and balanced treatment of a complex topic.

The six chapters that follow the introductory chapter deal largely with the occurrence and function of DNA methylation in prokaryotic organisms. This is an appropriate point of departure, for it is in prokaryotes, specifically in the bacterial restriction-modification enzyme systems, that the evidence for an important biological regulatory role for post-synthetic methylation of DNA is unequivocal. The authors of these chapters do an excellent job of succinctly summarizing the current ideas concerning the mechanisms and interactions of bacterial methylases and restriction enzymes. At the same time, enough selected experimental design is discussed to stimulate students to adopt a critical approach to the existing data. Chapters on the possible role of methylation in DNA replication and repair and on the establishment and maintenance of methylation patterns form a natural transition between chapters describing the established function of methylation in prokaryotic restriction-modification systems and those describing less clear-cut functions in both prokaryotes and eukaryotes.

The remaining chapters, which constitute the bulk of the volume, examine the major recent experimental evidence linking DNA methylation in eukaryotes to regulation of gene expression via effects on transcription, X-chromosome inactivation, cellular differentiation programs, and chromatin structure. Emphasis on these issues is quite appropriate since they are arguably the most exciting aspects of the subject and are currently the most intensively studied aspects of DNA methylation. The studies described involve three major lines of investigation: those concerned with the temporal and tissue-specific inverse relationship between methylation at specific 5′-methylated CpG sites in DNA and the expression of a wide variety of genes in vivo; those concerned with the effect of in-vitro methylation or the lack of methylation of cloned gene sequences upon the expression of those genes in cultured cells and organisms; and those concerned with the positive effects that agents that perturb DNA methylation (chiefly 5-azacytidine) have upon specific gene expression, X-chromosome activation, and overall cell differentiation. Each of these lines of investigation is presented by a leading experimentalist who has made major contributions concerning a particular aspect of the subject. Though the use of such authors predictably results in a strong bias in favor of the biological importance of DNA methylation, it also insures a thorough and historically correct discussion of the specific experiments that have contributed to our current understanding of the subject.

In fact, most of the authors present both positive and negative data concerning the regulatory role of DNA methylation in eukaryotes. For example, in a chapter entitled "DNA methylation and gene expression," Cedar concludes in effect that the balance of experimental evidence suggests that DNA methylation alone is probably neither the primary force in controlling gene regulation and differentiation nor a mere passive feature of most inactive genes or inactive X-chromosomes. It seems more likely that methylation constitutes one of perhaps several signals involved in such regulatory processes. Furthermore, it is pointed out elsewhere in the book that the absence of detectable cytosine methylation in arthropods argues strongly against a universal regulatory role for DNA methylation in eukaryotes. The viewpoint that higher eukaryotic gene regulation may involve multiple, perhaps even independent, factors may be offensive to the reductionist. However, the rapidly rising number of *cis*-acting DNA sequence elements and *trans*-acting (presumably nuclear protein) factors that have been associated with tissue-specific eukaryotic gene regulation and chromatin structure certainly lend support to this increasingly accepted view.

In a volume that is intended to summarize and organize a large quantity of experimental data in a rapidly progressing area of investigation the subject should not be presented dogmatically or in a way that leaves the reader stranded in a sea of disjointed data. In addition the data presented should be as current as is feasible in a bound volume. By these measures, this treatise is a definite success. It reflects the overriding evidence that DNA methylation is neither a trivial epiphenomenon nor a completely understood regulatory signal in higher eukaryotes. The only possible criticism of the book might be that the chapters dealing with methylation as it relates to gene expression overlap. However, this is not a serious flaw since each chapter can be used alone as a resource for investigators and the overlap should highlight the most important concepts for beginning students.

In summary, the book provides solid background on and a thought-provoking stimulus for future experiments aimed at defining the precise biological role (or roles) of DNA methylation. It fills an important need in every molecular biology resource library, and it would be a valuable addition to the personal libraries of investigators in this or related fields.

GORDON D. GINDER
Departments of Internal Medicine and Genetics, University of Iowa, College of Medicine, Iowa City 52242

Phosphoproteins

Protein Phosphorylation in the Nervous System. ERIC J. NESTLER and PAUL GREENGARD. Wiley, New York, 1984. xiv, 398 pp., illus. $59.50. Neurosciences Institute Publications Series.

Since the pioneering work of Sutherland and of Krebs in the 1950's and 1960's, the role of protein phosphorylation as a key regulatory process in biological systems has become increasingly evident. It is now clear that many hormones and neurotransmitters produce some of their effects on their target tissues through systems that reversibly phosphorylate effector proteins in the target.

In *Protein Phosphorylation in the Nervous System*, Eric Nestler and Paul Greengard redevelop the ideas that Greengard's laboratory has advanced both conceptually and experimentally for over ten years. The book aims to substantiate the view that protein phosphorylation is one of the major mechanisms underlying signaling in the nervous system and that the study of neural phosphoproteins, in addition to providing insights into cellular regulation, can also provide insights into a wide variety of neuronal processes.

The authors begin with a clear statement of goals and then launch into a discussion of various components of major protein kinase systems. Their review is not limited to the nervous system, since a great deal of what is known about protein kinases and protein phosphatases was learned from work on nonnervous tissues. The largest section of the book deals with phosphorylated substrate proteins specific to the nervous system. One chapter catalogues many of the substrates that have been studied biochemically and another examines electrophysiological support for the idea that ion channels are regulated by phosphorylation. The discussion not only illustrates how the study of protein phosphorylation can encompass a wealth of approaches but also highlights the gaps in our understanding: overall, very little is known about the functions of sub-

strates that have been studied biochemically, whereas substrates whose function is well understood, like ion channels, exist in such small amounts that their biochemistry can only be inferred from indirect experiments.

The main strength of the book lies in the critical approach it takes. Experimental results are usually presented with evaluations of both the experimental designs and the interpretations. One of the most useful parts of the book deals with possible pitfalls and artifacts in studies involving protein phosphorylation. It evaluates the kinds of experiments that are needed to demonstrate unambiguously that phosphorylation regulates the function of a protein. In this regard, the book is an excellent guide to experimental design as well as an introduction to the field and would be suitable for graduate students and seasoned investigators alike. There are abundant references to work published through 1983.

The authors' philosophy is highly evident throughout the book and is best illustrated by their development of the idea that phosphoproteins can provide valuable insights into neuronal function, not only by virtue of their regulatory roles but also by virtue of their cell biology. One of the valuable side benefits of studying protein phosphorylation is that a number of phosphoproteins have been identified that have very characteristic cellular or subcellular distributions. This permits the use of these proteins to trace neuronal pathways. Phosphoproteins have an advantage over plain neuronal antigens for this purpose because one can simultaneously study their distribution and their state of phosphorylation in response to neurotransmitters in order to make inferences about the chemistry of the impinging circuits. One can also make inferences about the kinds of receptors present on certain presynaptic nerve terminals by examining the phosphorylation of phosphoproteins localized to presynaptic terminals. Results arrived at by the use of these techniques, however, are quite preliminary.

Despite these rather impressive strong points, the book has a number of weaknesses. It is repetitive. Several stories are repeated in varying degrees of detail. The repetition is partly the result of trying to make each chapter self-sufficient, but it is also annoyingly frequent within chapters.

Although the book touches on most of the important areas of research in this field, the emphasis, naturally, is on work that was started in Greengard's lab. At several points, however, the authors spend too much time on their own work and neglect other interesting questions. For example, in the 100-page chapter on substrate proteins, a total of 40 pages is devoted to synapsin-I, a protein associated with synaptic vesicles, and DARPP-32, a phosphoprotein associated with dopaminoceptive neurons, but only passing notice is given to rhodopsin, phospholamban, and myosin. Although it is possible that these proteins are not considered by the authors to be bona fide neuronal proteins, their phosphorylation has interesting implications for nervous system function. The authors speculate extensively about the possible functions of synapsin-I and DARPP-32 but, in several cases, cite the maxim "correlation does not prove causality" in criticizing the hypotheses of others.

The main thesis of the book is that protein phosphorylation is a final common pathway of "paramount importance" in animal cells (p. vii, 1, 301, 334). There is no question that protein phosphorylation is an important regulatory process, but the data just do not support the assertion that it is the *most* important one. If one uses the stringent criteria advocated by the authors in the book, phosphorylation has been shown to play a physiological role in the regulation of the activity of only a very few proteins. For example, of all the substrate proteins discussed in chapter 4, tyrosine hydroxylase and tryptophan hydroxylase are the only ones for which there is even incomplete evidence of physiological regulation by phosphorylation. I agree with the authors' conviction that phosphorylation regulates the function of these proteins, but one must not fail to distinguish between conviction and fact.

H. CRISS HARTZELL
Department of Anatomy,
Emory University School of Medicine,
Atlanta, Georgia 30322

Molecular Biophysics

Ionic Channels of Excitable Membranes. BERTIL HILLE. Sinauer, Sunderland, Mass., 1984. xiv, 427 pp., illus. $32.50.

Ion channels are becoming universal in their importance in cell biology. Long studied in excitable membranes, channels have recently been studied in secretory cells, red blood cells, lymphocytes, and plant cell protoplasts, to name a few systems. They have been found in all cell types where they have been looked for. Channels have traditionally been the territory of membrane biophysicists, who have used electrical measurements of membrane currents to make inferences about the functional and structural properties of the underlying channel molecules. Recently, however, biochemical techniques have been brought to bear on these channels, and the most well-studied of them, the acetylcholine-activated channel and the voltage-gated sodium channel, have been cloned and sequenced. The future will bring a valuable confluence of these molecular techniques with the biophysical study of engineered structural mutants of ion channels. Bertil Hille's book on ion channels therefore appears at a particularly opportune time.

It is hard to imagine an author more qualified and capable than Hille to write a monograph on this subject. He has been responsible for much of the current conceptual framework of ion channel biophysics, and he is a lucid writer whose review articles have long been basic references for students in the field. In the book Hille provides a masterly explanation of the biophysical concepts that are necessary for making structural inferences about the channel molecules from measurements of the properties of the ionic currents that flow through them. He successfully reviews classic work, important physical theory, and new methodologies.

The book is divided into two parts. The first reviews the properties of the most well-known channel types—voltage-dependent sodium, potassium, and calcium channels and the chemically activated channels. It offers an excellent review of the classic axonal voltage clamp experiments and a summary of the current understanding of the properties of these channels. Unfortunately, as with most reviews, this section will probably date quickly. Already there is much important newer work, such as that on the effects of calcium channel agonists and the amino acid sequence of the sodium channel.

The second part of the book deals with the principles and mechanisms of channel function. The relevant physical theories of ions in solution and of diffusion through pores are discussed along with the fundamental concepts of ionic selectivity and gating. This section is more general, using specific channel types to illustrate the concepts and experimental results. It is clearly written and brings together topics that are spread out through the literature. A familiarity with these chapters would be excellent preparation for reading the biophysical literature on ion channels.