Book Reviews

Phenomena of Heredity

The Principles of Human Biochemical Genetics. HARRY HARRIS. North-Holland, Amsterdam, and Elsevier, New York, 1970. xiv, 330 pp., illus. Cloth, $15; paper, $6.95. Frontiers of Biology, vol. 19.

For nearly two decades Harry Harris, perhaps unknowingly, has been in the business of recruiting for human biochemical genetics. His earlier books, *Introduction to Human Biochemical Genetics* (Galton Laboratory Monographs, 1953) and *Human Biochemical Genetics* (Cambridge University Press, 1959) helped to enlist two generations of investigators. The latest version should attract a new cadre. Although the new book deals with many of the same general topics as before, it does so in a substantially different way. It attempts a degree of unity between what 11 years ago seemed unconnected classes of phenomena, such as the inborn errors of metabolism and the hemoglobin variations. The task is an ambitious one, even for the most perceptive, for our overall understanding of the topic is still very much in the natural history stage. There is no unifying view of the hierarchies of interactions existing between genes and phenotypes in higher organisms. Moreover, aside from a few uncommon disorders and some nice points of differential diagnosis, there is, as yet, comparatively little immediate utility from a field that consumes the interest of so many investigators and for which there are ultimately such great expectations. It is essential that the present-day fact of limited applicability be made clear. Our hopes are substantial but they are based on investigations still not done.

Despite such reservations, perspectives in human biochemical genetics are quite different now than a decade ago. Harris gives an excellent account of these. His tactic is to place emphasis on an illustrated set of fundamentals. These include the use of hemoglobins to typify the nature of visible mutations and the diverse kinds of phenotypic effects that can be produced by single amino acid substitutions; an exposition—exemplified by a variety of proteins—of the one-gene, one-polypeptide concept and the collateral one of the multigenic origin of some classes of polymorphic molecules; a description of gene duplications and deletions and their consequences to protein structure; a hemoglobin-centered treatment of inherited defects in protein biosynthesis; and a description of relationships between quantitative and qualitative variation of certain enzymes. A group of selected inherited metabolic errors is used to illustrate a variety of subsidiary topics such as isozymic differences between tissues, genetic heterogeneity among phenotypically similar diseases, and the detection of heterozygotes.

At the close of the book there are two more contemplative chapters. The first of these deals with the extent and sources of protein diversity in human populations. This is the topic wherein the biochemical geneticist has created controversy for the evolutionist and population geneticist. A portion of the difficulty is Harris's own doing; he is responsible for the signal finding that approximately one-third of human genetic loci seem to bear more than one common kind of allele. This result, together with similar polymorphic abundance in *Drosophila*, has provoked a widespread and still continuing reexamination of the relative roles of selective and nonselective factors in producing such unexpectedly great genetic diversity. Harris sets out the possible explanations in their simplest form. The final chapter is, in itself, worth the book. It is both a knitting together of earlier concepts in a discussion of the molecular pathology and heterogeneity of inherited disease and a straightforward recapitulation of the ways in which those men affected by variant genes interact with the world about them. In this connection the book ends on a paradox:

> The study of the genetics of many diseases may lead to their prevention or amelioration by purely environmental methods. Indeed it is very probable that one of the most important social and medical applications of genetical research will lie in the control of the environment, since the more it becomes possible to characterize the genetical constitution of an individual precisely, the more likely are we to see how to modify or tailor the environment according to his needs.

How far we can pursue this strategy and develop other therapeutic options depends on the strength of the new cadres of investigators and the will of governments to support them through all the twists and turns characteristic of life science in complex species.

What faults there are to the text are largely ones of omission, a possibility Harris foresees in his introduction. He tries to offset this with tabular appendices that serve as annotated catalogs of specific enzyme deficiencies and of protein polymorphisms. These may not be enough, since some important ideas are thereby lost. For example, the immunoglobulins of man are nowhere described despite the fact that genetic principles adduced from these seem to differ profoundly in some ways from the view of genes derived from, say, the study of hemoglobins. No matter, the book will still be eminently useful to all those who are curious as to what human biochemical genetics has been about and where it may lead.

SAMUEL H. BOYER
Division of Medical Genetics and
Clayton Laboratories, Department of Medicine, Johns Hopkins University School of Medicine,
Baltimore, Maryland

Biological Pigments

Heme and Chlorophyll. Chemical, Biochemical and Medical Aspects. GERALD S. MARKS. Van Nostrand, London, 1969 (U.S. distributor, Van Nostrand Reinhold, New York). xiv, 210 pp., illus. $12.

We are indebted to the long, dark, cold Canadian winter to which Marks attributes his undertaking of this valuable book on heme and chlorophyll. Marks has brought together in this volume not only recent knowledge of the organic chemistry of these pigments, but also much information relating to their biochemistry and pharmacology. Having worked in these several fields, and having already prepared two important reviews on related subjects, he writes with authority.

For a book that is rather slender in size it is a remarkably comprehensive one, packed with useful and essential information and concisely written. It will prove to be a required reference

work for students of bio- and organic chemistry interested in porphyrins, heme, and chlorophyll. In addition, because of the recently defined relations between the heme protein cytochrome P-450, microsomal oxygenase reactions, the induction of drug-metabolizing enzymes, and the control of heme formation via the induction of δ-aminolevulinate synthetase, the book will be of great interest to pharmacologists and clinicians as well.

In the first chapter, the reader is introduced to the nomenclature of the porphyrins and their metal complexes, the properties of various cytochromes, other heme proteins, and the various chlorophylls and vitamin B_{12}. The next two chapters summarize the organic chemistry of the pyrroles and pyrrolic pigments, describing the newer methods of synthesis and degradation of these compounds which have become available since the publication of the volumes by Fischer and Orth in the late 1930's. Included is a summary of the ingenious synthesis of chlorophyll devised by Woodward and his co-workers. These chapters are written with particular clarity and succinctness; they will be especially valuable to the biochemist since biochemical reviews on the porphyrins have generally not adequately covered the organic chemical aspects of these compounds. The physical-chemical properties of the porphyrins are covered in another chapter, which also includes the absorption-spectral characteristics of the tetrapyrroles in the visible, ultraviolet, and infrared regions and the newer proton magnetic resonance and mass spectral data relating to these substances. Another chapter describes the various analytical methods that have been applied to complex mixtures of porphyrins from biological and synthetic sources. These include countercurrent distribution, chromatography, and electrophoresis. It was highly satisfying for me—recalling the struggles of years past—to note how these various physical and physicochemical methods now make possible the routine analysis of trace amounts of these materials for structural, quantitative, and other determinations. The last two chapters review the various steps in heme and chlorophyll biosynthesis, the disorders of porphyrin metabolism associated with certain genetic defects in man, and the experimental porphyrias elicited by various drugs, chemicals, and natural steroids. These latter subjects are being quite actively investigated at present, so that reviews of them rapidly become dated. However, these last chapters should prove most useful as an introduction to the biochemistry and pharmacology of the porphyrias.

The book is, in brief, a much-needed and elegantly written text. Workers in this field—which has so many biologic and medical ramifications—will be grateful to Marks for this lucid compilation of information.

S. GRANICK

Rockefeller University, New York City

A Question about Periodicity

The Biological Clock. Two Views. FRANK A. BROWN, JR., J. WOODLAND HASTINGS, and JOHN D. PALMER. Academic Press, New York, 1970. viii, 94 pp., illus. Paper, $1.95.

In the preface of this brief volume the authors express the hope that it "will serve as an introduction to those uninitiated in the field. . . ." That the book fails to achieve this goal is due more to its overall organization than to the specific material it contains. It is focused exclusively on the question of whether biological clocks are driven by unknown exogenous periodic variables or derive their periodicity from endogenous biochemical oscillations. The uninitiated reader will certainly come away with the impression that this is the central question in the study of biological clocks. Nothing could be further from the truth. By any standard the field is a very broad one which has raised and continues to raise more exciting and more approachable questions. In fact, at the moment I do not know of a single laboratory in which the exogenous-endogenous question is being directly approached experimentally, for the very good reason that a definitive test must involve experiments mounted on a satellite in solar orbit to exclude all possible influences of the earth's rotation.

The book does provide a reasonably good introduction to the exogenous-endogenous controversy, an understanding of which is important to a full appreciation of the broader subject. It is, however, only an introduction and will not enable the reader to make an intelligent judgment without a good deal of further reading and study. This is not the fault of the authors but a result of the book's format. In such a brief, nontechnical treatment it is of course impossible to go into much detail in support of one's position. Unfortunately, in this particular controversy the side one is led to take depends precisely on a careful evaluation of such details—specifically, on one's judgments concerning statistical manipulation of data from particular experiments and the relative reliability of experiments that have yielded conflicting results. As an example, Brown describes at length conclusions based on studies of the oxygen consumption rhythms of the developing chick but does not discuss very careful studies by Heusner which led him to the conclusion that oxygen consumption in developing chicks is completely arhythmic.

The controversy described has had considerable impact on the development of the study of biological clocks and may yet reappear in modified form as an issue of central importance (although probably not until a great many more questions are answered). At the moment continued flogging of the exogenous-endogenous horse is not likely to yield even a muffled heuristic whinny. After all, the two sides agree that there must be a great deal of interesting biological machinery involved, the analysis of which is surely our major task.

MICHAEL MENAKER

Department of Zoology, University of Texas, Austin

Macromolecules

Progress in Molecular and Subcellular Biology. Vol. 1. B. W. AGRANOFF, J. DAVIES, F. E. HAHN, H. G. MANDEL, N. S. SCOTT, R. M. SMILLIE, and C. R. WOESE. Springer-Verlag, New York, 1969. viii, 238 pp., illus. $14.

Here we have the beginning of still another series, "Progress in. . . ." What is the area to be covered in this series and how well does the first volume fulfill its intended function? The title is not informative, since molecular and even subcellular biology can mean all things to all men. The lead article by Fred Hahn, "On molecular biology," does not answer the question but rather addresses itself to Stent's gloomy prognostication that all the molecular biology that will be, has been. This reviewer agrees with Hahn that this attitude is hardly a universal one. Hahn cites areas where our ignorance is overwhelming and where answers probably will not constitute a "simple extrapolation of the basic dogma."