BOOKS: IMMUNOLOGY

The Assembly of Antibody Explanations

Ian R. Mackay

The Generation of Diversity is a remarkable mixture of formal history, narrative, literature review, and "immunophilosophy." It traces the origins of Burnet's clonal selection theory (*1*) as a central paradigm of contemporary immunology, then reconciles that theory with the discoveries of the molecular era, and concludes with a consideration of "the immune self." Virginia Woolf remarked "on one hand there is truth; on the other there is personality" (*2*). Scott Podulsky and Alfred Tauber dig deep for truth but pass lightly over personalities. They present their interpretations with excerpts from the literature and from sustained interviews with surviving eminent immunologists. Judging from the number of lines different researchers receive in the index—33 for Tonegawa; 24 for Cohn; 19 or 20 each for Jerne, Burnet, and Hood; and 1 for Porter—the oral histories may have introduced some bias into the authors' coverage. Many of their extensive "footnotes," collected in a 57-page addendum, are as relevant as the text itself. Incorporating these within the text would have spared readers much distracting page-turning. Despite the details, Podulsky and Tauber's historical account is not complete; some important topics, including the antigen receptor on T lymphocytes and relations between the major histocompatibility complex and immune responses, are relatively neglected, although perhaps these topics lie beyond the scope of the authors' inquiry.

The Generation of Diversity
Clonal Selection Theory and the Rise of Molecular Immunology
by Scott H. Podulsky and Alfred I. Tauber
Harvard University Press, Cambridge, MA, 1997. 520 pp. $75. ISBN 0-674-77181-8.

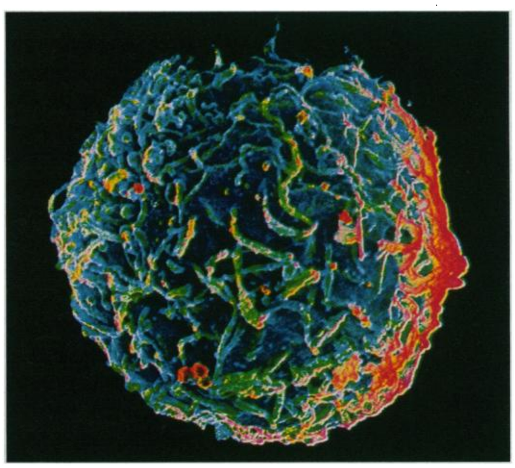
The specificity of antigen-antibody reactions gave rise to the key and lock analogy, which raised questions on how the locks (antibodies) were assembled and how so many locks could be made to fit the myriad keys. One early idea was that antigens had an "instructive" effect by acting as a template for complementary folding of corresponding antibody molecules. The selection theories of the 1950s were radically different. Jerne proposed that individuals innately possessed all requisite antibody specificities; antigens simply selected the antibody of best fit and promoted its amplification. Although initially unsympathetic, Burnet had a sudden change in mind—perhaps prompted by a prepublication review by Talmage that suggested receptor-bearing lymphocytes could replace naturally occurring antibodies as the primary units of selection, which is the essence of the clonal selection concept. Burnet's clonal selection theory appeared in a cameo version in 1957 and was then developed in a 1959 monograph, which Jerne, in 1969, generously acknowledged as "the complete solution to immunology" (*3*).

Podulsky and Tauber make liberal use of Jerne's whimsical "cis" and "trans" categorization of immunologists. Cis (biological) immunologists start at the beginning with antigenic exposure and hope to work forwards, whereas trans (molecular) immunologists start at the end, the structure of antibody molecules, and hope to work backwards. Molecular immunology began in the 1950s with biochemical studies aimed at relating biological activities of antibodies to structural features. Major progress was made in the early 1960s, especially by Porter and Edelman, who would share a Nobel Prize for their discoveries. They elucidated the now-familiar structure of the antibody molecule: the combination of two light and two heavy polypeptide chains, with "active" antibody-binding sites formed by linked light and heavy chains. The authors describe this research, but not the motivations that inspired it.

One of the critical observations in the mid-1960s came from Bence-Jones' proteins (fragments of myeloma proteins). Complete amino acid sequences revealed the clonal origin of antibodies from plasma cells, and the likely use of separate genes for the variable and constant regions of the molecule. (The sequencing is credited to Hilschmann, whose contribution is discussed on a single page and whose later destiny is undisclosed.) Then came the question of the nature of antibody diversity—how a limited genome could cope with a requirement for many millions of different antibodies. Bennet and Dreyer provided an initial model based on different combinations of the light and heavy chains of antibodies, and the encoding of light chains by two discontinuous stretches of DNA. But the issue was whether each and every antibody specificity was encoded by a single germline gene, or by somatic hypermutation from a limited set of precursor genes.

Five chapters and over 200 pages are directed to the eventual solution, that antibody diversity is generated during lymphocyte development by random combinational shuffling of gene fragments. Light chains of antibody molecules are generated by combinations of multiple V (variable) and J (joining region) genes, and heavy chains by V and J segments incorporating an additional D (diversity) region. These combinations, together with the random pairings of light and heavy chains of antibody molecules that can be amplified in postnatal life by point mutations, can form up to 18 billion different antibody molecules from only 300 original genes. Although Podulsky and Tauber believe they can "tell a different story, one in which recombinant DNA technology is only one factor in the solution to the question of antibody diversity but has nevertheless received nearly all of the ensuing credit" (p. 99), the molecular studies appear to be paramount. Whatever the case, the authors' meticulously detailed background to the experimental work is a tour de force, which one would never expect to be attempted again, and it stands as a vibrant testament to an extraordinary era for immunology.

Among the personalities in the antibody diversity endeavor, Podolsky and Tauber laud Tonegawa as the "most central," yet one who "entered this field with



Units of clonal selection. When antigen interacts with the receptor on a mature lymphocyte (such as the B cell shown in this scanning electron micrograph), that cell gives rise to a clone of identical progeny whose receptors bind the same antigen.

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perhaps the least knowledge of, or interest in, immunology itself." The authors discuss the circumstances of his installation at Jerne's newly formed Institute of Immunology at Basel, the individuals who influenced him towards his research on antibody synthesis, and his receipt of an undivided Nobel Prize in 1987, less than one month after sharing the Lasker Prize with Leder and Hood. Their account emphasizes Tonegawa's "singlemindedness" and "almost singlehandedness" in solving the problem of antibody diversity.

In their penultimate chapter, Podulsky and Tauber see the triumphs of molecular genetic approaches give way to contemporary concerns with regulation of immunological activity, beginning in 1970 as "suppressor cells," which inhibit other immune cells, were introduced into the lexicon. They then turn to the theoretical structure of immunology, but many readers will find too much immunophilosophy in these considerations of "the immune self." For example, they contrast "a genetically based formulation of selfhood with the notion of a deconstructed immune identity."

Finally, the authors lament that "for almost half a century immunologists have attempted to construct a theory of immune function on the foundation of a futuristic definition of the self, with no definition ever achieving consensus or proving adequate to account for immune function." Earlier understandings of how the immune system could distinguish self from nonself, in which all self-reactive immunocytes were eliminated during development, had wilted with the recognition of naturally self-reactive lymphocytes and anti-idiotypic networks (a series of autoantibodies directed to the reactive sites of antibodies that can regulate specific immune responses). Thus, the authors turn to the "cognitive paradigm" of Cohen to cast the immune system as an essentially self-sensing apparatus. Discrimination between self and nonself then becomes an untenable basis for immunological activity, and autoimmune disease is of no heuristic value in understanding immune function; this revised view is further developed by Matzinger's substitution of "danger" for "nonself" as the signal for immune activation. Readers may disagree here, because "self," however defined, must in some way be quarantined—if not from immune responses then at least from their harmful effects. The overall turgidity of this final section of the book is well illustrated by one of the concluding sentences: "The concern of selfhood per se has thus receded in these new models which may portend shifts more significant for new conceptual developments even than the power and influence of a new genetic methodology."

George Sarton once commented that the difference between throwing out ideas and writing a well-organized book may be compared to the difference between casual flirtations and a responsible marriage (*4*). But that was 50 years ago, and times do change. Those immunologists who seek the best of both worlds will appreciate the style of *The Generation of Diversity*.

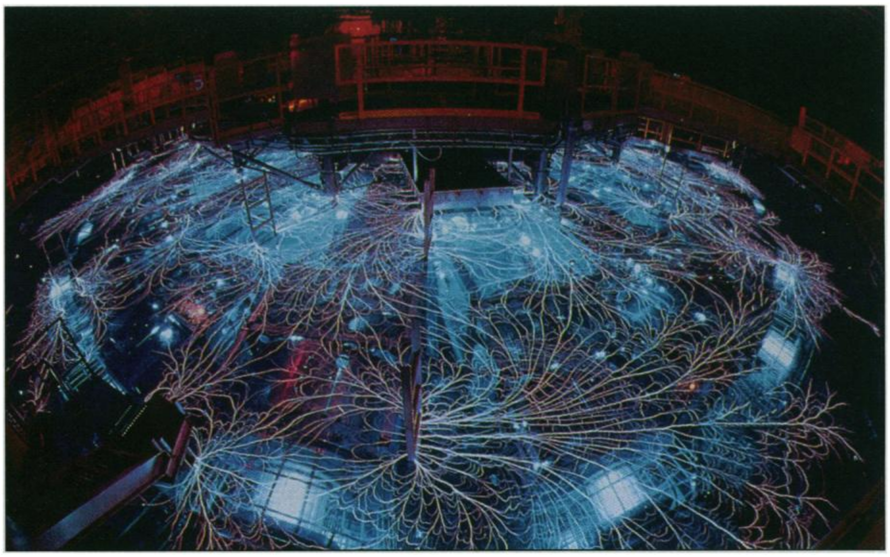
References and Notes

1. Burnet postulated that lymphocytes carry genetically predetermined cell-surface antigen receptors representative of the single antibody specificity they produce, and antigeneic stimulation elicits clonal proliferation and ensuing production of that single antibody.
2. V. Wolfe, in *Granite and Rainbow: Essays* (Hogarth, London,1958), pp. 149–153.
3. N. K. Jerne, *Australas. Ann. Med.* **18**, 345 (1969).
4. G. Sarton, *Isis* **41**, 149 (1950).

BROWSINGS

Physics in the 20th Century. *Curt Suplee.* Abrams, New York, 1999. 224 pp. $49.50. ISBN 0-8109-4364-6.

Surveying theoretical and experimental developments of the past 100 years, Suplee provides nonscientists with an excellent overview of physics from atoms to the cosmos. The book's 220 illustrations include many striking images of the physical world and experimental equipment, such as the time-lapse photograph (right) of the electric arcs that result when the Sandia National Laboratory's inertial confinement facility (for fusion research) is fired.



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The Science of Energy. A Cultural History of Energy Physics in Victorian England. *Crosbie Smith.* University of Chicago Press, Chicago, 1999. 416 pp. $60, £47.95. ISBN 0-226-76420-6. Paper, $25, £19.95. ISBN 0-226-76421-4.

Smith argues that the now-classical physics of energy was produced by a "North British" group (including Joule, Clerk Maxwell, the Thompsons, and Jenkin) seeking to enhance its own scientific credibility and radically reform physical science. He discusses how the group's theoretical and experimental researches were influenced by their roots in industry and engineering and by ongoing religious and philosophical debates.

Consumer Electronics for Engineers. *Philip Hoff.* Cambridge University Press, Cambridge, 1998. 573 pp. $110, £75. ISBN 0-521-58207-5. Paper, $44.95, £27.95. ISBN 0-521-58817-0.

For those who wonder how electronic devices actually work, Hoff provides detailed, technical accounts of the operating principles of radios, televisions, video cassette recorders, compact disc players, and telephones. These include numerous diagrams and extensive analyses of circuits as well as brief historical overviews and summaries of the present state-of-the-art.

Drawn From Life. Science and Art in the Portrayal of the New World. *Victoria Dickenson.* University of Toronto Press, Toronto, 1998. 340 pp. $80, £60. ISBN 0-8020-4225-2. Paper, $27.95, £18. ISBN 0-8020-8073-1.

Through discussions of images from the 15th through early 19th centuries, Dickenson examines how artists and writers portrayed the unfamiliar fauna, flora, and landscapes of northern North America to European readers. Her account explores both the changing understanding of nature and the role of visual communication in science.