Immunology made accessible

In immunology, abstract concepts are being made tangible by molecular structures. One new development shows that protein structure can evolve without changing common architecture.

THERE are two ways of regarding the recent spate of understanding gathered by molecular biologists of the molecules characteristically involved in the immune response of vertebrates: either more data mean that a field which is already too confusing may be further confused, or the point may have been reached at which confusion is dispelled. What follows is based on the assumption, hopeful though it may be, that the second is the better approximation to the truth, and that two articles elsewhere in this issue (pp.233 and 235) bear this out.

As in many other circumstances, concepts that at first must perforce be described in abstract terms (*gene* for example, or for that matter *electron*) are not easily turned over in the mind, or argued about. To begin with, the definitions of crucial concepts will be, at best, partial definitions. Historically, the electron began life as a carrier of electricity, charge and mass unspecified, and became a tangible entity only when J.J. Thomson had shown that the ratio of charge to mass is a constant. Genes began as abstractions, the propensity of an organism to have an external attribute of some kind, with only a few rules restricting the mechanism of their inheritance.

The classical concepts of immunology, *antigen* and *antibody*, have a similar and in many ways even more confusing history. Antigens began life empirically as materials that would evoke a neutralizing immune response in vertebrates into which they are injected, and antibodies were the agents of that neutralizing activity. This circular definition nevertheless had the merit of explaining a variety of phenomena, if predicting few.

Throughout the classical period in immunology, the outstanding puzzle was the capacity of the vertebrate immune system to respond specifically to an apparently infinite variety of antigens, some of them made only recently by organic synthesis and which thus can have played no part in animal evolution. Only in the past decade has this process been made tangible by the recognition that antibody molecules have a common molecular architecture, but that the common plan includes regions where the amino acid sequence may be widely varied as a consequence of the ways in which bits and pieces of genes are physically rearranged within the lymphocytes called B cells.

So here is one component of the immune system made tangible. Immunoglobin molecules are Y-shaped structures consisting of two identical halves, with the vertical stem of the Y anchored in the external membrane of the cell producing it. The anchor has the same amino acid structure for each class of immunoglobins. It is generally assumed that the immune system makes all possible combinations of the bits and pieces which constitute the variable genes, but that those which appear in measurable amounts are those required by the exigencies of survival. Little is known for certain of the degree to which the diversity provided by gene rearrangement is supplemented by mutation *in situ*, or of the mechanism by which genes are rearranged.

This is the stuff of which primers are written. Most of the excitement in the past four years that immunologists have mostly shared among themselves has centred on the lymphocytes called T cells, which produce no antibodies but which either kill off cells carrying antigens characteristic of, say, a virus infection or which assist the immune response in other ways.

So if T cells must have ways of recognizing antigens, what more natural than that they too should be constructed from the genes that make antibodies? Not so. By two years ago (see Jensenius, J.C. and Williams, A.F. *Nature* **300**, 583; 1982), all that was known of the "T-cell receptor" was that no substantial part of it has much in common with the immunoglobins.

What had however become apparent was that T cells will recognize antigens on other cells only if these are associated in the cell membrane with the antigens which control the histocompatibility (skin grafting) reaction; presumably the histocompatibility antigens which the body has learned to tolerate seem like those belonging to some other individual when associated with, say, a protein produced by a virus infection. And people were already surmising (Robertson, M. *Nature* **297**, 629; 1982) that T-cell receptors and the histocompatibility antigens are anchored in the cell surface in much the same way as antibody molecules, although the sources of variability and thus specificity are, of course, not gene rearrangements.

Earlier this year, the common features of the architecture of all these molecules — immunoglobulins, T-cell receptors and the two classes of histocompatibility antigens — were reasonably well understood. The class I antigens are, for practical purposes, those that provoke a cytotoxic immune response, the class II antigens those that stimulate the helper function. Nothing, however, is known of the ways in which these antigens interact with foreign antigens in the membrane of, say, virally infected cells to produce their immunological provocation. At the end of June, however, the structure of what seems to be the T-cell receptor was described (Saito, H. *et al. Nature* **309**, 757; 1984).

The article by P. Travers *et al.* (this issue, p. 295) is something of a diversion, but a cheerful one. What this group has done is to use a computer model to infer the structure of membrane-bound molecules of class II histocompatibility from their known (or inferred) amino acid sequence. Put simply, the conclusion is arresting: although the detailed correspondence between the structure of these molecules and those of the immunoglobins is insubstantial ("low homology" is what the molecular biologists would say), the general architecture of the molecules is very similar. Again, there is a stem anchored in the cell membrane by the hydrophobic character of its amino acids. Again, the external region is that which carries the variable (and thus the specific) part.

In spite of the element of circularity in this argument stemming from the way in which the structure of antibody molecules has been allowed to guide the model-building, the significance of this neat construction should not be overlooked. In passing, it says much about the power of computers as tools for building molecular models. More pointedly, it is a powerful demonstration that two molecules may differ considerably from each other in their detailed structure and yet have their general architectural shape in common.

Inevitably, as the authors point out, this bears directly on the evolution of the different components of the immune system. The rules of the game are that the changes may be rung on successive nucleotides in the genes, and thus on the amino acids, subject only to the constraint that the architecture of the molecules should be preserved. Their estimate that it has taken 500 million years to accomplish the specialism and diversity of the vertebrate immune system is less striking than their repetition of the suggestion that the immune system has evolved from some earlier means by which primitive aggregates of cells, sponges or corals, distinguished members of their own species.

John Maddox