Book Reviews

Cellular Immunology Today

Immunological Tolerance. Mechanisms and Potential Therapeutic Applications. Proceedings of a conference, Augusta, Mich., Apr. 1974. DAVID H. KATZ and BARUJ BENACERRAF, Eds. Academic Press, New York, 1974. xvi, 646 pp., illus. $21.

One of the central concerns of immunology has always been the mechanism by which the body does not react against itself. Burnet in his clonal selection hypothesis attempted to explain the phenomenon by invoking a mechanism in which clones of cells reactive to self antigens are deleted during an early stage of their differentiation. Experimentally, nonreactivity to specified antigens can be induced in a variety of ways, and the phenomenon is called immunological tolerance. The question of its mechanism is biologically profound and clinically important and constantly reappears in immunological thought. In 1968 Maurice Landy organized the first Brook Lodge Symposium in immunology, and the topic of that meeting, appropriately enough, was immunological tolerance. Some 40 workers spent several days discussing the state of the art, and even today the published proceedings, which consist of transcripts of the discussions, make lively reading. The importance of B cells, T cells, and their antigen receptors was just becoming clear in 1968. The time seemed right for making unifying grand schemes, and much of the conference was devoted to trying to place immunological tolerance into such schemes. Six years later, a group of generalists and specialists again gathered at Brook Lodge to discuss immunological tolerance. The volume under review is the proceedings of that recent conference.

The problems of cellular immunology have grown in complexity beyond most people's most creative thoughts in 1968. The central enterprise of cellular immunology is no longer the search for a unifying grand concept, but rather the unraveling of a very complicated network of interrelated and interacting systems. At the center of thought now is the fact that there is a distinct division of labor within the lymphocyte population; B cells produce antibody, T cells usually (but not always) act as helper cells and carry out cell-mediated reactions. Each reacts with a different portion of the antigen (B cells with hapten, T cells with carrier). How these interactions come about is often the subject of acrimonious debate. It is not clear, for example, whether the T cell communicates with the B cell by means of specific or nonspecific soluble substances or why some antigens are thymus-independent and others are not. How can we interpret experiments that shut down the response when we don't yet understand the events that initiate it? This is the dilemma in the study of immunological tolerance, for an understanding of tolerance must be part of any concept that hopes to explain the induction and control of the immune response. This volume serves as an update on progress in immunological tolerance relative to the advances in the rest of the field. The experiments showing that both T and B cells become tolerant but with different kinetics have become a pivot point to work around. Is the mechanism for induction and maintenance of tolerance the same in both populations? This turned out to be the real question of this symposium.

The 1968 meeting was essentially a large discussion with enough data thrown in to keep things moving. The 1974 meeting consisted of a series of formal papers with some discussion appended. The proceedings are divided into groups of papers on T cell tolerance, B cell tolerance, and antibody-mediated tolerance. The data in the papers vary in quality and the papers vary in clarity, but in general the quality of the science is high. Although each paper focuses on a small point, the volume as a whole makes several things rather clear. The first and most important is that we know precious little about how cells are specifically suppressed. Perhaps the best explanation of some apparently conflicting data is that there must be many avenues leading to the tolerant state. The three possible mechanisms most discussed in the book are clonal deletion, B cell "intoxication" by nonmetabolizable antigen, and suppressor T cells. Any or all of these could be responsible for the induction and maintenance of tolerance to self and artifical antigens. An event of such importance to the body economy could conceivably have multiple means of being maintained. Furthermore, the data are still equivocal concerning whether specific antigen-binding cells disappear in the tolerant animal. In some cases antigen-binding receptors seem to be frozen in the membrane, in others they are shed. Nor can one determine whether a cell that retains the ability to bind antigen is able to respond to it.

The emergence of the notion of the suppressor T cell has been one of the most interesting developments of the past few years, and a large proportion of the conference was devoted to this cell. Many earlier data are reconsidered in terms of suppressor T cells, and it seems that almost everyone who now looks for a suppressor T cell readily finds it. The biological significance of the suppressor T cell is of course open to question, but the consensus of the contributors is that it acts on other T cells rather than on B cells and seems to be by and large antigen-specific. Whether the mode of action is similar qualitatively to helper function but different quantitatively remains unknown.

The nature of the antigen also deservedly receives much attention. It has long been known that proteins in different form can be either immunogenic or tolerogenic. Some data presented here show that epitope density may be a factor in determining whether the "signal" given to the cell is "go" or "stop" (induction or tolerance). Whether the receptor-bridging model this seems to imply is correct remains to be determined, as does the validity of the notion that induction or tolerance signals are in part governed by quantities of antigen or determinants at the cell surface. It is pointed out several times that the immune response is a continuum. Within the lymphocyte population cells vary in the affinity of their receptors for antigen, and because of this the signal may be "go" to some cells and "stop" to others.

A small amount of optimism is expressed about the prospects for clinical

application of tolerance. Attempts to apply some of the findings discussed here to transplantation and allergy may find some direction as a result of this conference.

As for style, it seems to me that immunology, like opera singing and motor car racing, has more than its share of strong personalities. While there are rumors, conflicts, and scandals in all fields of science, cellular immunology seems to be a pacesetter. The 1968 volume, because of its discussion format, was full of the flavor of strong-headed people at work and play. As science it was good, as theater it was superb. The organizers of the 1974 conference (who also edited the proceedings) chose to have formal papers. This approach has the advantage of allowing workers in the field who were not fortunate enough to be invited to the meeting to see the data their colleagues are generating or to see new interpretations of data already published. But the discussions that follow each main section are short, and only occasionally does the fire of the real people come out. These moments, though rare, are wonderful; perhaps a compromise between the two formats can be arrived at next time. Having Macfarlane Burnet present to make a summary statement was a fine touch.

These proceedings demonstrate that the lines of research in immunological tolerance are being very clearly drawn. If the last six years gave us more questions, from this volume it looks as if the next six are likely to give us more answers.

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Nuclear Structure and Function

The Cell Nucleus. HARRIS BUSCH, Ed. Academic Press, New York, 1974. Three volumes. Vol. 1. xxiv, 668 pp., illus. $45. Vol. 2. xxiv, 564 pp., illus. $45. Vol. 3. xxiv, 584 pp., illus. $48.

Because of the complexity of the eukaryotic nucleus researchers interested in the system have tended to isolate one component or phenomenon (such as the nucleolus, DNA synthesis, or mitosis) for analysis. *The Cell Nucleus* provides a forum for presentation of the diverse problems that exist and the experimental approaches that have been taken to elucidate nuclear structure and function, and it permits rapid access to information available on the nucleus up to 1973.

The editor apparently chose to arrange the papers in order of increasing resolution, from nuclear structure to nuclear biochemistry. The transitions among the levels at which nuclear structure and function are studied might have been smoother, however, if the following sequence had been used: nuclear DNA; replication; transcription; nuclear RNA; nuclear enzymes; chromosome structure and mechanics; nuclear structure; and nuclear-cytoplasmic relationships.

Most of the papers represent active and promising kinds of research, but there are several contributions that could have been omitted or shortened without reducing the impact of the work. The replication of eukaryotic DNA has been extensively analyzed in the last few years, and significant problems that remain to be solved have been defined (for example, how are replicons turned on or off when the length of the S phase varies?). Given the sophistication of such questions, Stubblefield's superficial analysis of chromosome replication is disappointing, especially by comparison with the brief, incisive section on eukaryotic DNA replication in Strauss's article. Another paper that is not in the mainstream of chromosome research is the chapter on bird chromosomes by Shoffner. Our lack of knowledge of the function of most of the nuclear RNA's and proteins that are described at length in the two chapters from the editor's laboratory argues for a somewhat shorter treatment of these two subjects at the present time.

The majority of the papers, however, are significant and potentially of interest to nucleophiles in general, and several are outstanding. Franke and Scheer's article on the nuclear envelope is a review not only of the structure of the envelope but also of its complex relationship to the rest of the cell. The authors do not consider the envelope merely as a boundary; they treat it as one part of a multicomponent system that includes chromatin, chromosomes, RNA, cellular membranes, and other organelles. Nuclear pore complexes are extensively described, and there is an interesting discussion of the role pores may play in the translocation of ribonucleoprotein complexes from nucleus to cytoplasm. This chapter sets the stage for Goldstein's discussion of the movement of molecules between nucleus and cytoplasm. Such movement, frequently against a concentration gradient, is well documented, although selective permeability, or selective concentration, across the nuclear envelope is a sticky problem to attack because of the difficulty of setting up model systems. Goldstein's primary interest is not in the movement of molecules itself, but rather in why some proteins and RNA's prefer to be on one or the other side of the nuclear envelope. His discussion, based primarily on his work with *Amoeba*, is thought-provoking and relevant to gene expression in heterokaryons, discussed by Sidebottom, and the expression of transplanted nuclei in animal cells, discussed by Gurdon. Goldstein reiterates a popular hypothesis concerning the movement of proteins between cytoplasm and nucleus—the proteins assess changes in the cytoplasmic environment, move into the nucleus, and induce altered gene expression. Work on steroid-hormone-induced changes in RNA synthesis (mediated by protein receptors), reviewed and analyzed beautifully by O'Malley, provides experimental evidence supporting this hypothesis. But there are also RNA's that shuttle between cytoplasm and nucleus—what for? The discovery of RNA primers in DNA synthesis suggests to Goldstein that perhaps the shuttling RNA's are such molecules, a thesis that is testable, especially in light of the isolation of priming RNA's from several prokaryotic systems.

Fledgling investigators searching for an ideal eukaryotic system in which to study the metabolism of nonribosomal RNA biochemically and cytologically will do well to study the two chapters on polytene chromosomes. Hennig's chapter gives a general discussion of the structure of these specialized chromosomes when inactive and when activated (puffing), and Edström focuses on the elegant work from his laboratory on polytene chromosome transcription.

Those interested in new techniques for the differential analysis of chromosome structure will find the article on staining by Hecht *et al.* an encyclopedic source of information; the inclusion of specific steps in each of the staining procedures is welcome. One serious omission from these volumes is an account of the revolutionary technique of molecular hybridization in situ developed by Pardue and Gall and others. With the advent of this technique, molecular biology and cytogenetics become part of a single very powerful approach.

Although this collection of papers has