Homology as Applied to Proteins

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All this concern for the wildlife of the Amazon is encouraging. Let us hope that the Basin will escape the tragedies we have witnessed on our own continent. There still is plenty of time if they (and we) act wisely rather than impulsively. Our letters will have served a purpose if they help arouse intelligent concern for the largest remaining untouched wilderness in the world.

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"Do cats eat bats? Do cats eat bats?" and sometimes "Do bats eat cats?" for you see, as she couldn't answer either question, it didn't much matter which way she put it (*1*).

Our article entitled "Evolution of structure and function of proteases" dealing with the biochemical approach to the subject of evolution as exemplified by studies of proteolytic enzymes (*2*) put forth a definition of the term "homology" as it applies to similarities in protein structures. This word has been much bandied about and generally used by many to represent a host of ill-defined concepts. We proposed that the word be taken to connote the occurrence of a degree of structural similarity among proteins greater than might be anticipated by chance alone.

This definition has been criticized by Margoliash (*3*). His position is that since evolution is traditionally the province of the classical biologist, the classical biologist's definition of "homology" should prevail. This would add to our definition the additional qualification that the protein structures in question must have evolved from a common ancestral gene. The problem with this restrictive definition is that the word, although precisely defined, can seldom be used in a precise sense. For example, did ancestral genes common to divergent populations give rise to "homologous" proteins, or does the occurrence of "homologous" proteins mean that they arose from genes having a common ancestor? It really doesn't matter how we put it because like Lewis Carroll's *Alice,* we do not know the answer to either question. The perishable nature of the gene prevents us from obtaining concrete and objective evidence on the nature or existence of ancestral genes. This is in sharp contrast to the position of the classical biologist who has at his service an assemblage of fossil forms to provide independent evidence for the existence of ancestors embodying morphological features common to diverse modern populations. Thus if the evolutionary biologist concludes that the wing of a hummingbird and the foreleg of a gnu exhibit homology, he could present not only anatomical studies based on specimens from extant populations, but also a detailed fossil record substantiating the divergent evolution of these two structures from a common ancestor. The evolutionary biochemist is less fortunate. He can show the similarity of two or more protein structures but he has not and cannot have any independent experimental evidence relative to the question of ancestral genes. Applying the restriction that homology implies common ancestry, it would be impossible to conclude with certainty that two proteins are homologous. Of course, the argument is advanced that the probability of a group of structurally related genes arising independently is so small that they must have evolved from a common evolutionary progenitor. While this argument has validity in most cases, it seems possible that each gene prototype may have arisen more than once. When one considers that the ability to fly, for example, has evolved independently at least several times over the eons, as in the case of insects, birds, and bats, it does not seem in the least amazing that a single structural gene could have had several independent points of origin.

It seems clear that as our approach to an understanding of the living world changes, so must our experimental methods and so must the language we use to describe the results. It would indeed be unfortunate if, in pursuit of the science of change in living populations, it were not recognized that words, like organisms, cannot be allowed to become inflexible. They must either adapt to the changing needs of the scientific community that fosters them or fall into the extinction of disuse.

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References

1. L. Carroll, *Alice in Wonderland* (Random House, New York, 1957).
2. H. Neurath, K. A. Walsh, W. P. Winter, *Science* **158**, 1638 (1967).
3. C. Nolan and E. Margoliash, *Ann. Rev. Biochem.* **37**, 727 (1968).

Regulation of Indirect Costs

The recent furor over the Mansfield Amendment (News and Comment, 18 Oct., p. 337) again reveals the deep confusion by most responsible people in both universities and government on the subject of indirect costs—"overhead." Indirect costs are *real costs* incurred in the support of research activity. The rate is uniformly calculated —and subject to full audit—under Bureau of the Budget Circular A–21 which defines both allowable and unallowable expenditures for an institution and establishes for recovery an appropriate portion of such allowable costs based on level of research activity. The percentage rate, while widely variable as a function of the type and sophistication of a given university's approach to its accounting and budgeting, represents a base for legitimate and real costing.

These allowable costs in support of research are for such necessary functions as operation of the business office and other administrative support, maintenance and amortization of research-related equipment or space, use of library holdings, and so forth. Unfortunately although real institutional dollars are clearly spent for these purposes, many institutions view overhead dollars as a bonus or free money—university accounting systems or university administrators do play strange games at times. The allocation of these "free funds" to "research pools," "football fields," or the "president's contingency fund," is in violation of the intent and purpose of the indirect cost recovery process. If a university does not recognize the real costs of support and administration of research, it is guilty of a serious dereliction morally, and possibly legally, since in reality it is robbing general funds from many other functional areas.

Congressman Daddario and other concerned legislators must have the support of all institutions which have various methods of regulating indirect costs. Both faculty and administrators must understand the realities of the process—for the sake of their university, and for the growth of research on a solid fiscal base. One more definitive hearing on this topic may be of real value to both the universities and the government.

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