Never ending circuits

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The Biology of Idiotypes. Edited by Mark I. Greene and Alfred Nisonoff. *Plenum: 1984. Pp.507. $59.50, £56.53.*
Idiotypy in Biology and Medicine. Edited by Heinz Köhler, Jacques Urbain and Pierre-André Cazenave. *Academic: 1985. Pp.445. $78, £78.*

It is more than twenty years since immunoglobulin idiotypes were first described by Oudin and Kunkel, and more than ten since Niels Jerne proposed his theory of an idiotype-based immunoregulatory network. The recent award of a Nobel prize to Jerne is a recognition of the importance of his contribution, though many of the key observations were made before he proposed his theory and before the modern techniques of protein chemistry and molecular genetics became available.

After the initial description of specific antigenic determinants (idiotypes) present on antibody molecules raised against bacterial antigens, it was shown that the same idiotypes could also be detected on immunoglobulin unreactive with the immunogen. In addition idiotypes were shown to be under genetic control. None of this linked idiotypes to immunoregulation but the network theory soon did so. Supporting experimental evidence rapidly appeared, perhaps the earliest being the observation that (auto) anti-idiotype is produced during the course of a normal immune response. This theoretical and experimental base stimulated an enormous number of experiments which are the subject of the two books reviewed here. Two major topics are covered: the structural basis of idiotypes, and their role in regulation of immune responses in health and disease. The more practical question of whether anti-idiotype responses can be used to control aberrant immune responses underlies much of the thinking. None of these issues has yet been resolved but the attempts to do so make interesting and instructive reading.

Of the two books, *The Biology of Idiotypes* is the more biochemical and *Idiotypy in Biology and Medicine* is more concerned with networks and their role in disease. There is, however, considerable overlap between them, with several authors contributing to both.

The first half of *The Biology of Idiotypes* is devoted to the molecular, genetic and structural aspects of idiotypes, with several chapters presenting data on the expression of private and cross-reacting idiotypes on families of antibodies reacting with a simple, structurally defined antigen. These chapters illustrate the power of the hybridoma method for producing antibodies of defined specificity in mice of any desired genetic makeup, whereas previous work on the structural basis of idiotypy relied upon myeloma paraproteins, often of unknown antigen specificity and uncontrolled genetic origin. Nevertheless, in spite of the sequence data on families of related, defined-antigen-binding, monoclonal antibodies, there are still very few examples where a particular amino acid residue can be definitively associated with expression of an idiotypic determinant. (A new and intriguing example was described recently by Radbruch *et al.* in *Nature* **315**, 507 (1985), where an amino acid change in the diversity (D) segment of the antibody led to loss of idiotypy but not antigen specificity.) The reasons for this are made clear. Most antibodies, including anti-idiotypes, react with conformational determinants made up of amino acids which may be widely separated in terms of primary sequence. From the genetic point of view analysis is complicated by the observation that contributing to variability are not only variable region (*V*) genes, but also *D* and joining region (*J*) minigenes, as well as infidelity of VDJ assembly and somatic mutation. All of these issues are extensively and well discussed, as is the limited amount of information on the three-dimensional structure of immunoglobulin molecules, which, combined with sequence analysis, may ultimately hold the key to understanding the structural basis of idiotypes.

The second half of *The Biology of Idiotypes* and most of *Idiotypy in Biology and Medicine* deals with the regulation of idiotypes. The network theory itself is particularly well discussed in the latter book, by Köhler, and there are detailed accounts of experiments designed to test its validity. These sections are very much for cellular immunologists, covering cell transfer experiments, separation of T and B cells, induction of help and suppression and experimental immune diseases. Many of the experiments described exemplify the powerful effects which administration of idiotypes or anti-idiotypes can have on subsequent immune responses.

The problem with these chapters is that they have been overtaken by events of the past two years. Several contributors were wrestling with the difficulty of integrating T and B cells into a coherent network at a time when the T cell receptor had not been characterized. The ease with which T-cell idiotypes have subsequently been detected by monoclonal antibodies, and the general similarity of the T-cell receptor chains to immunoglobulin light chains, now make an integrated network much more credible. However, it is still not clear that T-cell receptors can respond to idiotypes on B cells or other T cells. In Köhler's reiteration of Jerne's view, the T-cell repertoire may be selected and expanded by the images of B-cell antibody receptors presented with self-antigen of major histocompatibility complex (MHC). This neatly explains the apparent genetic linkage between the two, a finding that can now be tested with much greater rigour.

Another question is whether or how to fit in antigen processing. Although not universally accepted, there is considerable evidence that helper T cells respond to processed (fragmented) antigens plus MHC Class II antigens. Are they able therefore to recognize idiotype processed and presented on T or B cells in a manner similar to other antigens? Although not known for T cells, B cells can clearly present foreign antigen. But are the rules different for self idiotypes (and allo-MHC antigens)? Should we be looking for idiotype determinants which are the same as those seen by B cells, or at short, linear amino acid sequences presented with the self-MHC antigen?

Further, there is another layer of complexity: the antigens could select the T cells in a positive fashion; it is known that the antibody to the T-cell antigen receptor can stimulate T-cell division, as can antibody to the associated CD3 glycoprotein. One experiment, described by Greene *et al.* in *Idiotypy in Biology and Medicine*, indicates that a B-cell hybridoma secreting anti-idiotype specific for anti-reovirus σ1 glycoprotein is killed by cytotoxic T cells specific for the same antigen. We need to know who recognizes whom.

These issues can now all be addressed and the appropriate experiments are surely in progress. For many readers, ultimate proof of the network hypothesis will depend upon clear understanding of the interactions between the receptors of T and B cells and between those of the T cell subsets. The two books contain many interesting data and ideas, and can be thoroughly recommended to those who wish to prepare themselves for these impending and, we can hope, conclusive advances. □

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New in paperback

- *The Nature of Mathematical Knowledge* by Philip Kitcher. Publisher is Oxford University Press, price is £6.95, $8.95. For review see *Nature* **307**, 189 (1984).
- C. Kittel's classic textbook *Quantum Theory of Solids*, which first appeared in 1963. Publisher is Wiley, price is $21.95, £21.95.

On disc

A.N. Barrett asks us to point out that the price of his book *Mathematics, Biology and Microcomputers* (reviewed in *Nature* **314**, 476; 1985) includes a floppy disc on which are included all the programs listed in the book.

The reference to prime number technique ("in press" in the book) is *Int. J. bio-med. Comput.* **16**, 149–155 (1985).