Advances in Cell Biology

Gap Junctions. ELLIOT L. HERTZBERG and ROSS G. JOHNSON, Eds. Liss, New York, 1988. xviii, 548 pp., illus. $96. Modern Cell Biology, vol. 7. From a conference, Pacific Grove, CA, July 1987.

Few research areas in cell biology have been more illuminated by the explosion of molecular, biochemical, immunological, and biophysical methods than the study of gap junctions and their role in intercellular communication. Much of the first two decades of study of these interesting membrane specializations focused on their structural simplicity and uniformity, their common permeability properties, and their ubiquitous distribution. Their biological importance was assumed or was the subject of broad speculation, but with little in the way of verification.

Over the past few years, the inadequacy of many of the earlier views has been dramatically revealed by the discovery of a plethora of unsuspected biochemical, structural, and regulatory variations in gap junctions. The implications of these new findings for our understanding of the biological functions of these structures are just beginning to be appreciated.

The current ferment in the field, the changing view of the gap junction, the unresolved controversies, and some of the functional questions beginning to be answered are captured in a timely fashion by this book of 36 papers from an international conference. Groups of related papers are introduced by brief background pieces, which place the issues in context and highlight the more significant findings. Most of the papers themselves focus on recent experimental results, generally from the laboratories of the authors, but a few provide conceptual or functional models and less experimental detail.

The book places heavy emphasis on biochemical, molecular, and immunological characterization (12 papers), basic regulation (9 papers), and function (12 papers) and less on structure (2 papers) and distribution (1 paper). An account of some of the issues defined and results reported in each of these areas will help convey the flavor of the book.

Molecular and immunological techniques have augmented the basic biochemical study of gap junctions and have uncovered an array of different proteins, each with some respectable claim to being part of gap junction subunits in some tissue. Some of these proteins, for example the 27-kD and 21-kD proteins in liver and the 47-kD protein in heart, are part of a family showing some sequence and antigenic homology. Others, for example the 26-kD protein in lens (MIP26) and the 16-kD protein in liver, have no homologies with the other family or with each other. It appears that different tissues have different specific gap junction proteins, some part of "families" and others less related biochemically. Not only are there tissue and species variations, there is even evidence that two gap junction proteins, 27 kD and 21 kD, coexist in the same gap junction, perhaps even being part of the same hexameric subunit. The simple view, held for some time and forming the basis of active controversies about which protein is "the" junctional protein, must be discarded. Yet with the loss of this "comfortable" unifying principle has come an exciting possibility for differential control of junctional development, synthesis and assembly, and channel regulation. Moreover, fundamental questions of the secondary and tertiary structure and arrangement of proteins in the membrane become even more fascinating as the diversity of proteins increases. For example, how similar are the extracellular portions of the different junctional proteins? How do the apposing extracellular portions of hemichannel subunits link up, especially when they have different sequences?

In parallel with the discovery of protein variants has come identification of an ever-expanding set of regulatory factors and mechanisms. Following Loewenstein's apt metaphor, the "regulation panorama" has moved (by volcanic action and multiple earthquakes?) from a simple one with a single calcium mountain to a "rugged" one with multiple peaks and valleys of ionic, voltage-dependent, and covalent modulators. The mood seems to be shifting from controversy about which factor is "the" modulator to an exploration of the varied nature and mechanisms of numerous modulators. In this vein, several papers refer, some in greater depth than others, to evidence for phosphorylation of gap junction proteins, either cAMP-dependent or not, as a possible functional control mechanism. Others bring us up to date on evidence for calcium and calcium-calmodulin as effectors.

The level of examination of junctional modulation also has changed, moving from the whole cell and whole junction to the channel itself. Studies of channel conductance have revealed intermediate conductances and variations in unitary conductances. Once again the theme is variability rather than uniformity and perhaps, if not probably, reflects the variability in proteins. In the extreme, it now appears possible that a cell might modulate the sieving characteristics of its junctions by closing or opening sets of channels with particular selectivities or diameters. This is far from the simple view once held that gap junctions were composed of fixed-dimension conduits.

The convergence of junctional biochemistry and single-channel analysis relying on reconstituted channels in artificial membranes holds considerable promise for dissecting the contributions of different proteins and the mechanisms of different regulators. One report carries with it some important cautions and indicates that there is still much to learn in utilizing this potentially powerful approach.

New perspectives on older functional themes and speculations are provided throughout the book and receive particular attention in the final three groups of papers. Evidence is presented, for example, suggesting that gap junctions limit excretory cell secretion, somewhat contrary to intuition. Equally intriguing, if not more surprising, is the immunohistochemical evidence suggesting widespread, though selective, distribution of gap junctions in the central nervous system. The patterns seen do not fit easily with either the more uniform and extensive distribution expected for glial gap junctions or the much more limited and specific distribution of neuronal gap junctions.

Another group of papers summarizes new evidence in support of the long-standing idea that junctional communication is important for cellular growth control and that the disruption of communication is a contributing factor in cellular transformation and carcinogenesis. Through numerous studies of tumor promoters, viral oncogenes and their cellular counterparts, and other growth factors, we are taken on a whirlwind tour covering general transformation models, more specific effects of the viral and cellular *src* gene, and an interesting and complex explanation for tumor promoter effects on communication patterns in skin. The linkages among the papers and models are obvious at many points, as they are with some of the regulatory papers, and one gets the sense that the researchers in this area are getting closer to pulling the diverse sets of observations together into a coherent whole.

From the time of the earliest studies of

gap junctions, their possible involvement in development and differentiation has been a frequent target of experimentation and speculation. Some of the latest episodes in this long story are presented in the final group of papers. With the exception of the lead-off paper on developing vertebrate limb, the various studies support the developmental importance of junctional communication. Evidence for communication compartments is reviewed for quite divergent species and related to developmental boundaries. Modulation of junctional selectivity as a function of developmental stage in insects and its possible mediation by L-glutamate is especially intriguing and brings one story at least closer to an understanding of mechanisms. In regenerating hydra, junctional involvement is strongly suggested by the effects of antibody blockade of junctional transfer, a method of "perturbation analysis" that is likely to appear more commonly in future investigations.

In all, the book provides the specialist a useful summary of most of the current themes in the gap junction field. For the generalist, the thoughtful introductions to each section give appropriate perspective to the specific experiments and models, the resolved conflicts and unanswered questions. Throughout, the impact of new technologies and approaches is evident and the prospects for exciting future discoveries are tantalizing.

At an earlier meeting, Lewis Wolpert stressed the "need" for gap junctions to answer the problems of limb patterning. Although his paper in the current book arrives at a less sanguine outlook for establishing a critical role for gap junctions in his own system, he once again sets the stage for the future when he says, "But it is early days, and exciting times are still to come." The contributors to this book would certainly agree.

JUDSON D. SHERIDAN
University of Missouri, Columbia, MO 65211

Chaos in Living Systems

From Clocks to Chaos. The Rhythms of Life. LEON GLASS and MICHAEL C. MACKEY. Princeton University Press, Princeton, NJ, 1988. xviii, 248 pp., illus. $45; paper, $13.95.

During the past several years a number of excellent books have been published on chaos and nonlinear dynamics. In most, some mention is made of applications in the life sciences, but for the most part the development is in terms of physical applications. This is hardly surprising. Physicists and chemists are generally able to carry out their experiments under cleaner conditions than their biological counterparts, and they can often amass considerably larger quantities of data. Thus the most convincing experimental evidence for chaos comes from physical systems—fluid dynamics, lasers, and chemical reactions such as the Belousov-Zhabotinskii system. At the same time, it has been remarked (A. Mandell, personal communication) that it is in biology that nonlinear science may ultimately find its most important applications. For it is in living systems that one sees overwhelming evidence of the complex behaviors—both temporal and spatial—that are grist for the dynamicist's mill. Indeed, one might argue that it is dynamical complexity that operationally distinguishes animate from inanimate matter.

From Clocks to Chaos provides a much-needed introductioin to complex dynamics from a biological point of view. Its authors, Leon Glass and Michael Mackey, have been major contributors to the field of biological dynamics for more than a decade. This book gives us an opportunity to view the role of chaos in biology through the eyes of pioneers.

Here are some specifics: The book is divided into nine chapters, of which the first provides an overall introduction. Chapter 2 develops some of the underlying mathematics—differential equations exhibiting stable equilibria and limit cycles; stability concepts; and period-doubling to chaos in the logistic map. Chapter 3 introduces the important problem of distinguishing noise from chaos. The authors point out that successive iterates of some chaotic difference equations have exponential probability distributions. Hence the observation of such a distribution cannot by itself be taken as evidence for a Poisson process. Here and throughout the book, biological observations provide the motivation, in this case data for miniature end-plate potentials in neuromuscular junctions. A second example of the "noise *vs.* chaos" problem is provided by cell cycle studies. Here, the authors argue that observations traditionally explained by models involving random transitions can be fit just as easily by deterministic models that generate chaos. The chapter concludes with a discussion of techniques, among them Poincaré maps, Lyapunov numbers, and fractal dimensions, for diagnosing chaotic