Book Reviews

Antibody Diversity

The Variation and Adaptive Expression of Antibodies. GEORGE P. SMITH. Harvard University Press, Cambridge, Mass., 1973. xiv, 220 pp., illus. $12.

Early in 1965 a meeting of the Antibody Workshop was held at Warner Springs, California, a small resort community about 60 miles east of San Diego. The meeting, with about 80 persons in attendance, was unique on several counts. Largely organized by Melvin Cohn (of the Salk Institute), a determined effort had been made to infiltrate the immunologic ranks with a galaxy of stellar molecular biologists, including James Watson, Francis Crick, Christian Anfinsen, Max Delbrück, Seymour Benzer, and a dozen other nonimmunologists of high repute. The program was simple enough—a few talks on immunologically competent cells, immunogenetics, antibody structure, and the like. For the first two days everything went according to schedule, predictable progress—but not much more—being reported, and the sessions were only slightly lengthened by the presence of the imported Brain Trust. On the third morning, however, the assemblage was electrified by the unexpected announcement from Norbert Hilschmann, reporting on work he had done in Lyman Craig's laboratory, that he had virtually completed the amino acid sequences of two very different Bence-Jones proteins (the equivalent of antibody light chains), and, with one quite explicable exception, had found that all the many amino acid replacements had occurred in the amino-terminal half of the molecules. Clearly, immunoglobulin light chains had a variable half and a constant half.

The impact on the meeting was instantaneous, something very close to pandemonium ensuing. Francis Crick made his way to the chalkboard and drew a flurry of twisted loops, implying that simple DNA rearrangements could now explain antibody diversity; Seymour Benzer declared that at last immunology had become a science. It was one of those rare moments when an entire group senses that a solution to a major problem is directly at hand but no one is quite sure of how to put the last piece in the puzzle, or even how to find it. Surely if only a few more sequences were obtained the pattern would become absolutely clear.

During the ensuing nine years the amino acid sequence data have reached avalanche proportions, and the one thing that has been completely borne out is that both heavy and light chains of immunoglobulins have variable and constant regions, the variability being the basis of antibody specificity. In this well-written and concise book, George Smith reviews the major theories on antibody diversity spawned by the Hilschmann-Craig discovery (although the roots of some of these theories predate that discovery considerably, of course). Essentially, the theories, all of which are consistent with the dogma of clonal selection as put forth by Burnet, can be divided into two groups, somatic and germ-line—which is to ask, Is the observed variability introduced during the development of the organism by some somatic process, or are there DNA counterparts in the genome for every one of the many variable regions involved in antibody specificity? For nine years the two schools of thought have collided at every opportunity, seeing the same data but usually coming up with different interpretations. Although Smith presents many arguments on both sides, he clearly favors the germ-line theory, especially as posed by Dreyer and Bennett in the immediate aftermath of Warner Springs.

The book opens with a brief but informative chapter on the general nature of the immune response, underscoring the ability of vertebrates to "expect the unexpected" in synthesizing antibodies which can combine with alien substances. Chapter 2 describes the fundamental structures of immunoglobulins (antibodies and their relatives) and introduces the reader to the complexity of merely naming the diverse types. Because one of the main purposes of the book is to show that the amino acid replacements found in the variable portions of immunoglobulins follow the same patterns found in comparisons of other proteins for which a known genealogy exists, there is next a chapter on the reconstruction of phylogenies using amino acid sequence data, especially along the lines developed by Walter Fitch. From there the author proceeds logically to a review of what is known about the evolution of constant regions and their evolutionary relationships to each other.

The controversy, as such, begins in chapter 5 with descriptions of the leading theories of antibody diversity. Smith gives a bit more space to translational theories than he ought, since no one has carried that banner for a long time, but he is looking for targets to shoot at and that one is certainly vulnerable. Similarly, apart from Oliver Smithies (with whom Smith formerly worked), most people have given up on simple recombinational schemes. But at the time of the writing there certainly were many who felt that some sort of somatic scheme must exist, if only because they couldn't swallow a strict germ-line mechanism.

The question the book seeks most to answer is, Are the amino acid replacements one observes in the variable regions of immunoglobulins the sort one would expect from some somatic hypermutability, or do they fit a pattern more akin to what would be expected from a large number of genes exposed to the usual pressures of natural selection?

The dust jacket claims that "the author uses a new and simplifying approach to this longstanding controversy . . . a comprehensive computerized analysis of . . . sequences, trac[ing] their evolution and match[ing] his results against the expectations of various theories." Actually, computer analyses of this sort were undertaken within days of the Warner Springs meeting, and have continued to accelerate in direct proportion to the available data. The conclusions remain equivocal at best, and the author, in his generous moments, concedes that it is not impossible for the observed patterns to have been produced by a somatic mechanism and points out that it might even be possible that some minor contributions due to somatic changes might be important. But his heart isn't in it.

In chapter 7 Smith meets the criticisms against the germ-line theory head on, these being the sometimes enigmatic nature of species-specific residues in variable regions, and certain allelic differences in heavy-chain variable regions of (rabbit) antibodies which are inherited in a simple Mendelian fashion.

In both cases he parries his own attack by invoking the possibility of hyperduplication during the course of evolution. Implicit in this argument—as I understand it—is the notion that if a system can generate enough gene copies in a given strand of DNA, then the tendency for further duplication will be so great that a steady state of invention and loss will be reached such that selection pressures on individual gene products cease to be an issue. Once past this critical point, only the system as a whole is subjected to Darwinian restraints—not a particular gene for a particular polypeptide sequence which may never encounter a suitable antigen in the course of countless generations.

Having disposed of these annoying challenges to germ-line supremacy, Smith goes on to a fine chapter on clonal selection, and then finishes up with a chapter of conjecture on the nature of joining up variable and constant regions in the genome. There are several appendices, one categorizing the known immunoglobulin sequences, another on allotypes, and finally an exposition on the phenomenon of multiple genes as it exists in the case of ribosomal RNA information.

The circumstantial evidence favoring a germ-line basis for antibody diversity has increased considerably over the past five years, and although one would have hoped that a clear-cut experiment (many have been proposed and some executed, but technical difficulties have rendered them equivocal) might have emerged to resolve the question once and for all, this review of the evidence for a germ-line basis is the next best thing. I enjoyed reading the book and believe it will prove useful to a wide range of persons in the fields of immunology and molecular biology.

RUSSELL F. DOOLITTLE
Department of Chemistry, University of California, San Diego, La Jolla

Essays in Ethology

Motivation of Human and Animal Behavior. An Ethological View. KONRAD LORENZ and PAUL LEYHAUSEN. Translated from the German by B. A. Tonkin. Van Nostrand Reinhold, New York, 1973. xx, 424 pp., illus. $15.95. Behavioral Science Series.

This is a collection of 11 essays that were originally published in German. The book is subtitled "An Ethological View," which is perhaps a better description than the title of this, the initial volume in Van Nostrand Reinhold's new Behavioral Science Series. The essays touch on all the major topics of concern to classical ethology.

Only the first essay is by Lorenz. This article was published in 1939 and is a classic. It sets forth the basic goal of ethology—the systematic and naturalistic study of animal behavior and the development of a theory of instinct to explain the empirical observations. The concepts of innate releasing mechanism, instinctive movements (fixed action patterns), and instinctive drive theory are presented clearly and enthusiastically. This essay defines the scope of the book and of the field.

The remainder of the book introduces the reader to the work and thought of Paul Leyhausen, who, as the editor of this series points out, is an important European ethologist not read sufficiently by American behavioral scientists. Leyhausen is important not just because he has made substantive contributions to our knowledge of animal behavior but because he is actively engaged in one of the most important enterprises of modern ethology: expanding the scope of the field from its early concentration on birds and fish to the more "complex" behavior of mammals, especially humans.

Leyhausen's ten essays cover most of the important problems in animal behavior. The papers are presented chronologically (they range in date from 1951 to 1967) instead of topically, so there is considerable contrast in material and treatment through the book. The second and last essays deal with expression and impression in social relations, a topic relatively neglected since Darwin's *The Expression of the Emotions in Man and Animals.* In his discussion of the topic, Leyhausen elaborates the difference between expression and impression in animals. This is an especially timely point since modern work in animal communication (such as that of W. J. Smith) is concerned with distinguishing the information contained in the signal from the meaning derived from it by the recipient.

In the third, fourth, and fifth essays, Leyhausen discusses with great analytic insight theoretical problems like the nature of displacement activities, the seminal work of von Holst on central nervous system automatisms and their relation to fixed action patterns, and the mechanisms responsible for creating new sequences of motor activity.

The interaction of animals' social behavior, social hierarchies, and territoriality is well treated in the sixth, eighth, and tenth essays. There is one long empirical study (essay 9), which is a comparative study of prey-catching in 15 species of cats. This includes a splendid discussion of the possible phylogeny of predatory behavior patterns. The precision of the Anglo-American laboratory is not present in this study, but the thorough and painstaking observations of the ethologist are. This article might prove useful for experimental psychologists to study as an essay in ethological method.

In general, Leyhausen's treatment of problems in animal behavior is intelligent and clear. There are, however, specific issues on which I think he is not totally successful. For example, in an attempt to reduce the complexity of mammalian behavior to ethological instinct theory, Leyhausen postulates the existence of more drives than exist in lower forms. Plasticity of mammalian behavior becomes a function of the interaction between these drives. Several authors, among them the British ethologist Robert Hinde, have been quite critical of the utility of classical drive theory. Although it is a brave attempt, Leyhausen's updated theory of drives seems susceptible to all the criticisms leveled against the older drive theory with the added disadvantage of postulating even more complexity.

It is, however, when Leyhausen expands his arguments to the human condition that his entire method can be criticized. The question whether theoretical ethology can successfully be applied to human behavior is really the question whether behavior in animals and men is the same in the sense of being biologically homologous. Both Lorenz and Leyhausen stress the importance of the phylogenetic history of behavior; and ever since the development of the concept by British anatomist Richard Owen, biological homology has been taken as the basis of phylogeny. The discovery of homologies in comparative anatomy is fairly straightforward: fossils are examined, embryological histories compared, and morphological details analyzed. Though the actual research is intellectually demanding, the objects of study are well defined. In the case of behavioral fixed action patterns, there is also a precision: the description of displays in ducks or killing movements in cats are exact and the behavior patterns stereotyped. With respect to behavioral phenomena like emotion, drive, and