Genes and Antibodies

from a Correspondent

WHY do some animals respond vigorously when injected with antigen whereas others exhibit only weak immunological responses? This important question was rigorously examined at a symposium on the genetic basis of the immune response held at the University of Aberdeen on September 18–20 during the annual meeting of the Scottish section of the British Society for Immunology.

On the first day of the symposium the genetic control of antigen recognition, which is primarily the responsibility of T lymphocytes, was discussed; B lymphocytes and antibody diversity were left to the second day. The specificity of antigen recognition and the Ir (immune response) gene puzzle were described by K. Rajewsky (University of Cologne) who used lactic dehydrogenase antigen in congenic strains of mice. He concluded that many Ir genes are linked to the H-2 complex of transplantation antigens and are expressed by T cells. Neonatal thymectomy of high-responding mice reduces the levels of cytotoxic antibody to bacteriophage antigen (E. Kölsch, University of Hamburg), but as this operation produces no change in low responders, T cells or a thymus factor are implicated in high responsiveness. E. Rüde (Max-Planck Institute for Immunobiology, Freiburg-Zahringen) also found that neonatal thymectomy of high-responding mice resulted in low responsiveness; he could restore high-type responsiveness by reconstituting such mice with polypeptide (TGAL)-primed T cells. This antigen may cross-react with transplantation antigens of low-responder mice (A. Ebringer, Queen Elizabeth College, London, and D. A. L. Davies, Searle Laboratories, High Wycombe).

Further evidence for a genetic linkage with a transplantation antigen (H-2; 5) in certain strains of mice was given by E. Gleichmann (University of Hanover) who thought there were interesting parallel relationships between the haemagglutinin response and capacity to induce graft-versus-host immune complex glomerulonephritis. E. E. Sercarz (University of California, Los Angeles) used lysozyme as antigen to obtain evidence of an Ir gene that controls haemolytic plaque-forming cells and isoelectric focusing patterns. Different gallinaceous lysozymes varied in their immunogenic qualities to elicit a response in his C57bl/6 mice.

In some contrast to these workers, E. Mozes (Weizmann Institute, Rehovoth) administered various proportions of T and B lymphocytes to syngeneic irradiated mice and drew three main conclusions from her experiments. B cells seemed to govern high-low responsiveness when her synthetic antigen 'Pro-Lys' acted as a haptenic determinant, but when 'Pro-Lys' was given the role of carrier the high responsiveness was governed by T cells; B cells and macrophages collaborate in high responders and a thymus-derived factor could correct low responsiveness.

During the day on genetic regulation of B cells G. Biozzi (Curie Institut de Radium, Paris) described his classic experiments on his high-low mice which were originally selected for their IgM and IgG agglutinin response to sheep erythrocyte antigen. As many as eight to eighteen loci (J. and N. Feingold, Hospital Necker, Paris) control the kinetics and duration of this response, the genes controlling division and differentiation of the antigenically-stimulated lymphocytes as well as antigen-macrophage interaction. Working with these Biozzi mice, J. G. Howard (Wellcome, Beckenham) found that a T-cell independent antigen, Levan, induces vigorous antibody responses in both high and low strains. Biozzi mice exhibit high-low responsiveness to both T-cell dependent and independent antigens; other differences may be due to "macrophage handling" of antigen causing extrinsic regulation of the B cells. C. Stiffel (Curie Institut de Radium, Paris) described how Biozzi mice which gave high agglutinin responses when injected with live *Salmonella typhimurium* died quite quickly, whereas low responders (agglutinins) survived somewhat longer. There was no difference between high and low-responder mice in resistance to Erhlich ascites tumour cells. J. Plant and A. A. Glynn (St Mary's Hospital, London) by cross-breeding mice differing in natural resistance confirmed that natural resistance to *S. typhimurium* is under genetic control. High-low responding mice may help to clarify the nature of immunological tolerance; already J. E. M. St Rose and B. Cinader (University of Toronto) find that low responders emerge from the tolerant state more slowly than their counterparts.

Finally, to remind the audience of another genetic aspect of immunology D. Secher (University of Cambridge) talked about his work related to antibody diversity. During screening of a mouse myeloma cell culture he found mutant clones secreting immunoglobulins of altered isoelectric point. These clones arose spontaneously at a frequency of about 10^{-5} per cell in each generation and peptide mapping showed that the mutation resulted in large deletions of H-chain domains. Immunoglobulin messenger RNA isolated from mutant cells was translated in a heterologous cell-free system and results proved that the mutation lay in an immunoglobulin structural gene.

The symposium was steered through this difficult topic by N. A. Mitchison (University College, London). High-low mice will obviously provide a stamping ground for cell-cooperationists for some years to come; meanwhile it is clear that T cells, Ir genes and their products (the immune complexes) are of paramount importance in responsiveness to many antigens, but B cells are also genetically regulated. In such a highly manipulative science it is comforting to remember that immune reactions, like most other physiological manifestations, are under genetic control.

CELL NUCLEUS

Poly ADP-ribose

from a Correspondent

THE second international conference on poly ADP-ribose, which was held at the Fogarty Conference Center, National Institutes of Health, Bethesda, from June 11 to 13, was organized by the John E. Fogarty International Center on the initiative of Professor O. Hayaishi.

Animal cell nuclei contain DNA, RNA and protein. A third type of polymer—poly ADP-ribose—is also known in these nuclei. The monomer unit is ADP-ribose; and the polymer is formed by glycosidic bonds between the 1′ carbon of the terminal ribose and the 2′ hydroxyl of the nucleoside ribose in an adjacent subunit. The substrate for the synthesis of this new polymer is not ATP, but is NAD. The polymer was first identified by Dr J. Doly working with Professors P. Mandel and P. Chambon (University of Strasbourg). Its structure was independently established in Strasbourg and by Professor O. Hayaishi (University of Kyoto) and by Professor T. Sugimura (University of Tokyo). Most of the currently available information comes from these last two laboratories and from that of Professor H. Hilz (University of Hamburg).

The enzyme responsible for the synthesis of this polymer is confined to the chromatin and has been found in all nucleated cells in which it has been sought, including frog liver nuclei and frog oocytes. It does not occur in bacteria. A striking characteristic of this enzyme system is that the activity is stimulated by DNA and by histones. The polymer is believed to be covalently linked to chromosomal proteins.

The *in vivo* existence of this polymer has not previously been unequivocally demonstrated. In her initial work Doly adduced some evidence for the *in vivo*