussion sections of *Evolving Genes and Proteins* (above, n. 55).

⁵⁷ G. G. Simpson to Ernst Mayr, April 27, 1964. Simpson Papers, American Philosophical Society Library, Philadelphia.

an irregular or specifically adaptive way”.⁵⁸ In other words, Simpson was trying to ward off the possibility that molecular evolution could be driven by a steady stream of mutations and not the environmentally driven process of natural selection. He explicitly argued against the possibility that an allele could be neutral with respect to selection or, in terms closer to those used by biochemists, that there could be variations in protein structure that did not result in changes in function. The influence of the discussion at the 1962 Wenner-Gren conference was very clear as Simpson reviewed many of the same arguments made for and against molecular evolution presented in Zuckerkandl’s paper.

Of special concern to Simpson was the process of adaptive change. Simpson took it upon himself to argue against the primacy of molecular approaches to evolution and phylogenetic reconstruction. One of his key arguments was that information about the adaptive process of evolution was gained by studying the morphological level, not the molecular level. In his words, “selection acts on the whole phenotype and can single out genes only to the extent that they have phenotypic effects separable both phenotypically and genetically from those of other genes. . . . On average, the farther we are from the genes the nearer we are to the action of selection, and thus the better able we are to interpret the adaptive processes going on”.⁵⁹ Zuckerkandl had not denied this understanding of the causal relationship between genes and phenotype at the Wenner-Gren conference two years earlier, but it is clear that Simpson felt that most scientists studying molecular evolution did not appreciate that focusing on the molecular level was not sufficient to generate an understanding of the processes of evolution. In the case of phylogeny reconstruction, Simpson thought that the preoccupation with comparisons based on single molecules, such as Zuckerkandl and Pauling’s use of hemoglobins, was dangerous and in the case of hemoglobins “tells us a lie” about the affinities between gorillas and humans.⁶⁰ Gorillas and humans were not as closely associated, according to Simpson, as Zuckerkandl and Pauling would have their readers believe. What was needed, in Simpson’s words, was a “balancing of points of view and the achievement of more complete explanations”.⁶¹

It is not clear how the audience in Bruges responded to Simpson’s paper. Simpson did think that the issues raised by molecular evolution were serious enough to republish his essay in *Science* later that same year. Simpson’s paper was definitely a topic of discussion at the Evolving Genes and Proteins

⁵⁸ Simpson, “Organisms and Molecules in Evolutions” (above, n. 56), 1535.

⁵⁹ Ibid., 1536–1537.

⁶⁰ Ibid., 1536.

⁶¹ Ibid., 1535.

Conference at Rutgers University later in 1964. His views were directly addressed in the paper presented by Zuckerkandl and Pauling.⁶²

Zuckerkandl and Pauling begin their paper by recognizing the tension between “organismal evolutionists and taxonomists” and “pure (very unorganismal) biochemists” and they side with the biochemists. In their words, “According to them [the biochemists] (and to us), what most counts in the life sciences today is the uncovering of the molecular mechanisms that underlay the observations of classical biology.”⁶³ They go on to argue for the significance of the molecular level in evolution by trying to subvert the idea that the causal processes of selection were guides to evolutionary significance. The “better tool” for “the analysis of reality”, according to Zuckerkandl and Pauling, was the concept of information. Molecular biologists referred to proteins, RNA, and DNA as informational macromolecules. To Zuckerkandl and Pauling, informational macromolecules represented the greatest concentration of information and causal factors in any organic system. The importance of studying all “processes of life” including evolution, at the molecular level, was based on the following propositions:

- (a) The level of biological integration that contains the greatest concentration of “causal factors” will further our understanding of life more than any other.
- (b) A concentration of information is a concentration of “causal factors”.
- (c) The largest concentration of information present in an organism, and perhaps the largest amount of information, and the only organically transmissible information, is in its semantides [informational macromolecules]. . . . [And,] semantides are potentially the most informative taxonomic characters and not, as has been contended at this meeting, just one type of characters among other, equivalent types.⁶⁴

It is important to note that this is not a reductionist argument. Zuckerkandl and Pauling were not declaring that all of organismal biology could be reduced to molecular biology. They were saying that the emphasis on causal processes that allowed evolutionary biologists to claim that the organismal level is the most important level of biological integration ought to be replaced by an emphasis on information. Framing biology in terms of information allowed Zuckerkandl and Pauling to invert the hierarchy of levels and insist that the molecular level is in fact much more important for “elucidating the most fundamental mechanisms underlying living systems” than the organismal

⁶²Emilé Zuckerkandl and Linus Pauling, “Evolutionary Divergence and Convergence in Proteins”, in *Evolving Genes and Proteins*, ed. V. Bryson and H. Vogel (New York: Academic Press, 1965), 97–166.

⁶³Ibid., 97.

⁶⁴Ibid., 98.

level.⁶⁵ Zuckerkandl and Pauling even suggested that information is a better guide to causation but seemed to back off this more general claim when it comes to the action of selection. Selection was still thought to occur wherever function occurred, but functions were found only at levels higher than that of the individual gene. Moreover, the further away one got from the individual gene, the easier it was to understand its function and “why selection occurred”. That said, Zuckerkandl and Pauling still stated that there was no other “level of organization as informative for tracing phyletic affinities as that of the informational macromolecules”.⁶⁶ Even if the manifestations of the information stored in macromolecules required higher levels of integration for their expression and recognition, the patterns of affinities and differences were thought to be discerned best at their most uncomplicated level – the molecular level.⁶⁷

Zuckerkandl and Pauling’s paper is not remembered for its argumentative introduction. It is remembered for its forceful advocacy of what they called the molecular clock. The idea of rate constancy at the molecular level had been introduced by Zuckerkandl and Pauling in 1962, but its name and first real defense came at the Evolving Genes and Proteins Conference. The idea behind the molecular clock was that the observed changes in the amino acid sequences of a protein from different species should be “approximately proportional in number to evolutionary time”.⁶⁸ Zuckerkandl and Pauling had argued in favor of the molecular clock as had Emmanuel Margoliash. Zuckerkandl and Pauling report that “Professor Ernst Mayr expressed the view here that evolution is too complex and too variable a process, connected with too many factors, for the time dependence of the evolutionary process at the molecular level to be a simple function”.⁶⁹ Zuckerkandl and Pauling’s response: the way to resolve this difference was by the empirical study of many different proteins. Zuckerkandl himself had entertained the possibility that morphological similarity ought to correspond to molecular similarity

⁶⁵ Emilé Zuckerkandl to Michael Dietrich, personal communication, November 23, 1996.

⁶⁶ Zuckerkandl and Pauling, “Evolutionary Divergence and Convergence in Proteins” (above, n. 62), 102.

⁶⁷ For more on the early emphasis on information in molecular biology, see Lily Kay, “Who Wrote the Book of Life? Information and the Transformation of Molecular Biology”, *Sci. Context*, 8 (1995), 609–634, originally published in *Experimentalsysteme in den Biologischen-Medizinischen Wissenschaften: Objekt, differenzen, Konjunkturen*, ed. Michael Hagner, Hans-Jörg Rheinberger, and Bettina Wahrig-Schmidt (Berlin: Akademie Verlag, 1994), 151–179; Evelyn Fox Keller, *Refiguring Life* (New York: Columbia University Press, 1995); Soraya De Chadarevian, “Sequences, Conformation, Information: Biochemists and Molecular Biologists in the 1950s”, *J. Hist. Biol.*, 29 (1996), 361–386.

⁶⁸ Zuckerkandl and Pauling, “Evolutionary Divergence and Convergence in Proteins” (above, n. 62), 148.

⁶⁹ *Ibid.*, 137.

with the suggestion that neither rate would be constant in his paper for the conference at Bruges. Nevertheless, Zuckerkandl and Pauling's conclusion was that "the evidence is so far not extensive enough for a final conclusion to be reached, nor is it altogether unequivocal".⁷⁰

The conciliatory tone in Zuckerkandl and Pauling's discussion of the empirical basis for the molecular clock was also reflected in the comments by Mayr and Margoliash recorded during the discussion session.⁷¹ Mayr agreed that one was better off using characters at the gene level for phylogenetic inference, but a single protein was not a reliable guide. Margoliash hastened to agree with Mayr and point out that there was "no fundamental discrepancy between their points of view". Margoliash then went on to address Simpson's argument about the action of selection:

One point should, however, be added, because it may be contributing to an erroneous impression of an opposition between cytochrome c data and ordinary evolutionary thought. This idea has been beautifully expressed by Dr. G. G. Simpson . . . and simply states that the further one is from the genetic machinery, the nearer one is to the site of selective action. . . . Is it therefore surprising that we have difficulties in relating primary-structure variations in cytochrome c to mechanisms of selection, or that it appears that changes in amino acid sequence may, in the minority of cases, have become fixed in populations through the relatively rare mechanisms that do not directly involve natural selection? The apparent disagreement is thus no more than a difference in emphasis.⁷²

Although Margoliash was trying to smooth over apparent differences in evolution at the morphological and molecular levels, his rhetorical question about different mechanisms of evolution at the two levels foreshadowed serious points of difference to come.

"Molecular Wars"

During these early conferences on molecular evolution, Mayr and Simpson were making specific claims about how evolution at the molecular level should be understood in relation to evolutionary biology in general, but their claims must also be seen in the context of the more general debate over the place

⁷⁰ Ibid., 139.

⁷¹ Mayr, "Discussion of Part III", *Evolving Genes and Proteins*, ed. V. Bryson and H. Vogel, (New York: Academic Press, 1965), 197–198. Simpson was not present at the Rutgers meeting.

⁷² E. Margoliash, "Discussion of Part III", in *Evolving Genes and Proteins*, ed. V. Bryson and H. Vogel (New York: Academic Press, 1965), 199.

of molecular biology. A key difference between evolution at the organismic and molecular levels was the immediacy of selection. A causal distinction marked the difference between the molecular and organismic levels in that the causal action of natural selection was understood to act only at the organismic level. A similar type of causal distinctiveness marked the divide that Mayr, Simpson, and Dobzhansky argued for with regard to explanations offered by organismal and molecular biology.

In 1961, Mayr first distinguished ultimate from proximate types of causes in biology.⁷³ Both types of causes were argued to be necessary for “complete understanding of the given phenomenon”. Ultimate causes were those that had a history and had “been incorporated into the system through many thousands of generations of natural selection”.⁷⁴ Proximate causes were those incorporated into the more immediate mechanisms responsible for the effect in question. Explanations invoking proximate causes (proximate explanations) were those answering questions of how something functioned. Ultimate explanations were those answering historical questions of how something came to have a particular function.⁷⁵ While proximate explanations were the concern of functional biologists, including molecular biologists, ultimate explanations were predominantly offered by evolutionary biologists. It was the ability of evolutionary biologists to offer these kinds of explanations that would allow them to claim that evolutionary biology was autonomous from chemistry and physics.

As the molecular wars heated up, this distinction was deployed by Mayr, Dobzhansky, and Simpson as a means of negotiating the division of the biological landscape with molecular biologists. Mayr, Dobzhansky, and Simpson were actively competing with molecular biologists for support from the Rockefeller Foundation and they were losing. As a result, when Mayr was asked to join the National Research Council’s Biology Council in order to chart the course of biology, he used the opportunity to put the proximate/ultimate distinction into action to “secure the place of evolutionary biology”.⁷⁶

In 1964 and 1966, Dobzhansky launched attacks on the preeminence of molecular biology by arguing for two distinct, “though overlapping and complementary rather than alternative”, strategies for biological research.⁷⁷ On the one hand there was the Cartesian or reductionist strategy, which aimed

⁷³ For an excellent discussion of the history of this distinction, see John Beatty, “The Proximate/Ultimate Distinction in the Multiple Careers of Ernst Mayr”, *Biol. Phil.*, 9 (1994), 333–356.

⁷⁴ Ernst Mayr, “Cause and Effect in Biology”, *Science*, 134 (1961), 1501–6, 150 at 1503.

⁷⁵ *Ibid.*, 1502.

⁷⁶ Beatty, “The Proximate/Ultimate Distinction” (above, n. 73), 348–349.

⁷⁷ Theodosius Dobzhansky, “Are Naturalists Old Fashioned?” *Amer. Nat.*, 100 (1966), 541–550, at 544.

“to describe biological phenomena in terms of chemistry and physics”.⁷⁸ On the other hand, there was the Darwinian or compositionist strategy. Borrowing from Simpson’s own attacks on the threat of reduction to molecular biology, Dobzhansky characterized the types of explanations sought under the Darwinian strategy as seeking to understand the “adaptive usefulness of structures and processes to the whole organism and to the species of which it is a part, and still further, in terms of ecological function in the communities in which the species occurs”.⁷⁹ Echoing Mayr’s distinction between proximate and ultimate, Dobzhansky argued that the Cartesian “most frequently asks ‘how things are’ while the Darwinian most frequently asks ‘how things got to be that way’”.⁸⁰ The crux of Dobzhansky’s argument was that these two strategies were complementary without “being either deducible from or reducible to each other.”⁸¹ Because organismic biology was usually Darwinian and molecular biology was usually Cartesian, Dobzhansky could then argue that organismic biology was not deducible from or reducible to molecular biology.⁸² Instead Dobzhansky claimed that both strategies were “essential for understanding the unity and diversity of life at all levels of interpretation”. Dobzhansky was explicit that his motivation was the worry that the success of molecular biology would lead to its use “as a bludgeon with which to destroy, or to reduce to insignificance, . . . organismic biology”. In this context, he made his now-famous pronouncement that “nothing makes sense in biology except in the light of evolution”.⁸³

Evolution and ultimate explanation became issues in the molecular wars as Dobzhansky and Simpson tried to maintain the central place of evolution within the biological sciences. While Dobzhansky, Mayr, and Simpson argued for complementarity between levels and explanations, they were not above taking a shot at molecular biology or emphasizing the greater importance of evolutionary biology. The strategy of arguing for distinct but complementary levels of organization was accepted by molecular evolutionists in terms of various distinctions between the molecular and the morphological. As will be shown below, molecular evolutionists, such as Allan Wilson, came to accept this distinction not because they relished the lower status it was intended to

⁷⁸ Ibid.

⁷⁹ G. G. Simpson, *This View of Life* (New York: Harcourt, Brace, 1964), 105, cited in Dobzhansky, “Are Naturalists Old Fashioned?” (above, n. 77), 544.

⁸⁰ Dobzhansky, “Are Naturalists Old Fashioned?” (above, n. 77), 544. Simpson’s essay on reduction and composition develops this distinction in terms of the types of questions asked. Simpson, *This View of Life* (above, n. 77), 108–120.

⁸¹ Dobzhansky, “Biology, Molecular and Organismic” (above, n. 2), 449.

⁸² Dobzhansky, “Are Naturalists Old Fashioned?” (above, n. 77), 546.

⁸³ Dobzhansky, “Biology, Molecular and Organismic” (above, n. 2), 449.

give to molecular evolution but because they could articulate this difference as a paradox that they could then resolve in favor of molecular evolution.

The Molecular/Morphological Paradox and Its Resolution

At the time of Zuckerkandl's and, later, Simpson's articles on the relative merits of molecular and organismic approaches to evolution, the idea of a molecular clock was very new and not widely accepted. Indeed, most of molecular evolution was very new and not widely accepted. In 1968 and 1969, however, molecular evolution became much more prominent in the larger biological community as a result of the advocacy of the neutral theory of molecular evolution by Motoo Kimura, and Jack King and Thomas Jukes.⁸⁴

The neutral theory was a radical hypothesis that directly challenged the omnipotence of natural selection in molecular evolution. The basis of its challenge was Kimura's proposal that most changes detected at the molecular level were not acted upon by natural selection; they were neutral and the mechanism of their change was random genetic drift.⁸⁵ Kimura's argument was a "cost of selection" argument common within evolutionary and population genetics.⁸⁶ But this familiar argument was used to create a rift between evolution at the molecular and morphological levels. According to historian William Provine, the idea that molecular and morphological evolution could be different in their principal mechanism and rate was very difficult for evolutionary biologists to accept.⁸⁷ Certainly part of the difficulty was that many of Kimura's readers did not realize that he was referring to *detected* changes, that is, changes that were not eliminated by selection or quickly swept to fixation. Kimura was not proposing that random drift and natural selection be mutually exclusive alternatives at the molecular level. That the molecular could be distinct from the morphological was not at all difficult to accept for many biochemists.⁸⁸ Indeed, the evidence that Kimura used to mount his

⁸⁴ Motoo Kimura, "Evolutionary Rate at the Molecular Level", *Nature*, 217 (1968), 624–626; Jack King and Thomas Jukes, "Non-Darwinian Evolution", *Science*, 164 (1969), 788–798.

⁸⁵ Kimura, "Evolutionary Rate at the Molecular Level" (above, n. 84), 624–626. Random drift can be understood as the random fluctuations of allele frequencies from generation to generation. It occurs in all finite populations but is more extensive in smaller populations. See Douglas Futuyma, *Evolutionary Biology*, 2d ed. (Sunderland, Mass.: Sinauer Associates, 1986), 130.

⁸⁶ Michael R. Dietrich, "The Origins of the Neutral Theory of Molecular Evolution", *J. Hist. Biol.*, 27 (1994), 21–59.

⁸⁷ William Provine, "The Neutral Theory of Molecular Evolution in Historical Perspective", in *Population Biology of Genes and Molecules*, ed. N. Takahata and J. Crow (Tokyo: Baifukan, 1990), 17–31, at 26.

⁸⁸ Thomas Jukes, "Early Developments of the Neutral Theory", *Perspect. Biol. Med.*, 34 (1991), 473–485, at 477.

argument was drawn from the papers of biochemists at the Evolving Genes and Proteins Conference, where rate constancy and the possibility of neutral mutations were openly discussed.⁸⁹

The neutral mutation, random drift controversy over the existence of large numbers of neutral mutations and their control by random drift was fueled the next year when King and Jukes bolstered Kimura's hypothesis with much more evidence from different research programs in molecular evolution. King and Jukes chose to give their paper the provocative title "Non-Darwinian Evolution".⁹⁰ According to a letter quoted by William Provine, Kimura was not fond of the "non-Darwinian" label and asked King and Jukes to change it to emphasize molecular evolution, instead of evolution in general.⁹¹ They did not. King and Jukes had chosen their title with the intention of provoking the evolutionary establishment.⁹² In particular, they were responding to Simpson's essay on molecular and organismic biology from 1962.

Jukes, a biochemist at University of California, Berkeley, had been active in the emerging molecular evolution community; had attended the conferences of the early 1960s; and in 1966 had published one of the first books on molecular evolution, *Molecules and Evolution*.⁹³ In collaboration with King, a population geneticist at the Donner Laboratory, Jukes attacked Simpson's attempt to impose evolutionary order on the molecular level from above. In their words,

We cannot agree with Simpson that DNA is a passive carrier of the evolutionary message. Evolutionary change is not imposed upon DNA from without; it arises from within. Natural selection is the editor, rather than the composer, of the genetic message. One thing the editor does *not* do is remove changes which it is not able to perceive.⁹⁴

In non-Darwinian evolution, Simpson's fears of a rift between molecular and organismal evolution were realized.

⁸⁹ Emilé Zuckerkandl and Linus Pauling, "Evolutionary Divergence and Convergence in Proteins" (above, n. 62). The following papers also appear in *Evolving Genes and Proteins*, ed. V. Bryson and H. Vogel (New York: Academic Press, 1965); J. Buettner-Janusch and R. Hill, "Evolution of Hemoglobin in Primates", 167–181; E. Margoliash and E. Smith, "Structural and Functional Aspects of Cytochrome c in Relation to Evolution", 221–242; N. Kaplan, "Evolution of Dehydrogenases", 243–277.

⁹⁰ The name stuck to the hypothesis until the early 1970s when it was redubbed the neutral theory of molecular evolution.

⁹¹ Provine, "The Neutral Theory of Molecular Evolution" (above, n. 87), 28.

⁹² Letter from Jack King to Theodosius Dobzhansky, June 11, 1970. Dobzhansky Papers, American Philosophical Society Library, Philadelphia. Thomas Jukes's recollections of these events are found in his "Early Developments of the Neutral Theory" (above, n. 88).

⁹³ Thomas Jukes, *Molecules and Evolution* (New York: Columbia University Press, 1966).

⁹⁴ King and Jukes, "Non-Darwinian Evolution" (above, n. 84), 788.

While the neutral theory certainly had its supporters, the more typical response to it was negative. James Crow, a close colleague of Kimura's characterized the initial response to the neutral theory as "one of dismay and disbelief. The reactions ranged from skepticism to outright rejection. To some it was utter nonsense."⁹⁵ In 1978, Simpson characterized it as one of the most formidable threats to the evolutionary synthesis. Noting that non-Darwinian evolution was "advanced by biochemists, not organismal biologists", Simpson argued:

The only mutations that are likely to be selectively neutral are those with no direct or indirect phenetic effects, and if any such really exist (a point difficult to prove), they are of no interest for organismal biologists as they are not involved in the evolution of whole organisms. That fixation of mutations in populations occurs at a constant rate is demonstrably false and the theory that base substitutions in proteins, for example, provide evolutionary clocks is not tenable.⁹⁶

As he had earlier, Simpson maintained that the "interesting" level of evolution was that of the whole organism. In correspondence with Kimura, Ernst Mayr made a very similar point. In his words, "[T]he target of selection is the whole individual and not any one gene or locus."⁹⁷ As a result, according to Mayr, Kimura's attempt to model neutral evolution in terms of independent loci was not warranted. For Mayr and Simpson, the functional integration of the organism and the action of selection at the organismic level could not be denied. But, by 1969, the molecular evolution community had heard these kinds of arguments before. They were ready to deal with the division of biology into different levels, the nonreducibility of one level to another, and the assignment of selection to the higher, organismal levels. In particular, Allan Wilson used these distinctions to negotiate the place of molecular evolution by framing the situation as a paradox to which he had a solution.

One of the main features differentiating non-Darwinians from selectionists, according to King and Jukes, was their belief in the constancy of the rate of molecular evolution because of the predominance of neutral alleles. The non-Darwinian (neutralist) expected the rate to be constant because if most changes were neutral, then they should not be affected by the environment. The neutral rate of evolution would then be merely a function of the mutation rate, which

⁹⁵ James Crow, "Motoo Kimura: An Appreciation", in *Population Genetics and Molecular Evolution*, ed. T. Ohta and K. Aoki (Tokyo: Japan Scientific Societies Press, 1985), 1.

⁹⁶ G. G. Simpson, *Concession to the Improbable: An Unconventional Autobiography* (New Haven: Yale University Press, 1978), 269.

⁹⁷ Ernst Mayr to Motoo Kimura, July 16, 1969. Quoted in Provine, "The Neutral Theory of Molecular Evolution" (above, n. 87), 25–26.

was thought to be a random process analogous to radioactive decay. The selectionist rate was not independent of environmental effects and the effects of population size and so fluctuated with environmental changes. Constant rates of change in the primary structures of hemoglobins and cytochrome c molecules, along with work on primate albumins done by Vincent Sarich and Allan Wilson, supported the non-Darwinian interpretation.⁹⁸

While many biochemists interested in evolution advocated rate constancy at the molecular level, including Margoliash, Zuckerkandl, and Pauling, the molecular clock was championed in the late 1960s and early 1970s by University of California, biochemist Allan Wilson. Wilson began his career in the early 1960s working on comparative biochemistry and biochemical taxonomy using immunological techniques, notably micro complement fixation (MC'F). Like Zuckerkandl, Wilson was trying to negotiate a place for the kind of comparative, biochemical taxonomy he wanted to pursue. In 1965, for instance, Leonard Kirschner, one of Wilson's professors, tried to persuade him to join the Comparative Physiology Division of the American Society of Zoologists and help with a new journal on comparative physiology and biochemistry. Wilson declined, citing Bradley Scheer's claim: "I don't think any great phylogenetic discovery will arise from physiological studies. . . ."⁹⁹ Kirschner thought that Wilson's assertion that comparative biochemistry would make a significant contribution to taxonomy was "garbage".¹⁰⁰ Wilson responded with a detailed defense of the new taxonomic biochemistry. He argued that it used properties "close to the gene, namely properties of proteins and nucleic acids" to "measure the degree of genetic homology between species"; this allowed biochemists "to make really significant contributions to taxonomy."¹⁰¹ Clearly, Wilson was trying to find his way in a new tradition blending biochemistry and taxonomy.¹⁰² To that end, also in 1965, he began to collaborate with his then graduate student Vincent Sarich on the biochemical taxonomy of the primates.

Using MC'F, Sarich and Wilson compared the immunological reactivity of albumins from twenty-two primate species. The data from these primates provided a proving ground for the technique of MC'F when the relative

⁹⁸ King and Jukes, "Non-Darwinian Evolution" (above, n. 84), 796.

⁹⁹ Bradley Scheer, "The Uses of Comparative Physiology", in *Taxonomic Biochemistry and Serology*, ed. C. Leone (New York: Ronald Press, 1964), pp. 101–117. Quoted in Allan Wilson to Leonard Kirschner, July 27, 1965, AWP.

¹⁰⁰ Leonard Kirschner to Allan Wilson, July 20, 1965, AWP.

¹⁰¹ Allan Wilson to Leonard Kirschner, July 27, 1965, AWP.

¹⁰² Angela Creager's analysis of the history of the departments of biochemistry and molecular biology at Berkeley raises important questions about Wilson's position as he began to create a strong connection between biochemistry and physical anthropology at Berkeley. A more detailed institutional study of Wilson's laboratory group will have to wait for the future, however. See Creager, "Wendell Stanley" (above, n. 20).

distances and relations between the primate species determined with MC'F agreed with the accepted phylogeny of these species.¹⁰³ In 1967, Sarich and Wilson used MC'F to argue for "a more recent common ancestry between ourselves and the living apes than is generally supposed."¹⁰⁴

Sarich and Wilson's conclusion differed strongly from the accepted position based on morphological evidence and the more established position of Morris Goodman based on immunological evidence. Sarich and Wilson, like Goodman, used immunological techniques to confirm the relative similarity of serum albumins among the hominoids. Beginning in the early 1960s, Goodman had argued for the similarity of chimpanzees, gorillas, and humans based on the similarity of the immunological reactivity of serum samples.¹⁰⁵ Goodman even went so far at the 1962 Wenner-Gren conference to suggest that chimpanzees and gorillas should be grouped in the same family as humans.¹⁰⁶ Goodman reports that he was strongly rebuked by Simpson and Mayr, who wanted to keep humans separate on the basis of distinctive adaptive differences.¹⁰⁷ Undoubtedly, part of Simpson's charge that the molecular data on gorillas actually tell a lie was directed at Goodman's claim.¹⁰⁸

Goodman ascribed the molecular similarity between chimpanzees, gorillas, and humans to a slowdown in their rates of evolution relative to the that of the Old World monkeys. This slowdown was explained as the result of increasing numbers of selective constraints in proteins as they evolve in a lineage. Increasing constraints would produce a trend away from selectively neutral mutations enjoyed in relatively unconstrained molecules toward detrimental mutations incurred by highly constrained molecules. This conservation of molecular structure was further bolstered by arguing that maternal-fetal immunological incompatibilities would have limited the development of the nervous system complexity characteristic of the primate lineage to humans.¹⁰⁹ Sarich and Wilson challenged Goodman's conclusions by embracing the

¹⁰³ Vincent Sarich and Allan Wilson, "Quantitative Immunochemistry and the Evolution of Primate Albumins: Micro-Complement Fixation", *Science*, 154 (1966), 1563–1566.

¹⁰⁴ Vincent Sarich and Allan Wilson, "Immunological Time Scale for Hominid Evolution", *Science*, 158 (1967), 1200–1203, at 1201.

¹⁰⁵ Morris Goodman, "On the Emergence of Intraspecific Differences in the Protein Antigens of Human Beings", *Amer. Nat.*, 94 (1960), 153.

¹⁰⁶ Morris Goodman, "Man's Place in the Phylogeny of Primates as Reflected in Serum Proteins", in *Classification and Human Evolution*, ed. S. Washburn (Chicago: Aldine, 1963), 204–234.

¹⁰⁷ Another part of the dispute here concerned the rise of cladistics in systematics. Mayr and Simpson were opposed to cladistic reasoning, while molecular data was noted for ease with which it lent itself to the efforts of numerical taxonomists and cladists. Morris Goodman was an advocate of molecular cladistics. See Morris Goodman, "Epilogue: A Personal Account of the Origins of a New Paradigm", *Mol. Phylogenet. Evol.*, 5 (1996), 269–285, at 272–276.

¹⁰⁸ *Ibid.*, 270.

¹⁰⁹ *Ibid.*

molecular clock and then arguing that immunological similarity implied a more recent time of divergence for chimpanzees, gorillas, and humans.¹¹⁰ In effect, Sarich and Wilson instigated a dispute with Goodman and with morphological evolutionists over the possibility of constant rates of molecular evolution.

Sarich and Wilson's advocacy of the clock had immediate consequences for the interpretation of an important piece of primate taxonomy, but it had even more far-reaching consequences for the relationship between morphological and molecular evolution. In arguing that there was a molecular clock, Sarich and Wilson were arguing for difference between the molecular and morphological levels and fueling the dispute between their respective advocates. Wilson and Sarich were, thus, challenged to find a way both to maintain their highly original research program and to persuade not just biochemists but evolutionary biologists of the plausibility of their results. It is in this immediate context that the molecular/morphological paradox was invoked and resolved.

In presentations, publications, and lectures during the early 1970s, Allan Wilson frequently invoked the molecular/morphological paradox and its resolution as a persuasive device to argue for the molecular clock and molecular evolution.¹¹¹ In a 1971 paper, he offered the paradox and its resolution as follows:

Molecular evolution proceeds in a rather regular fashion with respect to time. By contrast, organismal evolution is classically considered to be an irregular process, some species (e.g., placental mammals) changing rapidly, while others (e.g., frogs) change slowly. The paradox may be resolved by postulating the random fixation of mutations producing amino-acid substitutions that have no effect, favorable or unfavorable, on protein function and hence no effect on anatomy, physiology or behavior.¹¹²

Where King and Jukes made a headlong rush at Simpson and the selectionist position, Wilson and Sarich made use of this paradox to create the specter of the division of the biological world into divergent levels and approaches

¹¹⁰ Vincent Sarich and Allan Wilson, "Rates of Albumin Evolution in Primates", *Proc. Nat. Acad. Sci.*, 58 (1967), 142–148; Allan Wilson and Vincent Sarich, "A Molecular Time Scale for Human Evolution", *Proc. Nat. Acad. Sci.*, 63 (1969), 1088–1093.

¹¹¹ Wilson, "Protein Structure and the Role of Evolution" (above, n. 7), 4; Wilson, Seminar Notes (above, n. 7); Wilson, "Albumin Evolution in Frogs" (above, n. 7), 3129; Wilson, "Selectively Neutral Changes in Protein Evolution" (above, n. 7), 18; Allan Wilson, "Is Protein Evolution at the Basis of Organismal Evolution?" Biosystematists Group, February 11, 1975, Berkeley, Calif. AWP.

¹¹² Wilson, "Albumin Evolution in Frogs" (above, n. 7), 3129.

that could then be dispelled by demonstrating the complementarity of the levels. This paradox and its resolution were persuasive because they drew on the threat of competitive division between molecular and organismic biologists. They spoke to Simpson's fears that a wedge was being driven between the molecular and morphological and that once that distinction had been made, molecular biologists would argue for the predominance of molecular explanations of biological phenomena. In a world where molecular biology was the glamour field wielding imperialistic claims of reduction, to have the rate of morphological evolution differ so strongly from the rate of molecular evolution raised the question of which side was right about rates. Wilson and Sarich captured these concerns in the molecular/morphological paradox and then tried to put them to rest by declaring in effect that both claims about rates were correct. The molecular rate was constant because of neutral mutations and the morphological rate was variable as expected. Molecular and morphological evolution were not offering mutually exclusive interpretations but complementary interpretations.

Conclusion

The molecular/morphological paradox was used by molecular evolutionists such as Allan Wilson to differentiate molecular evolution from morphological evolution, as well as to maintain that molecular and morphological evolution were compatible. As such, the resolution of the molecular/morphological paradox in the early 1970s was a site of negotiation of the place of molecular evolution relative to evolutionary biology as a whole. The molecular/morphological paradox was a way of articulating the place of molecular evolution relative to morphological evolution. In particular, it was a way of advocating molecular evolution by marking its distinctiveness but then claiming that this distinctiveness did not form a barrier to the integration of the study of evolution at the molecular level with the study of evolution at other levels. In the controversy-ridden atmosphere of the 1960s and early 1970s, this made the paradox and its resolution powerfully appealing to Wilson, Vincent Sarich, and other molecular evolutionists.

The paradox and its resolution in terms of neutral mutations did not have universal appeal. For most biochemists, neutral mutations were not overly problematic; for many evolutionary biologists, they seemed to be, at least at first glance, a strange deviation from the panselctionism of the evolutionary synthesis. To many evolutionary biologists, the neutral theory advocated the causal diversification of evolution that set evolution at the molecular level apart from evolution at the morphological level. The confusion about levels, the rhetoric of non-Darwinian evolution, and the perceived threat to

the power of natural selection fanned the flames of the neutralist/selectionist controversy and probably made the resolution in terms of neutral mutations less persuasive to the larger evolutionary community. That said, it must be noted that my purpose here has not been to try to evaluate the success of the paradox and its resolution as persuasive tools but to try to understand why they would have been considered persuasive by Wilson and Sarich and how they were emblematic of the effort to negotiate a place for molecular evolution in the 1960s and early 1970s.

The molecular/morphological paradox and its resolution in terms of neutral mutations captures the larger problem of how molecular evolutionists were going to articulate their relationships to molecular biology and biochemistry, on the one hand, and evolutionary biology, on the other. Given the battles being fought by the architects of the synthesis over the reduction of all of biology to molecular biology, glamour fields, and classic biology, negotiating an intellectual place for a hybrid of molecular biology and evolutionary biology was a significant task. The molecular/morphological paradox is emblematic of what was involved in that task because it embodies the distinction between the molecular and organismic levels as well as the implied possibility that the disagreement between these two levels would further the division between the molecular and organismic biology. Resolving this division in terms of the neutral theory drew in the evolutionary biologists' arguments for the compatibility of different levels of biological organization as well as the idea that selection acts on higher levels of organization. The paradox and its resolution, thus, allowed molecular evolution to be understood as distinct and interesting in its own right, but compatible with evolution at the organismic level.

It speaks to the power of the molecular/morphological paradox that it continues as a site of negotiation for the place of molecular evolution. Beginning in 1974, Allan Wilson, Vincent Sarich, and Linda Maxson used the molecular/morphological paradox as a means to expand on Emilé Zuckerkandl's claim that the difference in rates was actually a result of relatively small changes in regulatory genes with large corresponding morphological consequences.¹¹³ In 1985, Motoo Kimura invoked the molecular/morphological paradox and offered a resolution in terms of stabilizing selection. Wanting to defend neutrality at the molecular level, Kimura argued that stabilizing selection at the morphological level was entirely compatible

¹¹³ Wilson, Maxson, and Sarich, "Two Types of Molecular Evolution" (above, n. 7); Wilson, Sarich, and Maxson, "The Importance of Gene Rearrangement in Evolution" (above, n. 7). See also King and Wilson, "Evolution at Two Levels in Humans and Chimpanzees" (above, n. 7); Zuckerkandl, "Perspectives in Molecular Anthropology" (above, n. 34), 243; Zuckerkandl and Pauling, "Evolutionary Divergence and Convergence in Proteins" (above, n. 62), 99–100.

with nearly neutral dynamics at the molecular level. As long as stabilizing selection predominated at the morphological level, compatibility was possible and the neutral theory created no rift.¹¹⁴ In 1987, Masatoshi Nei ended his lengthy and detailed analysis of molecular evolutionary genetics by reviewing different resolutions to the molecular/morphological paradox and arguing for the importance of mutation as an evolutionary force at both levels.¹¹⁵ These further resolutions represent efforts to negotiate the place of molecular evolution in the context of contemporary developments, but they also argue for the ubiquity of the rhetorical strategy of offering reconciliation between apparently divergent approaches. The paradox and resolution strategy acts as a means of both advocating a novel position and articulating its relationship to its parent fields.

Acknowledgments

I am indebted to a number of people for their helpful and generous advice; they include Angela Creager, Jim Griesemer, Ernst Mayr, Greg Morgan, Vincent Sarich, Betty Smocovitis, Paul Teller, and Emilé Zuckerkandl. I am especially grateful to the family of Allan Wilson for allowing me to have access to Professor Wilson's personal papers and to Laura Lovett for her patience and support. I am solely responsible for the views expressed in this article.

¹¹⁴Motoo Kimura, "Natural Selection and Neutral Evolution", in *What Darwin Began*, ed. L. R. Godfrey (Boston: Allyn and Bacon, 1985), 73–93.

¹¹⁵Masatoshi Nei, *Molecular Evolutionary Genetics* (New York: Columbia University Press, 1987), 414–431.