Immunology: Research at Mill Hill Institute

London.—The National Institute for Medical Research at Mill Hill includes what is probably the world's largest group in immunological research. Although the Institute's general responsibilities extend from parasitology to biomedical engineering, immunology represents the biggest single research enterprise. Sir Peter Medawar and J. H. Humphrey, the director and deputy director, have themselves made significant contributions in this field. Besides Humphrey's Division of Immunology, N. A. Mitchison's Division of Experimental Biology is engaged in the study of mechanisms of immunity, and several other divisions are concerned with other aspects of immunology. This pattern may not persist because, in current plans for enlarging the Institute, the emphasis is being placed on research in genetics and developmental biology and, as a matter of policy, the immunology program is not being expanded. Nevertheless, with a continuous influx of competent young investigators, there is no ground for anticipating any decline in Mill Hill's stature in the field.

The Mill Hill Institute is an arm of the British Medical Research Council. Its immunology group is naturally alert to clinical implications of its discoveries, whether in relation to infectious diseases, to the disorders of the immune response such as allergy and autoimmune diseases, or to the suppression of the immune response which limits the grafting of tissue from one individual to another. In this last connection, Medawar himself is concentrating on antilymphocyte serum (ALS) as a potential means for preventing the cell-mediated rejection of grafts without recourse to radiation and cytotoxic drugs. Humphrey, in the 1950's, was the first to use ALS as an immunosuppressive agent, but the current activity can be traced to the Edinburgh surgeon M. F. A. Woodruff who became interested in its clinical possibilities.

This serum is very promising. In a partially purified state, ALS is nontoxic, and it renders inert those immunological mechanisms which are mediated by lymphocytes, in particular those controlling graft-versus-host interaction. Apparently it interferes very little with the immunity to microorganisms, which is dependent on circulating antibody. Antilymphocyte serum is interesting not only because of its potential clinical applications, but also because it provides a useful tool for research into the mechanisms of immunity; for example, it can wipe out the immunological reactivity of previously sensitized animals.

Generally, the emphasis in immunological research has shifted from studies of the structures of antigens and antibodies to the location, reaction, and general biology of the responding cells. The central role of lymphocytes has become established, only within the last 10 years or so, largely as a result of J. L. Gowan's studies at Oxford. Mitchison's work is principally concerned with the initial step whereby a lymphocyte recognizes a foreign substance—the antigen. He starts from the concept of lymphocytes, in the lymph nodes, spleen, and bloodstream, which are genetically prepared to respond to an encounter with an appropriate antigen by multiplying and producing antibody. In this context, Mitchison has two recent findings of significance.

In the first place, much appears to depend on whether the antigen encounters the lymphocyte directly or whether it is presented to the lymphocyte via macrophages. That macrophages have a role in the immune system is well known, and this fact figures prominently in the research of Humphrey's group. Mitchison's experiments have been made with purified antigens such as crystalline bovine serum albumin and lysozyme. His results indicate that direct encounter with the lymphocyte evokes immunological tolerance rather than an immune response; and only through the mediation of a macrophage does immunity ensue. His group has explored the immunological consequences of injecting small smounts of antigen. The work by D. R. Bainbridge at the London Hospital Medical College has revealed a pattern of tolerance or sensitization in response to minute quantities of grafted tissue cells, and Mitchison sees in this an effect similar to his own observations.

The second of Mitchison's results supports the hypothesis that lymphocytes have "holes" on their surface into which antigens fit. Possibly these receptors, or recognition units, are preexistent antibodies. Be that as it may (and it is a matter of current investigation), Mitchison has demonstrated that the stimulation of cells can be inhibited by small molecules corresponding in shape to the immunologically specific portions of antigen molecules. He has used, as his antigen, purified protein modified by the attachment of 4-hydroxy-3-iodo-5-nitrophenylacetic acid (NIP) to a lysine portion of the protein and has found that mice have receptors for this hapten. Alone, NIP acts as an inhibitor. M. J. Crumpton of the Division of Biochemistry is now attempting to identify the antigenic sites of myoglobin with a view to testing whether the same kind of blocking can be achieved with portions of naturally occurring proteins.

One of the difficulties arising from a model based on the assumption that there are preexisting receptors to suit every antigen, natural or artificial, is that of explaining how an organism can possess such versatility. However, the number of types of receptors would be drastically reduced if there were provision for improving the antigen-antibody fit in the course of the immune response. This possibility is now being tested by Mitchison and his colleagues.

Dominating the work of Humphrey's group, in the Division of Immunology at Mill Hill, is the effort to trace the cellular history of antibody formation. One line of experimentation, jointly with M. Sela's group at the Weizmann Institute in Israel, has borne out and extended findings of G. J. V. Nossal and his colleagues at the Walter and Eliza Hall Institute in Australia. Nossal used *Salmonella* flagella, labeled with iodine-125, to show that, in an immunologically responding animal, antigen was concentrated in specialized cells in the germinal centers toward the periphery of the lymph nodes. In similar experiments, Humphrey and his colleagues have used synthetic multichain polymer (T,G)–A—L (tyrosine-glutamic acid-alanine-lysine) and various purified proteins such as hemocyanin, as antigens, and the same concentration of antigen in the germinal centers was observed.

There is, however, disagreement with

the suggestion of Nossal's group that macrophages in the germinal centers are themselves capable of recognizing foreign tissues. Macrophages in the medulla of the nodes apparently take up antigen regardless of the state of the animal. Brigid Balfour and Humphrey have shown, by autoradiography and immunofluorescent staining, that immunoglobulin (antibody protein) was distributed in much the same way as the antigen was in the macrophages of the germinal centers. In the cells of animals totally lacking in antibody, there is no corresponding concentration of antigen, and Humphrey and M. M. Frank (from the National Institutes of Health) have found that there is no concentration of antigen either in fully tolerant animals or in animals that have not yet started to make antibody. It is still not clear whether the antibody responsible for binding antigen in the germinal centers is a fair sample of the antibodies present in the animal, or whether it is some specialized fraction of the total antibody.

Antigen trapped by antibody in germinal centers may be a peculiarly effective stimulus for lymphocytes which have already been primed by antigen and which are committed to making an immunological response on meeting the antigen again. At Mill Hill, experiments to test this possibility are in progress; these involve the transfusion of primed cells (with a radioactive label in the nucleus) into mice that were first treated with two antigens in such a way as to cause each of the antigens to settle in the germinal centers of the lymph nodes on only one side of the animals.

Whether antigen has to be present as a continuing stimulus within cells which make antibody has not yet been resolved. Nossal and his colleagues concluded that there was no detectable antigen in such cells, and, in their recent experiments with (T,G)–A—L, the Mill Hill workers found that many cells were making antibody while fewer than 15 molecules of intact antigen were present. However, both groups used iodine-125 as a label, and there is evidence that the label can be selectively lost when antigen molecules are degraded in vivo. Accordingly, Humphrey is now working with a highly iodinated form of (T,G)–A—L, Tigal, which evokes antibody largely against the iodinated tyrosine groups, so that the label and the antigenic determinants are inseparable. This antigen can be made about 100 times as radioactive as the material used previously, and even a small fragment of a single Tigal molecule will be revealed by autoradiography; a whole molecule will blacken more than 50 grains of emulsion. Not only should this material give the definitive answer to this question—which is plainly of central importance to understanding the biology of immunity—but it opens up a general prospect of anatomical study of the localization of individual molecules, provided the radiation is not too destructive. For example, the antigen pathways in initial recognition, suggested by Mitchison's experiment mentioned earlier, can be checked.

There is growing belief that one immunological role of the macrophage cells is that of boosting the antigenicity of the antigen. The testing of such a concept is not simple. E. R. Unanue and Brigitte Askonas in Humphrey's group find that different, but in many ways similar, molecules may give apparently contradictory results. For example, after ingestion by free macrophages, hemocyanin from one source is much more immunogenic than the uningested hemocyanin is, whereas hemocyanin from another source is much more immunogenic before than after ingestion. Such findings should provide a clue to the role of macrophages. This role might involve actual modification of the antigen, but it could involve alteration of the specialized environment within lymphoid tissues where the lymphocytes encounter the antigen. Investigation of what the macrophages do, and what happens inside them, is continuing.

There are two populations of lymphocytes in mammals: those that persist for long periods (about 10 years in man) and those in which the turnover is much more rapid. The natural assumption would be that all long-term immunological memory is associated with the long-lived lymphocytes. Gowans in Oxford, who has already established that the immunological memory resides in small lymphocytes, inclines to this view and is currently engaged in experiments to test it, with cells carrying a label in the nucleus. On the other hand, and partly on the basis of the work of Medawar and his colleagues with ALS, Humphrey suspects that the assumption may not be true, and he is testing it in his experiments involving transfer of prime and labeled cells, but arranging that in some cases the long-lived lymphocytes carry the label, and in other cases the short-lived lymphocytes do so.

Where is the diversity generated that enables an organism to respond to an arbitrarily chosen antigen? At Mill Hill, C. A. Janeway showed that even polymers of D-amino acids are immunogenic at small doses. L. Brent and Medawar have confirmed that lymphocytes which have previously experienced no specific stimulation can recognize graft antigens. Is this diversity determined genetically? Some evidence that it is comes from work by D. W. Dresser (in Mitchison's group) who has studied the antibodies in plaque-forming mouse cells that attack red blood cells. He finds that the antibodies differ from one strain of mouse to another.

The immunological work of other Divisions of the National Institute for Medical Research varies from the safety control of immunological products such as polio vaccine, to investigations of the biosynthesis of immunoglobulin. Brigitte Askonas, A. R. Williamson, and Z. Awdeh are studying the formation of immunoglobulin from the light and heavy chains of which it is composed, and the way in which a balanced synthesis of both types of chains is achieved. They have studied myeloma tumor cells which synthesize a uniform immunoglobulin, and also lymph nodes stimulated to make specific antibody. They have evidence that the two kinds of chains are made independently on different polyribosomes, and that the release of the heavy chains is normally controlled by the presence of a small number of free light chains in each cell.

Two other discoveries, one fundamental and one very practical, have recently been made. H. G. Pereira, A. C. Allison, and their colleagues in the Virology Division have confirmed that virus-infected tumor cells evoke an immune response from the lymphocytes of the host, very like the reaction to grafted tissue; they also find that administration of antilymphocyte serum will prevent the response.

The other discovery, concerning the development of immunity to malaria, was made in the Parasitology Division at Mill Hill. A human develops resistance to malaria only very slowly, and during an attack suffers relapses as the parasite changes its antigenic character. The same pattern occurs in monkeys. Frozen red blood cells from a malaria-infected monkey retain their infectivity on thawing and can be conveniently separated from other blood constitu-

ents with a sucrose gradient and a low-speed centrifuge. Thin-layer chromatography of parasite material from these red cells has yielded five different antigenic proteins, the commonest of which behaves chromatographically very like hemoglobin. As the parasite is known to attack hemoglobin, this antigen may be a converted form of host material.—NIGEL CALDER

APPOINTMENTS

Wilfred W. Westerfeld, dean of the School of Graduate Studies and professor and chairman of the department of biochemistry at the State University of New York Upstate Medical Center, to acting president, an additional position at the Center. . . . **Alan D. Freas**, assistant to the director of the U.S. Forest Products Laboratory, to chief of the division of solid-wood products research at the laboratory. . . . **E. Leonard Jossem,** professor of physics, Ohio State University, to professor and chairman of the department of physics at the university. . . . **James E. Oldfield**, professor of animal science, Oregon State University, to head of the department of animal science at the university, succeeding **James C. Miller**, who will retire. . . . **E. Richard Harrell, Jr.**, professor of dermatology, University of Michigan, to chairman of the dermatology department at the university's medical school. He succeeds **Arthur C. Curtis**, who will retire. . . . **Boyce D. McDaniel**, professor of physics, Cornell University, to director of the university's Laboratory of Nuclear Studies. . . . **James O. Hepner,** associate director of the Jewish Hospital of St. Louis and part-time assistant professor Washington University Medical School, to director of the department of hospital administration at the University. . . . **Stephen A. McCarthy**, director of the Cornell University Library System, to executive director of the Association of Research Libraries. . . . **John R. Platt**, research biophysicist, Mental Health Research Institute, University of Michigan, to acting director of the institute, and **Warren T. Norman**, professor of psychology at the university, to acting chairman of the department of psychology. . . . **Liberto J. A. DiDio,** professor of anatomy, Northwestern University Medical School, to chairman of the Department of Anatomy, Toledo State College of Medicine. . . . **Raymond F. Dixon**, deputy chief of the Training Resources Branch, PHS, to director of the newly established Division of Health Manpower Educational Services, PHS. . . . **David Hubel**, professor of medicine, Harvard University, to George Packer Berry Professor of Physiology and head of the department of physiology, Harvard Medical School. . . . **William D. Schroger**, professor of anthropology, University of Michigan, to chairman of the Literary College's anthropology department at the University. . . . **James R. Neely**, research associate in physiology, Vanderbilt University School of Medicine, to head of the multidiscipline laboratories, Pennsylvania State University College of Medicine at the Milton S. Hershey Medical Center. . . . **Rulon W. Rawson**, professor of medicine, Cornell University Medical School, and chief of the department of medicine of the Memorial Sloan-Kettering Cancer Center, to dean of medicine, New Jersey College of Medicine and Dentistry. . . . **Howard O. Lorenzen**, head of the Countermeasures Branch, Radio Division, Naval Research Laboratory, to superintendent of the Laboratory's Electronic Warfare Division. . . . **John G. Daunt**, professor of physics and electrical engineering, Stevens Institute of Technology, to director of proposed center for cryogenics at the Institute. . . . **Donald J. Hillman**, chairman of the department of philosophy, Lehigh University, to an additional post of director of the Center for the Information Sciences at the University. . . . **Robert G. Loewy**, director of the University of Rochester's Space Science Center, to dean of the university's College of Engineering and Applied Science. . . . **Martin Morrison**, head of the Section of Respiratory Enzymology, City of Hope Medical Center, Duarte, California, to chairman of biochemistry, St. Jude Children's Research Hospital and professor of biochemistry the University of Memphis. . . . **Donald C. Harrison**, assistant professor of medicine, Palo Alto--Stanford Hospital Center, to head of the division of cardiology, Stanford University School of Medicine. . . . **Charles M. Plotz**, associate professor of medicine, Downstate Medical Center, Brooklyn, New York, to director of the newly established Office of Continuing Education at the Center. . . . **Robert W. Morse**, president of Case Institute of Technology, to first president of the newly established Case Western Reserve University, and **John S. Millis**, president of Western Reserve University, to first chancellor of the new University. . . . **Martha E. Peterson**, dean of the University of Wisconsin, to president of Barnard College. . . . **Boris Magasanik**, professor of microbiology, to head of the department of biology.

RECENT DEATHS

Robert McEwen, 60; retired president of Hamilton College, Clinton, N.Y., and chairman of the Empire State Foundation of Independent Liberal Arts Colleges; 30 May.

Donald B. McMullen, 64; scientific adviser to the director of the Walter Reed Army Institute of Research, Washington, D.C.; 27 May.

Heinrich K. Matt, 60; manager of the testing operations branch of the propulsion wind tunnel for Aro Inc., Tullahoma, Tenn. During World War II, he was chief of testing programs and design for the German Research and Aeronautics Branch of the Luftwaffe; 4 June.

Edmund S. Merriam, 87; professor emeritus of chemistry, Marietta College, Ohio; 12 June.

Richard E. Ogborn, 47; director of the nuclear medicine service for the Veterans Administration in Washington, D.C., and former professor in the School of Medicine, Creighton University, Nebraska, and at the College of Medicine, University of Nebraska; 1 June.

Elmer Rebol, 50; chief of the materials branch of the AEC's Division of International Affairs; 24 May.

William M. Silliphant, 66; former director of the Armed Forces Institute of Pathology; 29 May.

John Francis Tighe, 47; pharmacologist in the Bureau of Science, Food and Drug Administration; 4 June.

Arthur Q. Tool, 89; retired physicist with the National Bureau of Standards; 4 June.

Otis C. Trimble, 70; educational and cultural exchange officer for the State Department; 5 June.

Lawrence Northcote Upjohn, 93; director and honorary chairman of the board of the Upjohn Company; 2 June.

Laura H. Zirbes, 83; professor emeritus of education at Ohio State University; 9 June.