Book Reviews

A Historical Account

Machina Carnis. The Biochemistry of Muscular Contraction in Its Historical Development. DOROTHY M. NEEDHAM. Cambridge University Press, New York, 1972. xvi, 782 pp., illus. $55.

A large part of our contemporary biochemical and molecular-physiological knowledge has come about as a result of the investigation of questions pertaining to muscle. Work on muscle has been in the forefront of the research that has led, for example, to the elucidation of the role played by fibrous proteins in the structure of tissues (both in the contemporary epoch of electron microscopy and x-ray diffraction and in the earlier days of their polarization-optical forerunners), to the elucidation of fermentative and glycolytic pathways and all the knowledge that came with it regarding enzymes and coenzymes and the discovery of adenosine triphosphate, and to the discoveries on the mechanism of contraction as prototypes of biological energy transduction. It is a welcome occasion, therefore, to report the appearance of a book that represents scholarship of a high order in which our knowledge of major aspects of muscle activity is traced from its origins and which is yet in remarkably close touch with even the most recent trends, allowing for the few years that must be granted for the preparation of a work of this scope and quality.

Its author has been a contributor to research in this field since the 1920's. Her main subjects of interest have been the functional differences between white and red muscles, the glycolytic oxidoreductive reactions and their coupling, the comparative biochemistry of the phosphagens, and the myofibrillar proteins of the uterus—and these were those remarkable investigations in the early 1940's when she and her husband, and their colleagues, came close to the work going on contemporaneously in Szent-Györgyi's laboratory but for the realization of the differences between myosin and actomyosin which was crucial for the success of the latter group.

In the initial chapters of *Machina Carnis*, the author digs deeply into the early origins of muscle biochemistry, tracing, via Vesalius, Galen, and Rufus, how muscles became recognized as separate organs of motion and going on to our direct predecessors in the 19th century. These passages are a fine guide through history and, being not merely antiquarian, provide food for thought. For instance, would one necessarily interpret the passage quoted from J. R. Mayer (1842) as indicating that he took muscle for a heat engine in the present sense of the word? His language on "heat in statu nascens" may be an anticipation of the later distinction between enthalpy and free energy.

The next chapters deal with the classical and modern phases of research on glycolysis and its relation to heat and work, the discovery of adenosine triphosphate and phosphagen. The occurrence and possible role of carnosine and anserine (but for a brief reference later) and of glutamine are not treated in equal measure, but otherwise the major points of development and controversy appear to be well covered. This includes bibliographical treatment with due attention to the Eggletons and to Fiske and Subbarow with respect to phosphorylcreatine, to Lohmann and to Fiske and Subbarow with respect to adenosine triphosphate, to the Embdem and Meyerhof schools in their various controversies, to the various contributors on the problem of ammonia formation, to Lundsgaard and to Schwartz and Oschmann concerning the discovery of alactacidogenic contraction, and to Lipmann and Kalckar in the establishment of the concept of the "energy-rich phosphate bond."

Likewise, in the following chapters, there is a full exposition of the growth of our ultrastructural knowledge and the discovery of the myofibrillar proteins. The modern period is, correctly, introduced with H. H. Weber and reference to Von Muralt and Edsall, though I missed the interesting historical point that Weber's interest resulted in part from the motivation to study the heats of ionization of proteins as buffers, which led him in turn to contribute early to the recognition of proteins as amphoteric giant ions. The subsequent treatments of myosin, actin, and actomyosin and their interactions with adenosine triphosphate are highly informative. Bibliographically difficult areas, such as those involving the molecular weight and subunit structure of myosin and the molecular transformations of actin, are handled with skill and objectivity. A very thorough treatment is given of the sliding-filament theory and the various facts pertaining to it, followed by an account of the discovery of troponin and the various aspects of excitation-contraction coupling including the nature of the "relaxing factor." Concerning the identification of the primary chemical reaction and the thermochemical balance, the author does about as well as possible, given that the controversies on these matters, at least a few years back, may have been too much for any judge to handle.

Chapters on oxidation and on the regulation of metabolism complete the account of what one may call the general or central problems, but another one-fourth of the book deals with topics fully as welcome. There are comparisons of red and white and of slow and fast muscle, with a remarkably up-to-date discussion of the effects of nerve-crossing, discussions of developing muscle and protein synthesis, and of some muscle diseases, and valuable chapters on invertebrates, smooth muscle, and nonmuscular effector functions.

Throughout the book, one is struck with the author's gift for presenting the essential point of well-nigh each cited paper (of which there are close to 3000). She has obviously read the sources thoroughly even between the lines sometimes, and almost every such discussion is comprehensive without study of the references. As a result, also, the book lends itself well to browsing; one can often learn from a separate paragraph without the benefit of the preceding build-up.

Every author has to set limits somewhere, and thus one cannot take issue with the omission of certain topics such as the nature of the active state or the use of the giant muscle fiber of the barnacle for fundamental membrane studies. I find the treatment of A. F. Huxley's theory too short in comparison to others, however, as if it merely were one of the many proposals that came and went, and I would have expected something on muscle as a diffraction grating, on the possible role of myoglobin in promoting O_2-diffusion, on the Solandt effect and related phenomena, on Aubert's extensive myothermal studies, and on the uncoupling of contraction and activation by disruption of the T-tubules. But even 600 pages of text do not allow a full treatment of such a vast subject. The remarkable thing is how much has been covered, how well, and how readably, of a many-splendored field which is notoriously difficult even for the expert.

One would wish the book to be widely available to graduate students and advanced workers alike. But here is a catch—the price.

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Statistical Inference

Likelihood. An Account of the Statistical Concept of Likelihood and Its Application to Scientific Inference. A. W. F. EDWARDS. Cambridge University Press, New York, 1972. xvi, 236 pp., illus. $13.50.

The technical construct *likelihood* was isolated and named 50 years ago by R. A. Fisher. Since then, many theories of statistical inference based on assumed parametric families of probability models have been elaborated, including Fisher's own theories of information and fiducial probability, the frequentist operating characteristic theories originating with J. Neyman, E. S. Pearson, and A. Wald, and the more recent resurgence of Bayesian theory. Likelihood can be recognized as playing a uniquely important and unifying role *inside* each of these theories. A small group of statisticians has maintained that likelihood is itself the *whole* of statistical inference, meaning that the sole task of the statistician is to compute and directly interpret likelihood functions determined by observed data, and implying that the working statistician has little need for the large corpus of theory which has occupied mathematical statisticians for many decades. Fisher advocated direct likelihood inference in circumstances where his fiducial methods could not be applied. G. A. Barnard in England and A. Birnbaum in the United States have ably defended inference from likelihood alone. A. W. F. Edwards gives an account of the exclusively likelihood viewpoint in the book under review, which is "aimed at the scientist rather than the statistician."

To fix ideas, consider a sequence of independent trials which can result in success (S) or failure (F) where the probability of success on a single trial is an unknown constant p. If a sequence of eight trials produces the data

SSFSFSSS,

then the statistician computes the likelihood function

$$L(p) = p \times p \times (1-p) \times p \times (1-p) \times p \times p \times p = p^6 (1-p)^2.$$

Thus likelihood can be succinctly described as the *probability of what happened* considered after the fact. In general, a sequence of n trials including a successes and $n-a$ failures, in any order, yields

$$L(p) = p^a(1-p)^{n-a},$$

which is a likelihood function on $0 < p < 1$. This function is convex with a maximum at $p = a/n$, where the width of the peak is roughly proportional to $n^{-1/2}$. Edwards uses the term *support* for the natural logarithm of likelihood. Likelihood is regarded as defined only up to an undetermined scalar multiple, so that only relative values such as $L(p_1)/L(p_2)$ are meaningful. Correspondingly, only support differences are meaningful. Edwards introduces the handy concept of *m-unit support limits,* meaning the extremes of the range of parameter values such that the support is within m units of its maximum. It turns out that 2-unit support limits from reasonably large samples on many common models are similar to ± 2 (standard deviation) limits for parameter determinations, as given by Bayesian or frequentist theory, thus forming a bridge to more traditional methods of inference.

Edwards clearly and simply describes ideas extending those sketched above, using mainly examples of frequency counts drawn from genetic studies. The short and readable chapters follow a common format of introduction, technical discussion, and summary. After chapters presenting basic concepts, there are chapters which relate and contrast likelihood inference with familiar alternatives such as Bayesian inference, maximum likelihood, and significance testing. Other chapters explore technical matters such as the handling of several parameters, the relation of likelihood to information, and anomalous or pathological behavior of certain likelihood functions.

The tone of the book is good-naturedly polemical. Much space is devoted to oft-heard criticisms of different approaches to inference, especially those well represented at Cambridge University past and present, but virtually no self-critical judgment is directed at the difficulties of the exclusively likelihood school. This lack of balance is a serious defect in a book on a subject so controversial as statistical inference. Also, I believe that professional statisticians will find the treatment rather superficial. For example, the illustrations chosen by Edwards give no feeling for how likelihood ideas could possibly cope with real data sets of even moderate size and complexity, where 20 or 30 parameters are more typical than 2 or 3. For another example, I am unable to see what general principle is invoked to permit the use of likelihood based on the t-distribution as a device for eliminating σ when μ is the parameter of interest (pp. 116–17, 194–95).

Edwards ignores two fundamental difficulties of the likelihood school. First, any use of likelihood is predicated on an assumed family of precise parametric probability models, but Edwards does not discuss where these come from, how one assesses their fit to data, or what are the consequences of using false models. On the contrary, he criticizes as unnecessary and illogical the main tool of statistical inference which purports to assess fit between data and a family of models, namely significance tests. Instead, he offers *support tests* which are really estimation devices in disguise. It is one thing to warn the user of tests about their limitations, but an extreme step to rule out altogether the practice of retaining null hypotheses until they are overturned by empirical data.

Second, there is a major question of what likelihood means. Edwards asserts that the log likelihood of a hypothesis measures support for that hypothesis in the data, but how does this formal definition correspond to an intuitive concept of support? For an intuitive understanding, one must go back to the original definition of likelihood as the probability of what happened. It follows that likelihoods resemble the tail areas of significance testing, which Edwards derides, in the sense of being probabilities considered after the fact. As with significance tests, therefore, the direct interpretation of likelihood can only be to rule out certain hypotheses and not to offer positive support for the remaining hypotheses. If hypothesis H_0 has likelihood 1/20 or 1/100 of the likelihood of another contemplated hypothesis H_1, then I