Homology in Classical and Molecular Biology[1]

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Hypotheses of homology are the basis of comparative morphology and comparative molecular biology. The kinds of homologous and nonhomologous relations in classical and molecular biology are explored through the three tests that may be applied to a hypothesis of homology: congruence, conjunction, and similarity. The same three tests apply in molecular comparisons and in morphology, and in each field they differentiate eight kinds of relation. These various relations are discussed and compared. The unit or standard of comparison differs in morphology and in molecular biology; in morphology it is the adult or life cycle, but with molecules it is the haploid genome. In morphology the congruence test is decisive in separating homology and nonhomology, whereas with molecular sequence data similarity is the decisive test. Consequences of this difference are that the boundary between homology and nonhomology is not the same in molecular biology as in morphology, that homology and synapomorphy can be equated in morphology but not in all molecular comparisons, and that there is no detected molecular equivalent of convergence. Since molecular homology may reflect either species phylogeny or gene phylogeny, there are more kinds of homologous relation between molecular sequences than in morphology. The terms *paraxenology* and *plerology* are proposed for two of these kinds—respectively, the consequence of multiple xenology and of gene conversion.

Introduction

A recent multiauthored letter to the editor of *Cell* (Reeck et al. 1987) was concerned with "a terminology muddle and a way out of it" in the use of the term *homology* in molecular sequence comparisons. *Homology* was defined there as "having a common evolutionary origin." The loose use of the term to mean similarity—and the consequent "muddy writing" or "muddy thinking"—were the muddle referred to. The letter was of sufficient general interest for a page of comment in the editorial section of *Science* (Lewin 1987). Such muddles will not occur in *Molecular Biology and Evolution,* for the instructions to contributors are explicit on usage: *homology* should be used to mean "inferred common ancestry," because observed similarity between sequences may have been "acquired by convergence (analogy) rather than retained after divergence (homology)." No recommendations of that sort are to be found in the instructions to contributors for *Journal of Morphology* or other journals used by morphologists. Of course, this is not a real difference between classical and

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molecular biology, but many morphologists might be surprised or disconcerted to find *homology* defined simply as "having a common evolutionary origin" or as "inferred common ancestry" and to find analogy equated with convergence. Their surprise could arise from the feeling that a lot of dust, some of it historical and some lexical, was being swept under the carpet—and from the knowledge that, while analogy was historically the antonym of homology, in original and much subsequent usage analogy has contained more than convergence (e.g., parallelism and functional similarity between homologues; Hailman 1976, p. 190), just as convergence has contained less than nonhomology (or homoplasy; e.g., see Simpson 1961, p. 78). But morphologists would agree with a point well made in the letter in *Cell:* similarity can be factual, whereas homology "must usually remain a hypothesis." This draws attention to the distinction between the theoretical definitions of terms—which may be established by custom or fiat, may change with time, and need not be operational—and the empirical criteria that might be used to determine whether a particular definition is met. In science, one aim is to test hypotheses; given that homologies are hypothetical, how do we test them? How do we decide that an observed similarity is a valid inference of common ancestry? If similarity must be discriminated from homology, its assessment (statistically significant or not, for example) is not necessarily synonymous with testing a hypothesis of homology. My aim here is to explore the similarities and differences between the various categories of homology and homoplasy (nonhomology) in classical morphology and in molecular biology. I shall use tests of hypotheses of homology as the way into the analysis.

In a discussion of morphological homology (Patterson 1982), I proposed that there are three ways of testing hypotheses of homology and that different categories of homology and of homoplasy can be discriminated by the results of the tests. Two tests will distinguish four categories (table 1), and all three will pick out eight (table 2). In that paper I remarked that paralogy (Fitch 1970*a*) is the molecular equivalent of serial homology and other such relations in morphology (mass or multiple homology, collectively called homonomy) but left the idea to be followed through on another occasion. Correspondence between paralogy and homonomy is one instance of how different categories of homology and homoplasy might be matched in molecules and in morphology. In particular, I am interested here in the question of convergence, the old pitfall in morphology. According to several recent commentators (see below, pp. 615–617), molecular comparisons are immune to convergence and molecular phylogenies cannot be misled by it. If this is true, it is a crucial difference between classical and molecular biology; in deciding whether it is true, there must be agreed criteria for recognizing convergence. In more general terms, it is important to ask whether molecular homologies introduce entirely new concepts or whether they are still the classical kinds of homology and nonhomology brought into a new focus.

One problem needs brief preliminary discussion, the question of "character" and "character state." Many systematists find it necessary or useful to distinguish these two concepts in discussing homologous features; for example, in mammals the character "cochlea" may have the states "curved" (monotremes) or "spiral" (therians), or in angiosperms the character "flower" may have the states "red" or "blue." In the same way, in comparative molecular biology the character "position 86 in myoglobin" may have the states "Ile," "Leu," etc. In agreement with many other systematists (e.g., see Wiley 1981, p. 9; Schoch 1986, p. 75; Ax 1987, p. 108), I find this distinction neither necessary nor useful. The essence of systematics is hierarchy, and in a hierarchic framework homologous "characters" and their "states" each represent characters—but at more and less inclusive levels, just as "spiral cochlea" delimits a subset of the

Table 1
Relations Differentiated by Similarity and Congruence Testing of Morphological Characters

Relation	Similarity Test	Congruence Test
Homology	Pass	Pass
Parallelism	Pass	Fail
Complement	Fail	Pass
Convergence	Fail	Fail

SOURCE.—Patterson 1982, table 1.

group of organisms having "cochlea" and "myoglobin 86 Ile" delimits a subset of those having "myoglobin 86." So, in what follows, no distinction is necessary or intended between characters or features and their states. It follows from this view of characters that hypotheses of homology between them may be framed at any level. For instance, it might be hypothesized that a virus is homologous with a human being or with any distinguishable part of one or that a bristle on a fly is homologous with anything whatever. All such hypotheses stand or fall through testing.

Tests and Categories of Morphological Homology

The three tests of homology are similarity, conjunction, and congruence. Testing by *similarity* is the traditional method of comparative morphology, in use at least since Aristotle (Russell 1916, p. 7), and in Owen's (1843, p. 379) original definition of homology similarity is the only criterion implied ("the same organ under every variety of form and function"). Topographic correspondence and ontogenetic transformation are the usual criteria, and correspondences that pass such tests merit the same name (Owen 1849, p. 71: "the namesake or 'homologue' "). I have written (Patterson 1982, p. 38) that morphological similarity hardly tests a hypothesis of homology but validates it as worthy of testing or evaluates its internal consistency. Cracraft (1981, p. 25) has argued that similarity is not a test of homology because nonhomology also implies similarity; instead, "similarity is the factor that compels us to *postulate* homology," or, as Stevens (1984, p. 403) puts it, "without some similarity, we should not even dream of homology." For these reasons, the similarity test in morphology is a weak one; it has "low resolving power" (Bock 1977, p. 882); it has so far resisted quantification (and is unlikely to submit), and it cannot be concisely defined. Although homology is not identity, comparisons passing the similarity test do so by virtue of an abstracted identity or 1:1 correspondence, which may be as general as that common to the hyomandibula of a shark and the stapes of a mouse or as precise as that between the stapes of two mice.

Conjunction is the name I gave to a test that will disprove homologies as "anatomical singulars," Riedl's (1979, p. 52) apt term for homologues. If two supposed homologues are found together in one organism, they cannot be homologous. For example, the theory that the human arm (a mammalian forelimb) and the wings of birds are homologous would be shown to be mistaken if angels (with both arms *and* wings) are ever discovered.

The third and most decisive test of homology is by *congruence* with other homologies. This test depends on the equivalence of homology and synapomorphy, with the corollary that homologies specify groups that are rendered monophyletic by them. In testing a proposal of homology by congruence, one checks the distribution of the

Table 2
Relations Differentiated by All Three Tests of Morphological Characters

Relation	Congruence Test	Similarity Test	Conjunction Test
Homology	Pass	Pass	Pass
Homonomy	Pass	Pass	Fail
Complement	Pass	Fail	Pass
Two homologies	Pass	Fail	Fail
Parallelism	Fail	Pass	Pass
Homoeosis and multiple parallelism	Fail	Pass	Fail
Convergence	Fail	Fail	Pass
Endoparasitism and multiple convergence	Fail	Fail	Fail

SOURCE.— Patterson 1982, table 2.

feature (what species does it occur in and group together?) against the distribution of other supposed homologies. The wings of birds and bats are nonhomologous (as wings) because the group they specify is incongruent with or is contradicted by all the features relating bats to other mammals and birds to crocodiles. A true homology will circumscribe a group that is congruent with those specified by other homologies: it may include them as subgroups or be included by them as a subgroup, or it may specify the same group. Wagner (1986) calls this "the criterion of coincidence" or testing by consistency, and it is allied to compatibility methods in numerical cladistics (Meacham and Estabrook 1985).

Given three tests with yes/no answers, any two will differentiate four categories (table 1), and all three will differentiate eight (table 2). [In fact, the eight categories in table 2 specify three two-by-two tables like table 1, each with the eight categories grouped in four different pairs (tables 5–7).] It is necessary to comment on some of the eight categories in table 2.

Homonomy differs from homology in failing the conjunction test because several or many copies of the homologue occur in one individual; the distinction is between anatomical singulars and plurals (Riedl 1979). The *complement* relation is presence of a homology versus its absence (absence complements presence, the two states constituting a whole with no other possible condition), and "two homologies" means two occurring in the same organism so that the conjunction test is failed; further comment on these two categories—and, in particular, on the importance of the life cycle—is given by Patterson (1982, p. 48).

Parallelism and convergence are distinguished in table 2 by the similarity test: *parallelisms* are rejected as homologies because they do not characterize monophyletic groups (they fail congruence), whereas *convergences* are "not really the same" and fail similarity as well. Since one aim of this paper is to determine whether convergence occurs in molecular sequence data, I need to discuss alternative views of convergence and parallelism in morphology in some detail here. And as with homology, it is necessary to bear in mind the distinction between theoretical definition of these terms, and empirical criteria that might be applied to determine that a given definition is met.

Haas and Simpson (1946) gave a full account of the history of the terms *parallelism* and *convergence*. They noted the difficulty of discriminating the two phenomena in practice, even when a clear theoretical distinction is made, and remind us of the origin of these terms (and of the term *divergence*) in geometry. The geometrical source of

divergence, parallelism, and convergence makes it easy for us to form a mental picture of their meaning: divergent features correspond less closely now than in the past; in convergence the correspondence is closer now than in the past; and in parallelism, the correspondence has stayed the same. But to translate this into adequate theoretical definitions of parallelism and convergence has proved remarkably difficult, and, perhaps in consequence, current usage is hardly standardized or coherent. For instance, the instructions to contributors for *Molecular Biology and Evolution* imply that nonhomologous similarity (homoplasy) equals convergence, whereas some authors (Stevens 1987, p. 162; Wiener 1987, p. 220) imply that homoplasy equals parallelism.

As one of a few recent examples, Schoch (1986, pp. 334, 337) defines convergence as similarity of characters in distantly related lineages and defines parallelism as nonhomologous similarity in closely related lineages. These definitions match those used by Mayr (1969, pp. 401, 408) and are essentially the same as those given by Simpson (1961, p. 78; Schoch 1986, p. 130). [Note that Mayr (1974, p. 116) includes parallelism in homology, whereas Simpson (1961) excludes it; but this is not the point at issue here; see below, p. 619.] The definitions imply no absolute difference between convergence and parallelism, but one of degree. Holmes (1980, p. 49) reworded Simpson's (1961) definitions to differentiate parallelism from convergence by citing "inherited genotypic similarity" as the basis in the former but not in the latter. Holmes agreed that parallelism and convergence intergrade at some point. Ghiselin (1976) defined convergence and parallelism in terms of two kinds of evolution and also saw the difference between the two as one of degree. He later (1981, p. 276; 1984) suggested spatiotemporal restriction as a feature of parallelism that would differentiate it from convergence, which is not so restricted. The significance of this distinction is that Ghiselin sees convergence as a relation among members of a class (a universal, not restricted in time or space) and homology as a relation among parts of a whole (monophyletic group, spatiotemporally restricted individual). But I see no way of applying spatiotemporal restriction to distinguish parallelism from convergence, since all the candidates for either category are so far confined to one monophyletic group (life), restricted in time and space to the history of this planet.

Some have felt that distinction between parallelism and convergence is unnecessary or irrelevant (e.g., see Nelson and Platnick 1981; Wiley 1981; Ax 1987), since only two concepts are necessary: homology (synapomorphy) and nonhomology (homoplasy; convergence, etc.). Eldredge and Cracraft (1980, p. 72) proposed that "the only meaningful distinction" between convergence and parallelism is that the second invokes a derived character in sister groups whereas the first does not. They concluded that parallelism is merely unrecognized synapomorphy and that the concept therefore should be dropped. In the hypothetical example of parallelism used by Eldredge and Cracraft (see fig. 1A), the "parallel" character is universal in two sister groups and is synapomorphy or parallelism according to the condition assumed in their immediate common ancestor. Eldredge and Cracraft did not address the situation in which evolutionists would generally apply the term *parallelism,* where the "parallel" character is more or less widely distributed in each of two sister groups but universal in neither. Gosliner and Ghiselin (1984) evidently missed this aspect of Eldredge and Cracraft's example and credited them with a definition of *parallelism* as independently acquired similarity between sister groups. Gosliner and Ghiselin pointed out difficulties with that definition "because sister-groups occur at all systematic levels," and indeed, when their version of the definition is applied to figure 1B, the "convergence" between A and D becomes a parallelism between the sister taxa ABC and D. Gosliner and Ghiselin concluded that in this case the only real convergences would be where there

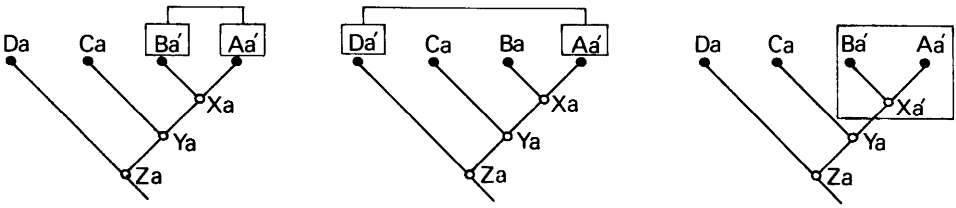

FIG. 1.—Concepts of parallelism and convergence, as illustrated by Eldredge and Cracraft (1980, fig. 2.16). A, An example of parallelism. B, An example of convergence. C, An alternative hypothesis to example A in which the parallelism between taxa A and B is converted to synapomorphy (homology) by revising the condition postulated in ancestral species X. Capital letters denote extant taxa and ancestral species; a′ denotes a derived condition of character a.

is no common ancestry, in different galaxies. Their own definition of parallelism is that taxa begin with the same condition and independently undergo the same changes: it follows that the end result will be characters that are indistinguishable or "the same." Gosliner and Ghiselin's definition of convergence is that taxa begin with different conditions and arrive at a similar condition by different paths: since they allow that convergence like that between cephalopod and vertebrate eyes shows "important differences resulting from remoteness of initial conditions," it evidently follows that the end result of convergence will be characters that are distinguishable or "not really the same."

Hennig (1966) and Riedl (1979) use the term *homoiology* to denote correspondence resulting from parallel evolution; homoiologies are similarities developed on a homologous base or are repeated occurrences of the same transformation, as contrasted with the transformation of different characters in convergence (Hennig 1966, p. 93). The distinction here, in terms of properties of the resulting characters, seems again to be identity or "sameness" in parallelism or homoiology and nonidentity or difference in convergence.

To sum up this review, given that parallelism and convergence represent distinct theoretical concepts, there are three basic ways of viewing the distinction between them: that it is unnecessary or irrelevant (e.g., see Ax 1987); that interpretation of the end products, the observed characters, depends on an understanding of the evolutionary processes concerned (e.g., see Simpson 1961); and that the evolutionary processes invoked as explanation depend on an interpretation of the end products (e.g., see Patterson 1982). Four factors are mentioned in the various definitions of parallelism and convergence: (1) the relationships of the taxa exhibiting the characters (close or remote), (2) the condition in the common ancestor of each taxon (identical or not), (3) the evolutionary pathway or process invoked (parallel or convergent), and (4) the characters themselves (similar or dissimilar). As with definitions of homology, theory and practice intertwine in these criteria. My principal concern with parallelism and convergence here is how we may discriminate them in practice, rather than how we should define them in theory, since theoretical concepts that are operationally indistinguishable are of questionable value. In practice, among the four factors just listed, (4) is directly available, (1) is less directly available, and (2) and (3) are inferences from (1) and (4). Distinguishing parallelism and convergence in terms of factor (1) (close or remote relationship) seems impractical, as discussed above (fig. 1). So it follows that we must rely on factor (4), the similarity (parallelism) or dissimilarity (convergence) of the characters concerned. Considerations such as this in-

fluenced my decision to discriminate parallelism and convergence by the similarity test in table 2, and this seems to match the opinions of others such as Hennig (1966) and Gosliner and Ghiselin (1984), cited above.

The final two categories in table 2 are the relation passing only the similarity test and the one failing all three tests. In 1982 I suggested that homoeosis might fit the first case and that endoparasitism might fit the second. As an example of homoeosis, if one compared a bithorax *Drosophila* hindwing with a hindwing of a hymenopteran, the relation might pass similarity but would fail congruence and conjunction. And if one mistook an endoparasite for part of its host and compared part of the parasite (or the whole parasite in multiple infections) with part of another organism, all three tests would fail. Two other relations meet the requirements of the sixth and eighth categories in table 2: just as the conjunction test discriminates homology from homonomy (multiple homology), it will discriminate both parallelism in single characters and convergence in single characters from multiple parallelism and convergence. To illustrate multiple parallelism and convergence, it has been proposed (Løvtrup 1977) that metameric segmentation in amphioxus and in vertebrates is not homologous, whereas metamery in chordates and in annelids or arthropods is generally regarded as nonhomologous. When the three tests are applied to those two propositions, the relation between segments in amphioxus and in a lamprey would be multiple parallelism (since the two have not been shown to differ) and that between segments in amphioxus and an earthworm would be multiple convergence (since the two differ).

An important point about table 2 is the way that each of the three tests splits the eight relations into a different set of four that pass and four that fail. The congruence test passes four: homology, homonomy (multiple homology; e.g., feathers or enucleate erythrocytes), complement (presence vs. absence), and two homologies (with the inclusion relationship, such that the group circumscribed by one includes or equals that circumscribed by the other—e.g., notochord and femur or heart and ear ossicles—in the unlikely event that anyone might seek to test a hypothesis of homology between the members of either pair). All four are useful in systematics, in that they enable us to characterize monophyletic groups and build up a hierarchy of such groups. The four relations that fail congruence (parallelism, convergence, homoeosis and multiple parallelism, and endoparasitism and multiple convergence) are collectively homoplasy—or hindrances in systematics. The other two tests pass a mixture of useful and useless relations. This is why the congruence test is the most powerful of the three, as the only test discriminating homology and homoplasy.

Tests and Categories of Molecular Homology

In morphology, there has been argument and discussion on homology for a century and a half, and there is no real sign that the debate is running down. Molecular biology inherited the term *homology* from classical evolutionary biology, and in the early molecular biology literature one can find greatly foreshortened versions of some of the long-running debates in classical biology.

As one instance, Neurath et al. (1967) discussed homology among proteolytic enzymes and expressed their conclusions in a nice mixture of evolutionary and preevolutionary terms, writing that some of the proteins concerned "probably evolved from a common archetype." They treated homology among proteins as "similarity in amino acid sequence," and it was therefore in order for them to speak, for example, of two proteins showing "40 percent homology." Nolan and Margoliash (1968) criticized this definition of homology in terms of similarity as likely to cause confusion

and as unlikely to supplant well-established usage. Referring to Fitch (1966), Nolan and Margoliash argued that *similarity* is a general term that must be distinguished from *analogy* and *homology,* with their connotations of ancestral conditions. Responding to this criticism, Winter et al. (1968) defined homology as "structural similarity among proteins greater than might be anticipated by chance alone," which is the criterion used by Fitch (1966) to *detect* rather than to *define* homology. Winter et al. preferred this to the definition in terms of common ancestry advocated by Nolan and Margoliash because biochemists lack a fossil record; in Winter et al.'s belief, morphologists have "a detailed fossil record substantiating the divergent evolution of . . . structures from a common ancestor," whereas if biochemists had to define homology in terms of common ancestry, "it would be impossible to conclude with certainty that two proteins are homologous." Apart from their faith in the fossil record, Winter et al. duplicate the opinions of pheneticists (e.g., see Sokal and Sneath 1963, pp. 70, 71), in asking for a concept of homology that is susceptible to direct proof. Fitch (1970*a*) responded to Winter et al. by arguing that discrimination of analogous (convergent) from homologous (divergent) similarity between two groups of sequences could be accomplished without a fossil record, given the assumptions of common descent and parsimony, by constructing ancestral sequences and asking whether the inferred ancestors are more or less similar than the observed descendants.

So, within 4 or 5 years, molecular biologists concluded, first, that "similarity itself is not homology" (Margoliash et al. 1968, p. 262); second, that similarity in sequence data could be analyzed by statistical methods (Fitch 1966, 1970*b*), which would eliminate randomness or chance as the cause; and, third, given nonrandom similarity interpretable as homology, that "mere homology is not sufficient" (Margoliash et al., 1968, p. 267), because homology must be split into the categories that Fitch (1970*a*) called orthology and paralogy. Orthology is homology reflecting the descent of species, and paralogy is homology reflecting the descent of genes; the theoretical distinction concerns whether speciation precedes gene duplication (Fitch and Margoliash 1967). The practical distinction will depend on whether homologous genes and their products coexist in the same organism (paralogy, as with α and β hemoglobins) or do not coexist (orthology, as with β hemoglobins alone), and this recalls the conjunction test in morphology. But in morphology there is no real equivalent of the statistical versions of similarity testing employed with molecular sequence data. A computer program to find morphological homologies has been written (Jardine and Jardine 1967), but it was soon acknowledged to be "only an aid" (Jardine 1970, p. 332) and has not been followed up. Molecular sequence homology is "detectable" in a way that morphological homology is not, primarily because molecular sequences are one-dimensional, whereas morphological homologies are at least three-dimensional (Woese 1987), may be four-dimensional if ontogeny is taken into account, and may be still more complex if composition (e.g., cell type) is considered. Homology between two molecular sequences will be "discovered" if they can be aligned (with a penalty for gaps) in such a way that matches between them score ≥3.0 SDs above the score of scrambled versions of the same sequences (Doolittle 1981). Matches with scores below this may still be homologous, and although other measures and techniques exist [some being more sensitive (e.g., see Dayhoff et al. 1983; Karlin et al. 1983; Bishop and Thompson 1984; Kanehisa 1984; Lipman et al. 1984; White et al. 1984)], there is no method of proving (or disproving) molecular sequence homology at the limits of likelihood.

Table 3
Relations Differentiated by All Three Tests of Molecular (left) and Morphological (right) Characters

Molecular Relation	Congruence Test	Similarity Test	Conjunction Test	Morphological Relation
Orthology	Pass	Pass	Pass	Homology
Paralogy	Pass	Pass	Fail	Homonomy
Complement	Pass	Fail	Pass	Complement
Two orthologies	Pass	Fail	Fail	Two homologies
Xenology	Fail	Pass	Pass	Parallelism
Paraxenology, gene conversion	Fail	Pass	Fail	Homoeosis, multiparallelism
[Convergence]	Fail	Fail	Pass	Convergence
...	Fail	Fail	Fail	Endoparasitism, multiconvergence

Paralogy and orthology are two categories of molecular homology distinguishable by the conjunction test, and similarity testing is the most sensitive method of discriminating sequence homology and nonhomology. What of congruence testing, which is the real arbiter in morphology? Obviously it applies, as shown by table 3, for in terms of the formal analysis used here, if congruence testing did not apply, only four categories of molecular homology and nonhomology would be distinguishable. Some molecular homologies that fail congruence are relegated from orthology to paralogy, so that the incongruence is explained away or made congruent by a postulated gene duplication (e.g., see Beintema and Campagne 1987, p. 11). Other possible resolutions of incongruence are discussed below.

It seems that the same three tests of homology—and no others—apply to molecular and morphological homology. It follows that eight categories of molecular homology and homoplasy can be discriminated by the three tests, corresponding to the eight in morphology. Eight molecular categories are suggested in table 3 and are commented on below. Illustrative examples of the categories in morphological and molecular comparisons are given in table 4.

As table 3 shows, orthology is the molecular equivalent of classical homology and paralogy is the molecular equivalent of homonomy, including mass homology (as with feathers, hairs, or erythrocytes) and serial homology. In fact, most orthologues are present in multiple copies in the organism and so fail the conjunction test. This multiplicity is true of all gene products and of all genes and other fragments of the genome in multicellular organisms—metazoans and metaphytes. In unicellular eukaryotes, orthologous genes and nucleotide sequences are present in two copies, allelic pairs that we could equate with the right and left members of paired morphological homologues in bilaterally symmetrical organisms; in prokaryotes, parts of the genome occur in single copies only. Although orthologues (save those in unicellular genomes) fail the conjunction test when the whole organism is considered, I am sure it is correct to equate orthology and homology. I believe that we evade the technical failure in conjunction by abstracting the haploid genome as the standard of comparison, so that we think of, say, the myoglobin or α-crystallin A of a mammal as present in only a single copy (or an allelic pair). In morphology we are accustomed to a similar abstraction, for we treat the adult or life cycle as the standard of comparison. As examples,

we think of a given molar tooth and the mammary glands as homologous (synapomorphous) throughout mammals, despite the fact that neither occurs until quite late in ontogeny. So it seems that one difference between comparative morphology and comparative molecular biology is in the "essence" that is compared: in morphology it is the adult or life cycle; in molecular biology it is the genome.

Paralogy, the relation between α and β hemoglobin—or, more generally, among members of any gene family—is the molecular equivalent of homonomy, serial and mass homology in morphology. The obvious difference between paralogy and homonomy is that in homonomy the multiplication or duplication occurs in ontogeny, so that it is in principle observable, whereas in paralogy the duplication has occurred in phylogeny, so that it is inference rather than observation.

The relations in the third and fourth rows of table 3 do not differ between molecules and morphology. The complement relation (presence of an orthology vs. its absence) and "two orthologies" (presence of two orthologies with the inclusion relationship, such that the group circumscribed by one includes or equals that circumscribed by the other—e.g., cytochrome *c* and myoglobin; cf. notochord and femur) are the same in molecular as in morphological comparisons.

The fifth row of table 3, failing congruence but passing the other two tests and matching parallelism in morphology, is xenology (Gray and Fitch 1983). This is a form of homology (inferred common ancestry) in which the sequence (gene) homology is incongruent with that of the organisms carrying the gene, and horizontal gene transfer or transfection is the assumed cause. Xenology implies "foreign genes" (Gray and Fitch 1983, p. 64), and, in the example on which Gray and Fitch based the concept, two of the four sequences compared are encoded by transposable elements. Gray and Fitch noted that symbiosis and endoparasitism, like transfection, are ways "that cells and organisms have acquired foreign genes in the past." In table 2, endoparasitism is entered in row eight, as the morphological relation failing all three tests; but obviously if one compared an endoparasite in one organism with an endoparasite in another, and if the parasites were either more closely or more distantly related than the hosts, the relation would fail congruence with the host phylogeny but could pass the other two tests and fall out as a version of parallelism, i.e., independent acquisition of "the same" feature.

The interesting difference between parallelism in comparative morphology and xenology in molecular comparisons is that parallelism is usually regarded as nonhomology (because of incongruence), whereas xenology *is* regarded as homology (because of similarity). This emphasizes the dominance of congruence testing in morphology and of similarity testing in molecular biology, for the implication is that the distinction between homology and nonhomology among molecules depends on similarity, whereas in morphology it depends on congruence. However, not all morphologists regard parallelism as nonhomology, a point to which I will return (see below, p. 619).

As a relation fitting the sixth row of table 3, passing similarity but failing the other two tests and corresponding to homoeosis or multiple parallelism in morphology, I have entered paraxenology. This is a new term meaning duplicate or multiple xenology, differing from xenology by the presence of two or more copies of the foreign gene in the host genome; paraxenology is to xenology as paralogy is to orthology, and, in terms of the formal analysis summarized in table 3, the difference within each pair is their performance in the conjunction test. The name *xenology* was first applied (Gray and Fitch 1983) to a situation in prokaryotes in which some of the genes involved are encoded by transposable elements and/or plasmids, so that paraxenology

Table 4
Morphological and Molecular Examples of the Relations Named in Table 3

Morphology	Example	Example	Molecules
Homology	Lens in Vertebrata[a]	Myoglobin in Craniata[b]	Orthology
Homonomy	Lenses of compound eye in Arthropoda[c]	Hemoglobins in Gnathostomata	Paralogy
Complement	Lens present: Vertebrata Absent: Myxinoidea[d]	Lens crystallin: Vertebrata Absent: Myxinoidea[d]	Complement
Two homologies	Rectus muscles and pyramidalis muscle[e]	Myoglobin in Craniata and lens crystallin in Vertebrata	Two orthologies
Parallelism	Mobile nictitans in Reptilia and Carnivora[f]	Globin locus in soybean and in mammals[g]	Xenology
Homoeosis	Replacement of eye by antenna in arthropods[h]	Globin genes in soybean and in mammals[g]	Paraxenology
Multiple parallelism	Ommatidia in Insecta and Crustacea[i]	Gamma globins in hominoids[j]	Gene conversion
Convergence	Lens in Vertebrata and dibranchiate Cephalopoda	[?Lysozyme in cow and langur[k]]	[Convergence]
Endoparasitism	[l]		. . .
Multiple convergence			

NOTE.—Morphological examples (left) are drawn from eyes, and molecular ones (right) are mainly from globins.

[a] Vertebrata = lampreys and gnathostomes, excluding their sister group, the hagfishes.

[b] Craniata = Vertebrata and Myxinoidea (hagfishes).

[c] Compound eyes interpreted as primitive for a monophyletic Arthropoda (Paulus 1979).

[d] Myxinoids (hagfishes) have no lens and so far lack identified homologues of lens crystallins.

[e] Rectus muscles characterize Vertebrata; pyramidalis muscle occurs in turtles, crocodiles, and birds (Gauthier et al. 1988).

[f] Reptilia here in the sense of Gauthier et al. (1988), including birds. According to Gauthier et al. (1988, p. 144) the mobile nictitans is independently developed in derived mammals and in reptiles. It is not known to differ in structure in the two.

[g] Lee et al. (1983) cited the proposal that leghemoglobin (Lb; so far characterized in legumes, *Parasponia*, and *Casuarina*) might have entered angiosperms by horizontal transfer from vertebrates, and they noted the similarity in organization between the soybean Lb locus and mammalian hemoglobin loci, with a central pseudogene flanked by functional genes. They mentioned the possibility that this common organization might reflect transfer of an intact locus from animal to plant. The horizontal transfer theory used to account for plant globins is losing ground (Bogusz et al. 1988) but for illustrative purposes is here assumed to be correct. If the soybean Lb locus were transferred as a unit, the relation with the mammalian globin locus would be xenology, whereas the relation between one Lb gene and a paralogous mammalian gene would be paraxenology.

[h] Bateson (1894, p. 151) illustrated an instance in the crustacean *Palinurus; ophthalmopedia* in *Drosophila* may produce similar effects.

[i] On Manton's (1977) theory of arthropod phylogeny, crustaceans and insects are related only through nonarthropods, and their compound eyes have arisen in parallel. If this theory were true, the relation between their ommatidia would be multiple parallelism.

[j] Slightom et al. (1985).

[k] See text, pp. 617–618.

[l] Morphological examples from the eye seem too contrived; mistaking cysticerci (larval tapeworms) in a vertebrate for part of the host eye might fit here.

rather than xenology is likely, since among prokaryotes *Escherichia coli* strains frequently have both plasmids and chromosomal transposable elements in multiple copies (Hartl et al. 1986). Extrachromosomal elements such as plasmids may generally be

involved in the gene transfer causing xenology among prokaryotes. In eukaryotes an analogous example, producing paraxenology among extrachromosomal elements, is the transspecific introgression reported in Scandinavian *Mus musculus,* with mitochondrial DNA (mtDNA) related not to that of conspecific mice but to mtDNA of the neighboring species *M. domesticus* (see Avise 1986 for review of this and other possible examples involving mtDNA). With regard to the nuclear genome of eukaryotes, Busslinger et al. (1982) have suggested that the h19 histone gene clone of the sea urchin *Psammechinus miliaris* was acquired by horizontal transfer from *Strongylocentrotus,* and Gray and Fitch (1983) cite this as a likely instance of xenology. But since h19 contains paralogous genes and occurs in 3–5 copies/haploid genome in *Psammechinus,* this would be paraxenology rather than xenology. [It now seems that the original observations of Busslinger et al. may have been faulty (Roy Britten, personal communication), but this does not affect the principle here.] The distribution of some of the mobile elements in *Drosophila* suggests that they are xenologous rather than orthologous (Engels 1986; Stacey et al. 1986), so that these repeated elements are another example of paraxenology. An illustrative but unlikely example is given in table 4. Stacey et al. (1986) discuss the possibility of repeated horizontal transmission of transposable elements between species, which could be one source of paraxenologous sequences. Other possibilities are duplication before transmission and duplication after transmission; the intricacies that might result from a combination of these processes are easily imagined and would probably be opaque to analysis. The extent to which paraxenologous sequences may diverge within a lineage is yet to be learned, as is the taxonomic distance that both xenology and paraxenology may span in eukaryotes.

Paraxenology fits in the sixth row of table 3, but it seems very different from one of the corresponding morphological relations, homoeosis. Because genes and species may have different histories, there are two possible ways that sequence comparisons may fail congruence: the inferred history of the sequences may be incongruent either with that of the species, as in xenology, or with that of other sequences within the genome. Incongruence (or unusual similarity) of this second sort is exemplified by gene conversion, which is entered beneath paraxenology in table 3 and provides a closer match with homoeosis. Bateson (1894, p. 85) coined the word *homoeosis* for a form of meristic variation in which "something has been changed into the likeness of something else," and his phrase makes good sense of a correspondence with gene conversion. Gene conversion is not the name of a relation but of a process inferred to explain that similarity between paralogous sequences which implies a relationship between paralogues that is incongruent with that based on other paralogies, because the similarity is too great. The relation has no name, but *plerology* [from the Greek *pleres* (full of, complete)] might serve to emphasize the extra similarity observed. As an example, Goodman et al. (1987, p. 149) cite the two nonallelic loci coding identical α-hemoglobin sequences in many primates. As they say, gene conversion may cause all or part of paralogous sequences to masquerade as orthologues. The comparison between plerology and homoeosis seems apt, for in homoeotic mutants either all of one segment (e.g., bithorax) or part of one segment (e.g., antennapedia) is "converted" into structures normally confined to another segment. But as with the comparison between duplication in homonomy and in paralogy, the "conversion" is an ontogenetic process in homoeosis and an inference about phylogeny in plerology. In this respect and in the kind of mechanism invoked, plerology seems more akin to parallelism in morphology, but the two relations differ in that plerology is within a lineage whereas parallelism is between lineages.

The seventh row of table 3 shows the relation passing conjunction but failing the other two tests. In morphology, convergence fits here, according to my analysis. Is there any equivalent of convergence in molecular sequence comparisons? Several authors have recently denied that there is. On the popular level, Gould (1985) wrote an account of Sibley and Ahlquist's work on DNA-DNA hybridization in birds. He judged the technique "conceptually superior to all others . . . because DNA is complex enough to preclude analogy [=convergence in this context] as a cause of overall similarity. . . . We finally have a method that can sort homology from analogy." Gould's comments imply that convergent similarity is ruled out in comparisons of DNA from different species, and Sibley and Ahlquist agree. They state (1987, p. 100) that "DNA-DNA hybridization data are immune to convergence, because the conditions of the experiments preclude the formation of heteroduplexes between nonhomologous sequences." Goodman et al. (1987, p. 147) also agree, saying that "in terms of nucleotide sequences, there seems to be no equivalent of convergence, or close similarity produced by evolution from different precursors." Woese (1987, p. 226), in a recent review of his work on bacterial phylogeny through sequence analysis, states that "since the number of possible functional configurations for a given gene is enormous by any standards, similarity at the genotypic level (i.e., extensive sequence homology) can never reflect convergent evolution." In these quotations the reasons offered for the absence of convergence in molecular data boil down to the statistical argument justifying algorithms used in searching for molecular homology. Convergence between molecular sequences is too improbable to occur, just as similarity between sequences is too improbable to be explained except by common ancestry. Some might view this argument as viciously or vacuously circular, but the same argument is routinely advocated in morphology [e.g., see Simpson 1961, p. 89; Mayr 1969, p. 220; Bock 1977, p. 890; Riedl 1979, pp. 34 (quoting Remane), 45]. This is the argument from complexity: if two structures are complex enough and similar in detail, probability dictates that they must be homologous rather than convergent.

Probability apart, it is hard to find arguments for convergence at the molecular level. Fitch (1982) presented such an argument and cited one example, illustrated in figure 2. The example concerns two galactose operator nucleotide sequences in *E. coli*, between which Rosenberg and Court (1979) advocated the alignment shown in figure 2A, keyed to the in vitro mRNA initiation site and the adjacent Pribnow box. Smith et al. (1981) showed that the alignment in figure 2B, shifting one sequence by 12 nucleotides, achieves 44 matches in 45 nucleotides. The increase in similarity, from 19 matches (fig. 2A) to 44 (fig. 2B), surely shows the true homology, thereby emphasizing the power of similarity testing with sequence data. The argument of Smith et al. (1981) and Fitch (1982, p. 1134) is, to quote Fitch, that the "similarity [shown in fig. 2A] is a result of convergence, not ancestry." However, Maquat and Reznikoff (1980) showed that the difference between the wild-type *lac* promoter and *lac* P^r 115 is an A/T→T/A transversion at +1, the position of in vitro *lac* transcription initiation. *lac* P^r 115 RNA is estimated to be 12 bases shorter than the wild-type *lac* RNA, and Maquat and Reznikoff published the alignment shown in figure 2C to show how the transversion at +1 in *lac* P^r 115 generates the leading nucleotide of a new Pribnow box (A-A-T-T-G-T-G→T-A-T-T-G-T-G) that includes the three most conserved positions (underlined). The new +1 initiation site of *lac* P^r 115 RNA is ~10 bp downstream from this new box, at +13 in the wild-type sequence, and between positions −26 and −40 in the new *lac* P^r 115 sequence there are matches with some of the highly conserved sequences in promoters, underlined in figure 2C.

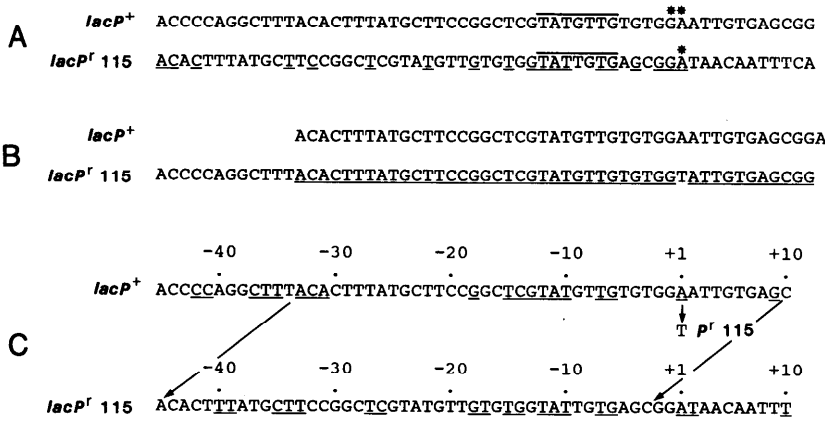

FIG. 2.—Example cited by Smith et al. (1981) and Fitch (1982) as an instance of convergence between molecular sequences. A, Alignment of two *Escherichia coli lac* promoter sequences published by Rosenberg and Court (1979), keyed to the mRNA start site (asterisked) and to the first, second, and sixth nucleotides of the Pribnow box (overlined); the 19 matching nucleotides are underlined. B, The two sequences in A as realigned by Smith et al. (1981), with matches between 44 of 45 nucleotides. C, Alignment of the same two sequences published by Maquat and Reznikoff (1980), with the base pairs numbered relative to the mRNA start site at +1. In the *lacP*$^+$ sequence the A→T change at +1 generating *lacP*^{r} 115 is shown, and the arrows show the 12-bp displacement necessary to align the start sites. Underlined nucleotides are those which Maquat and Reznikoff found to show similarities with conserved sequences described by Rosenberg and Court (1979).

For Fitch (1982), molecular convergence was demonstrated by the alignment in figure 2A. In terms of the three tests advocated here (table 3), categorizing the relation in figure 2A depends on whether that alignment is deemed to pass or fail similarity and congruence. As to similarity, Smith et al. (1981) pointed out that the 19 matches (among 57 bases) in alignment 2A do not exceed random expectation, but Rosenberg and Court keyed their alignment on the Pribnow box and the adjacent, empirically determined initiation site. As to congruence, the *lac P*^{r} 115 sequence was an unpublished personal communication to Rosenberg and Court, and obviously no attempt was made at testing by congruence—for example, by searching for similar sequences in *E. coli* and related species. Any such search would have revealed the virtual identity between *lac P*^{r} 115 and the wild-type *lac* promoter and so would have enforced the alignment found by Maquat and Reznikoff (1980) and Smith et al. (1981). If congruence and similarity are deemed passed by the alignment shown in figure 2A, conjunction is failed (because both sequences were treated by Rosenberg and Court as coexisting in *E. coli*) and the relation is paralogy; if similarity is failed, the relation is "two orthologies." Either of those results matches the way in which Rosenberg and Court treated the alignments. If congruence is deemed failed by the alignment shown in figure 2A, the relation is paraxenology or gene conversion (if similarity is passed) or the nameless relation in the last line of table 3 (if similarity is failed); neither result seems sensible. Alignment 2A cannot be classed as convergence (line seven of table 3) because the conjunction test is failed, both sequences occurring in *E. coli.* The morphological analogy of Fitch's view, that alignment 2A demonstrates convergence, would be "convergence" between two structures in the same organism; naturally, no morphologist would see that as convergence.

The general explanation for convergence is functional adaptation to similar en-

vironments, and it was the "functional equivalence of the region from the proposed Pribnow box to the initiation site" (shown in fig. 2A) that formed the basis for Smith et al.'s (1981) remarks on convergence; there are nine matches in 13 bases, "a rather significant result." But it is clear from figure 2C that the change from the wild-type *lac* promoter to *lac* P^r 115 is divergent. The functional equivalence of the two might be regarded as chance similarity (see Simpson 1961, p. 79) or possibly as preadaptation; it cannot be seen as convergence.

As for other possible examples of molecular convergence by functional adaptation to similar environments, the most thorough study of adaptation in a molecule, Perutz's (1983) review of hemoglobin, yields no instance of what might be convergent adaptation (e.g., to high altitude or to diving) involving more than one or two substitutions (see also Braunitzer et al. 1984); this is hardly the ordered similarity we expect from convergence in morphology, as between canid and marsupial wolves or between the forelimbs of whales and plesiosaurs, to cite a couple of classic examples. The matching asparagine at position 2 in the β hemoglobin chain of elephants and llama (Braunitzer et al. 1984), though it may be germane to Hannibal's passage of the Alps, seems to me again to exemplify chance similarity rather than convergence.

As another, more complex example, Beintema and Lenstra (1982) and Beintema et al. (1986) have discussed the distribution of carbohydrate-attachment sites in mammalian pancreatic ribonucleases. These sites require a sequence of Asn-X-Ser/Thr (X may be any residue except Pro), but not all such sequences possess attached carbohydrate. Six different carbohydrate-attachment sites are known in mammalian pancreatic ribonuclease sequences; they are thought to be advantageous in cecal digestion, and so are candidates for adaptive convergence. Among the six Asn-X-Ser/Thr sites (see the distribution in Beintema et al. 1986, fig. 7), two are known in only one species, and three of the remainder may be primitive for mammals (Beintema and Lenstra 1982, fig. 11). The sixth site is at positions 21–23; there hippopotamus has Asn-Asp-Ser, without attached carbohydrate, whereas pig and guinea pig B have Asn-Ser-Ser, with carbohydrate. Hippopotamus, pig, and guinea pig B are among the labile taxa in pancreatic ribonuclease cladograms (Beintema et al. 1986, fig. 3), and none of the more parsimonious versions reproduces the morphologists' conviction that pigs and hippopotami are sister groups (e.g., see Gentry and Hooker 1988). Although Asn-X-Ser at positions 21–23 is apparently primitive for artiodactyls, pig and guinea pig have surely "converged" in acquiring the carbohydrate-attachment sequence. However, by my estimate, the basis for this "convergence" in these two taxa involves change from Ser to Asn at position 21 in guinea pig B, reversion (from Asn) to the primitive Ser at position 22 in guinea pig B, and retention of the primitive Ser at position 23 in both; it can be accounted for by two nucleotide changes, one of which is a reversal. Like the elephant/llama example above, it seems to exemplify chance resemblance more than it does the ordered or misleading similarity that the morphologist understands by convergence.

As a final example, the most substantial yet found, Stewart et al. (1987) reported sequence convergence between the stomach lysozymes of a ruminant (cow, *Bos taurus*) and a colobine primate (hanuman langur, *Presbytis entelus*), groups that have adopted lysozyme *c* to bacterial digestion in the stomach. The langur shares amino acids at five (among 130) positions with cow rather than with its primate relatives, and at four of those positions the shared residue is unique to colobines and ruminants among known vertebrate lysozyme sequences. These characters were sufficient to make the tree grouping cow and langur equally parsimonious to the "biological" tree grouping

langur with other primates, and the matches exceeded chance expectation ($P < 0.05$). By the criterion of identity (parallelism) or difference (convergence) in the inferred ancestral residue, Stewart et al. divided the five homoplastic cow/langur amino acid matches into parallel and convergent changes and concluded that three appear to be in parallel and two appear to be convergent. Nucleotide sequences are not yet available to determine whether ambiguity in parsimony trees persists at the DNA level—or whether these matching amino acids are "the same" at that level.

The general problem here involves the two levels at which molecular sequences may be compared. In table 3 and in the preceding discussion of molecular relations I have treated sequences (of amino acids or nucleotides) as the units in comparative molecular biology. Once two or more sequences are aligned and homology between them is regarded as established, comparison may move to the detail of corresponding amino acids or nucleotides at homologous sites. In any two sequences these will be identical or will differ. If different, one or both are taken to have diverged from identity; if identical, the identity may be (*a*) primary, i.e., owing to common ancestry, (*b*) secondary, i.e., owing to change in one or both. These two kinds of identity will be inferred from a tree in which reconstructed ancestral sequences occupy the nodes. Primary identity is symplesiomorphy, whereas there might be four possible explanations for secondary identity: reversal, parallelism, convergence, and chance similarity. A reviewer commented that if two nucleotide sequences possess G at a particular position and if the inferred history is A→T→G in one case and A→G in the other, convergence would be the correct explanation. This example recalls the problems that morphologists have found in the theoretical distinction between parallelism and convergence, for it matches the example of parallelism given by Holmes (1980, p. 48): the initial and terminal condition are the same in two lineages, and similarity with respect to the character between the lineages decreases and then increases. The implication may be that, at this level of secondary identity at individual homologous nucleotide positions, discrimination of convergence or parallelism from reversal and chance similarity may be no more than a matter of taste or conviction, not to be profitably discussed further. If reversal can be excluded, the null hypothesis in secondary nucleotide identity will be chance similarity, to be expected at about a quarter of positions, and therefore some additional argument seems necessary if convergence or parallelism is to be invoked. By the criteria (tests) advocated here, secondary identity at a nucleotide position will be parallelism (passing similarity but failing congruence; incongruence is the reason for inferring the identity to be secondary). Secondary identity in amino acid sequences will generally not be assessable until nucleotide sequences are available—for if, say, the lysines at locus 14 in cow and langur lysozyme *c* are coded by AAA and AAG, they are not "the same."

Responding to criticism of their argument for convergence in lysozyme (Cornish-Bowden 1988), Stewart et al. (1988) wrote of their example: "the most plausible case available . . . is not yet conclusive." So with the possible exception of cow/langur lysozyme, it seems true that there is no detected molecular equivalent of convergence—or of misleading similarity—except in the most trivial sense. This surprising conclusion can be seen either as a consequence of the power of similarity testing in molecular sequences or as a consequence of a concept of homology in terms of similarity. The level at which the cut-off between homology and nonhomology is set in molecular similarity testing (e.g., 3.0 SDs above chance expectation) will surely result in some distant homologies being rejected as nonhomology, and it may result in some convergences being accepted as homologous. But this is not a problem unique to molecular

comparisons. In morphology, where congruence is the decisive test, all similarities that pass congruence are accepted as homologies—but some proportion of those similarities would surely be seen as having arisen by convergence or parallelism, were their true history known.

The last row of table 3—i.e., failing of all three tests—would be some relation matching endoparasitism or multiple convergence, put there in table 2. Endoparasitism does occur at the molecular level, as exemplified by xenology, in which the relation is recognized by similarity between the parasite and its source. But whereas in morphology it might be credible that one should mistake parts of an endoparasite for parts of its host and mistakenly compare them with superficially similar parts of another organism, no such mistake seems conceivable at the molecular level. This is because, in Stevens's (1984) phrase, "without some similarity, we should not even dream of homology," and, if there is no deceptive similarity to cause molecular convergence, there is no deceptive similarity to cause the kind of mistake that would occupy the last row of table 3.

Discussion

Concepts of molecular homology differ from those in morphology in one obvious way: they developed entirely within evolutionary biology, whereas morphological concepts were taken over intact from preevolutionary biology. As Russell (1916, pp. 247, 302) put it, "current morphology, Darwin found, could be taken over, lock, stock and barrel, to the evolutionary camp," and it followed "that the coming of evolution made comparatively little difference to pure morphology, that no new criteria of homology were introduced." Molecular homology has brought in concepts such as gene duplication and transfection, concepts undreamed of by Darwin and his successors. Nevertheless, the criteria or tests of homology are no different in morphology and molecular biology, as I have tried to show. There are, however, three differences between morphological and molecular homology, and they will be discussed here. First, the relative importance of the three tests differs in the morphological and molecular fields. Second, because molecular homologies may reflect the phylogeny of either organisms (e.g., orthology) or bits of DNA (e.g., xenology), the way in which the three tests split relations into useful and useless categories is different and more intricate with molecules than with morphology. And, third, it is a consequence of the first two points that molecular homology is not exactly equivalent to synapomorphy.

First, as for the importance of the three tests, in morphology the congruence test is the arbiter separating homologous from nonhomologous relations, whereas with molecular sequence data similarity testing has this dominant role. One result of this is molecular comparisons' apparent immunity to mistakes caused by convergence, as discussed above. Another consequence is that the boundary between homology and nonhomology is set in a different place in the morphological and molecular fields. In morphology, the "gray zone" (Bock 1969, p. 416) between homology and nonhomology concerns congruence—or inferred common ancestry—and whether parallelism (which does invoke common ancestry) should be included or excluded from homology. Most biologists have excluded it, as I have (table 2), but a few (Mayr 1974, p. 116; Hecht and Edwards 1977, p. 7) have included it. Others include a part of parallelism in homology (Saether 1983). Hailman (1976, p. 195) calls parallelism "a difficult concept and one that has always proved troublesome" because it "does not fit nicely" in either homology or analogy. Van Valen (1982, p. 307) sees it as "perhaps a matter of taste" whether one includes or excludes parallelism in homology, and Roth (1984,

Table 5
Results of Congruence and Similarity Testing in Morphology and in Molecules

Congruence Test	Similarity Test	Morphological Relations	Molecular Relations
Pass	Pass	Homology; H, S	Orthology; H, S
		Homonomy; H, S	Paralogy; H, G
Pass	Fail	Complement; S	Complement; S
		Two homologies; S	Two orthologies; S
Fail	Pass	Parallelism	Xenology; H, G
		Homoeosis	Paraxenology; H, G
			Plerology; H
Fail	Fail	Convergence	. . .
		Endoparasitism	. . .

NOTE.—The suffixes H, S, and G after the relations in columns 3 and 4 indicate that the relation is regarded as homology (H), is useful in systematics (or in reconstructing species phylogeny) (S), or is useful in reconstructing gene phylogeny (G).

p. 23) states that "at some level, distinguishing homology from parallelism will neither be possible nor useful."

In molecular sequence comparisons the "gray zone" between homology and nonhomology concerns similarity—and whether similarities (say, 2.0 SDs above chance expectation) are or are not homologous. It is thus a problem of statistics rather than of common ancestry. But in molecular comparisons there may be another "gray zone," one that does concern common ancestry: this is the distinction between orthologous (latest common ancestry through speciation) and paralogous (latest common ancestry through gene duplication) sequences. As Goodman (1976, p. 325) says, "in practice . . . one must use 'operationally orthologous' sequences without being sure that all are strictly orthologous" (see also Goodman et al. 1987, p. 150, on this "loose definition" of orthology).

As for the distinction between useful and useless comparisons, tables 5–7 show the morphological and molecular relations (distinguished in table 3) divided into three different sets according to their performance in two of the three tests. As the

Table 6
Results of Congruence and Conjunction Testing in Morphology and in Molecules

Congruence Test	Conjunction Test	Morphological Relations	Molecular Relations
Pass	Pass	Homology; H, S	Orthology; H, S
		Complement; S	Complement; S
Pass	Fail	Homonomy; H, S	Paralogy; H, G
		Two homologies; S	Two orthologies, S
Fail	Pass	Parallelism	Xenology; H, G
		Convergence	. . .
Fail	Fail	Homoeosis	Paraxenology; H, G
		Endoparasitism	Plerology; H
			. . .

NOTE.—Abbreviations are as in table 5.

Table 7
Results of Similarity and Conjunction Testing in Morphology and in Molecules

Similarity Test	Conjunction Test	Morphological Relations	Molecular Relations
Pass	Pass	Homology; H, S Parallelism	Orthology; H, S Xenology; H, G
Pass	Fail	Homonomy; H, S Homoeosis	Paralogy; H, G Paraxenology; H, G Plerology; H
Fail	Pass	Complement; S Convergence	Complement; S . . .
Fail	Fail	Two homologies; S Endoparasitism	Two orthologies; S . . .

NOTE.—Abbreviations are as in table 5.

tables show, in morphology the only useful relations are the four passing congruence, and among those only two (homology and homonomy) are homologous, although the other two—the complement relation (presence vs. absence) and "two homologies"—also involve homology. In molecular comparisons the only useful relations for species phylogeny are those passing congruence, but among the four relations passing it one (paralogy) helps with gene phylogeny, not species phylogeny. There are five homologous relations in molecular comparisons, all of those which pass similarity. Only one of the five, orthology, contributes to species phylogeny, and, among the other four, three (paralogy, xenology, and paraxenology) contribute to gene phylogeny and the third (plerology) is a hindrance to both gene and species phylogeny, having a role much like parallelism or convergence in morphology.

The conclusion one might draw from all this is that the criterion used to *define* homology—i.e., the criterion of common ancestry—is a theoretical concept. Like truth, we must approximate it as best we can, and we have no touchstone to tell whether we have found it. The criteria we use to *recognize* homology are the same in morphology and in molecular biology. But because molecular sequences are one-dimensional, recognition of molecular homology is a statistical problem, and the limit between homology and nonhomology is set by the resolving power of statistical procedures. In morphology, homologies concern three- or four-dimensional structures, and recognition of homology is a problem of systematics. In morphology the limit between homology and nonhomology is set by the resolving power of systematics, the confidence with which we can resolve monophyletic groups by congruence of features; and so in morphology it is legitimate to equate homology and synapomorphy. In molecular phylogenetics, there is no exact equation between homology and synapomorphy, first because the operational limit between molecular homology and nonhomology is statistical, and second because the theoretical criterion of homology—i.e., the criterion of common ancestry—does not distinguish between taxon lineages and gene lineages, which may ramify between and within taxa.

Reeck et al.'s (1987) letter to *Cell,* with which I began this paper, provoked some response (Aboitiz 1987; Dover 1987; Wegnez 1987). Dover made an interesting distinction between homology as a concept of *quality,* as in inferred common ancestry or all-or-none correspondence, and homology as a concept of *quantity,* as in degree of similarity. Suggesting that the quantity and the quality are inextricably bound, he

recommended that we either drop the word *homology* or learn to live with loose usage of it. Wegnez also distinguished the all-or-none morphological concept of homology from the quantitative sequence-comparison version, and he recommended *isology* as a name for the latter. Aboitiz wrote that "strictly speaking, 'homology' as understood in anatomy has no parallel in molecular biology." I have tried to show that most aspects of molecular homology *do* have exact parallels or counterparts in morphology. Although some molecular versions of homology bring in wholly new ideas, surely morphologists and molecular biologists should do all they can to maintain a common language and a common comparative discipline. In particular, the all-or-none theoretical distinction between homology and nonhomology is one we should seek to conserve.

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LITERATURE CITED

ABOITIZ, F. 1987. Letter to the editor. Cell **51**:515–516.

AVISE, J. C. 1986. Mitochondrial DNA and the evolutionary genetics of higher animals. Philos. Trans. R. Soc. Lond. [Biol.] **312**:325–342.

AX, P. 1987. The phylogenetic system. John Wiley & Sons, Chichester, England.

BATESON, W. 1894. Materials for the study of variation. Macmillan, London.

BEINTEMA, J. J., and R. N. CAMPAGNE. 1987. Molecular evolution of rodent insulins. Mol. Biol. Evol. **4**:10–18.

BEINTEMA, J. J., W. M. FITCH, and A. CARSANA. 1986. Molecular evolution of pancreatic-type ribonucleases. Mol. Biol. Evol. **3**:262–275.

BEINTEMA, J. J., and J. A. LENSTRA. 1982. Evolution of mammalian pancreatic ribonucleases. Pp. 43–73 *in* M. Goodman, ed. Macromolecular sequences in systematic and evolutionary biology. Plenum, New York.

BISHOP, M. J., and E. A. THOMPSON. 1984. Fast computer search for similar DNA sequences. Nucleic Acids Res. **12**:5471–5474.

BOCK, W. J. 1969. Comparative morphology in systematics. Pp. 411–448 *in* Systematic biology. National Academy of Sciences Publication 1692. National Academy of Sciences, Washington, D.C.

———, 1977. Foundations and methods of evolutionary classification. Pp. 851–895 *in* M. K. Hecht, P. C. Goody, and B. M. Hecht, eds. Major patterns in vertebrate evolution. Plenum, New York.

BOGUSZ, D., C. A. APPLEBY, J. LANDSMANN, E. S. DENNIS, M. J. TRINICK, and W. J. PEACOCK. 1988. Functioning haemoglobin genes in non-nodulating plants. Nature **331**:178–180.

BRAUNITZER, G., A. STANGL, B. SCHRANK, C. KROMBACH, and H. WIESNER. 1984. The primary structure of the haemoglobin of the African elephant (*Loxodonta africana,* Proboscidea): asparagine in position 2 of the β-chain. Hoppe-Seyler's Z. Physiol. Chem. **365**:743–749.

BUSSLINGER, M., S. RUSCONI, and M. L. BIRNSTIEL. 1982. An unusual evolutionary behaviour of a sea urchin histone gene cluster. EMBO J. **1**:27–33.

CORNISH-BOWDEN, A. 1988. Convergent evolution of lysozyme sequences? Nature **332**:787–788.

CRACRAFT. J. 1981. The use of functional and adaptive criteria in phylogenetic systematics. Am. Zool. **21**:21–36.

DAYHOFF, M. O., W. C. BARKER, and L. T. HUNT. 1983. Establishing distant homologies in protein sequences. Methods Enzymol. **91**:524–545.

DOOLITTLE, R. F. 1981. Similar amino acid sequences: chance or common ancestry? Science **214**:149–159.

DOVER, G. A. 1987. Letter to the editor. Cell **51**:515.

ELDREDGE, N., and J. CRACRAFT. 1980. Phylogenetic patterns and the evolutionary process. Columbia University Press, New York.

ENGELS, W. R. 1986. On the evolution and population genetics of hybrid-dysgenesis-causing transposable elements in *Drosophila.* Philos. Trans. R. Soc. Lond. [Biol.] **312**:205–215.

FITCH, W. M. 1966. An improved method of testing for evolutionary homology. J. Mol. Biol. **16**:9–16.

———. 1970*a*. Distinguishing homologous from analogous proteins. Syst. Zool. **19**:99–113.

———. 1970*b*. Further improvements in the method of testing for evolutionary homology among proteins. J. Mol. Biol. **49**:1–14.

———. 1982. The challenges to Darwinism since the last centennial and the impact of molecular studies. Evolution **36**:1133–1143.

FITCH, W. M., and E. MARGOLIASH. 1967. Construction of phylogenetic trees. Science **155**: 279–284.

GAUTHIER, J., A. G. KLUGE, and T. ROWE. 1988. Amniote phylogeny and the importance of fossils. Cladistics **4**:105–209.

GENTRY, A. W., and J. J. HOOKER. 1988. The phylogeny of the Artiodactyla. Pp. 235–272 *in* M. J. BENTON, ed. The phylogeny and classification of tetrapods. Vol. **2**: Mammals. Clarendon, Oxford.

GHISELIN, M. T. 1976. The nomenclature of correspondence: a new look at "homology" and "analogy." Pp. 129–142 *in* R. B. Masterson, W. Hodos, and H. Jerison, eds. Evolution, brain and behavior: persistent problems. Lawrence Erlbaum, Hillsdale, N.J.

———. 1981. Categories, life and thinking. Behav. Brain Sci. **4**:269–313.

———. 1984. "Definition," "character," and other equivocal terms. Syst. Zool. **33**:104–110.

GOODMAN, M. 1976. Toward a genealogical description of the primates. Pp. 321–353 *in* M. Goodman and R. E. Tashian, eds. Molecular anthropology. Plenum, New York.

GOODMAN, M., M. M. MIYAMOTO, and J. CZELUSNIAK. 1987. Pattern and process in vertebrate phylogeny revealed by coevolution of molecules and morphologies. Pp. 141–176 *in* C. Patterson, ed. Molecules and morphology in evolution: conflict or compromise. Cambridge University Press, Cambridge.

GOSLINER, T. M., and M. T. GHISELIN. 1984. Parallel evolution in opisthobranch gastropods and its implications for phylogenetic methodology. Syst. Zool. **33**:255–274.

GOULD, S. J. 1985. A clock of evolution. Nat. Hist. **94**(4): 12–20.

GRAY, G. S., and W. M. FITCH. 1983. Evolution of antibiotic resistance genes: the DNA sequence of a kanamycin resistance gene from *Staphylococcus aureus.* Mol. Biol. Evol. **1**:57–66.

HAAS, O., and G. G. SIMPSON. 1946. Analysis of some phylogenetic terms, with attempts at redefinition. Proc. Am. Philos. Soc. **90**:319–349.

HAILMAN, J. P. 1976. Homology: logic, information, and efficiency. Pp. 181–198 *in* R. B. Masterson, W. Hodos, and H. Jerison, eds. Evolution, brain and behavior: persistent problems. Lawrence Erlbaum, Hillsdale, N.J.

HARTL, D. L., M. MEDHORA, L. GREEN, and D. E. DYKHUISEN. 1986. The evolution of DNA sequences in *Escherichia coli.* Philos. Trans. R. Soc. Lond. [Biol.] **312**:191–204.

HECHT, M. K., and J. L. EDWARDS. 1977. The methodology of phylogenetic inference above the species level. Pp. 3–51 *in* M. K. Hecht, P. C. Goody, and B. M. Hecht, eds. Major patterns in vertebrate evolution. Plenum, New York.

HENNIG, W. 1966. Phylogenetic systematics. University of Illinois Press, Urbana.

HOLMES, E. B. 1980. Reconsideration of some systematic concepts and terms. Evol. Theory **5**: 35–87.

JARDINE, N. 1970. The observational and theoretical components of homology: a study based

on the morphology of the dermal skull-roofs of rhipidistian fishes. Biol. J. Linnean Soc. **1**: 327–361.

JARDINE, N., and C. J. JARDINE. 1967. Numerical homology. Nature **216**:301–302.

KANEHISA, M. 1984. Use of statistical criteria for screening potential homologies in nucleic acid sequences. Nucleic Acids Res. **12**:203–213.

KARLIN, S., G. GHANDOUR, F. OST, S. TAVARE, and L. J. KORN. 1983. New approaches for computer analysis of nucleic acid sequences. Proc. Natl. Acad. Sci. USA **80**:5660–5664.

LEE, J. S., G. G. BROWN, and D. P. S. VERMA. 1983. Chromosomal arrangement of leghemoglobin genes in soybean. Nucleic Acids Res. **11**:5541–5553.

LEWIN, R. 1987. When does homology mean something else? Science **237**:1570.

LIPMAN, D. J., W. J. WILBUR, T. F. SMITH, and M. S. WATERMAN. 1984. On the statistical significance of nucleic acid similarities. Nucleic Acids Res. **12**:215–226.

LØVTRUP, S. 1977. The phylogeny of vertebrates. John Wiley & Sons, London.

MANTON, S. M. 1977. The Arthropoda: habits, functional morphology and evolution. Oxford University Press, Oxford.

MAQUAT, L. E., and W. S. REZNIKOFF. 1980. *lac* Promoter mutation *Pr* 115 generates a new transcription initiation point. J. Mol. Biol. **139**:551–556.

MARGOLIASH, E., W. M. FITCH, and R. E. DICKERSON. 1968. Molecular expression of evolutionary phenomena in the primary and tertiary structures of cytochrome *c*. Brookhaven Symp. Biol. **21**:259–305.

MAYR, E. 1969. Principles of systematic zoology. McGraw-Hill, New York.

———. 1974. Cladistic analysis or cladistic classification? Z. Zool. Syst. Evolutionsforch. **12**: 94–128.

MEACHAM, C. A., and G. F. ESTABROOK. 1985. Compatibility methods in systematics. Annu. Rev. Ecol. Syst. **16**:431–446.

NELSON, G. J., and N. I. PLATNICK. 1981. Systematics and biogeography. Columbia University Press, New York.

NEURATH, H., K. A. WALSH, and W. P. WINTER. 1967. Evolution of structure and function of proteases. Science **158**:1638–1644.

NOLAN, C., and E. MARGOLIASH. 1968. Comparative aspects of primary structure of proteins. Annu. Rev. Biochem. **37**:727–790.

OWEN, R. 1843. Lectures on the comparative anatomy and physiology of the invertebrate animals. Longman, Brown, Green, & Longmans, London.

———. 1849. On the nature of limbs. John van Voorst, London.

PATTERSON, C. 1982. Morphological characters and homology. Pp. 21–74 *in* K. A. Joysey and A. E. Friday, eds. Problems of phylogenetic reconstruction. Academic Press, London.

PAULUS, H. F. 1979. Eye structure and the monophyly of the Arthropoda. Pp. 299–383 *in* A. P. Gupta, ed. Arthropod phylogeny. Van Nostrand-Reinhold, New York.

PERUTZ, M. F. 1983. Species adaptation in a protein molecule. Mol. Biol. Evol. **1**:1–28.

REECK, G. R., C. DE HÄEN, D. C. TELLER, R. F. DOOLITTLE, W. M. FITCH, R. E. DICKERSON, P. CHAMBON, A. D. MCLACHLAN, E. MARGOLIASH, T. H. JUKES, and E. ZUCKERKANDL. 1987. "Homology" in proteins and nucleic acids: a terminology muddle and a way out of it. Cell **50**:667.

RIEDL, R. 1979. Order in living organisms. John Wiley & Sons, Chichester, England.

ROSENBERG, M., and D. COURT. 1979. Regulatory sequences involved in the promotion and termination of RNA transcription. Annu. Rev. Genet. **13**:319–353.

ROTH, V. L. 1984. On homology. Biol. J. Linnean Soc. **22**:13–29.

RUSSELL, E. S. 1916. Form and function. John Murray, London.

SAETHER, O. A. 1983. The canalized evolutionary potential: inconsistencies in phylogenetic reasoning. Syst. Zool. **32**:343–359.

SCHOCH, R. M. 1986. Phylogeny reconstruction in paleontology. Van Nostrand-Reinhold, New York.

SIBLEY, C. G., and J. E. AHLQUIST. 1987. Avian phylogeny reconstructed from comparison of the genetic material, DNA. Pp. 95–121 *in* C. Patterson, ed. Molecules and morphology in evolution: conflict or compromise. Cambridge University Press, Cambridge.

SIMPSON, G. G. 1961. Principles of animal taxonomy. Columbia University Press, New York.

SLIGHTOM, J. L., L.-Y. E. CHANG, B. F. KOOP, and M. GOODMAN. 1985. Chimpanzee fetal $^{G}\gamma$ and $^{A}\gamma$ globin gene nucleotide sequences provide further evidence of gene conversions in hominine evolution. Mol. Biol. Evol. **2**:370–389.

SMITH, T. F., M. S. WATERMAN, and W. M. FITCH. 1981. Comparative biosequence metrics. J. Mol. Evol. **18**:38–46.

SOKAL, R. R., and P. H. A. SNEATH. 1963. Principles of numerical taxonomy. W. H. Freeman, San Francisco.

STACEY, S. N., R. A. LANSMAN, H. W. BROCK, and T. A. GRIGLIATTI. 1986. Distribution and conservation of mobile elements in the genus *Drosophila.* Mol. Biol. Evol. **3**:522–534.

STEVENS, P. F. 1984. Homology and phylogeny: morphology and systematics. Syst. Botany **9**: 395–409.

———. 1987. Pattern and process: phylogenetic reconstruction in botany. Pp. 155–179 *in* H. M. Hoenigswald and L. F. Wiener, eds. Biological metaphor and cladistic classification. Frances Pinter, London.

STEWART, C.-B., J. W. SCHILLING, and A. C. WILSON. 1987. Adaptive evolution in the stomach lysozymes of foregut fermenters. Nature **330**:401–404.

———. 1988. Reply to Cornish-Bowden. Nature **332**:788.

VAN VALEN, L. M. 1982. Homology and causes. J. Morphol. **173**:305–312.

WAGNER, G. P. 1986. The systems approach: an interface between development and population genetic aspects of evolution. Pp. 149–165 *in* D. M. Raup and D. Jablonski, eds. Patterns and processes in the history of life. Springer, Berlin.

WEGNEZ, M. 1987. Letter to the editor. Cell **51**:516.

WHITE, C. T., S. C. HARDIES, C. A. HUTCHINSON, and M. H. EDGELL. 1984. The diagonal-traverse homology search algorithm for locating similarities between two sequences. Nucleic Acids Res. **12**:751–766.

WIENER, L. F. 1987. Of phonetics and genetics: a comparison of classification in linguistic and organic systems. Pp. 217–226 *in* H. M. Hoenigswald and L. F. Wiener, eds. Biological metaphor and cladistic classification. Frances Pinter, London.

WILEY, E. O. 1981. Phylogenetics. John Wiley & Sons, New York.

WINTER, W. P., K. A. WALSH, and H. NEURATH. 1968. Homology as applied to proteins. Science **162**:1433.

WOESE, C. R. 1987. Bacterial evolution. Microbiol. Rev. **51**:221–271.

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