Meetings

Cellular Immunity

An international conference devoted to "Mediators of Cellular Immunity" was held on 28 to 30 April 1969 at Brook Lodge, Michigan, and sponsored by the National Institute of Allergy and Infectious Diseases. Interest centered on new information about the effector molecules, such as transfer factor (TF), migration inhibitory factor (MIF), and lymphotoxin (LT). However, cell-mediated immunity in a more general sense was also extensively discussed. The meeting followed, in series, a previous one on "Immunological Tolerance." Emphasis was on informal interaction among the 40 conferees with an absence of presented papers.

Hirschhorn opened the conference with a discussion of lymphocyte activation. A wide range of agents, some specific (antigens, allogenic cells) and others nonspecific [phytohemagglutinin (PHA), antibodies to immunoglobulins, or other components of the lymphocyte surface], can stimulate transformation of lymphocytes in vitro. Transformation involves a well-defined sequence of events which run from an early increase in phospholipid turnover and pinocytosis, through a variety of biochemical steps including increases in RNA and protein synthesis, to DNA synthesis and cell division. The requirements for stimulation are not always the same. Thus macrophages have to be present for soluble antigens to stimulate human lymphocytes, but not for PHA; the action of pokeweed mitogen becomes irreversible far more rapidly than that of antiserum to immunoglobulin. Furthermore, lymphocytes do not respond uniformly; some cells go on to divide, while others proceed only as far as RNA synthesis. Nevertheless, much of the same sequence of events occurs not only in lymphocyte transformation but also in the immune response in vivo, as well as in fertilization and hormonal induction. So much occurs in common, in fact, that some of the immunologists present were disappointed at the apparent absence of any biochemically unique feature once specific antigenic stimulation has been initiated.

Transformation in vitro has been much used for determining the origin (thymus or bursa derived) and frequency of antigen-sensitive cells. The validity of the method depends on the absence of cell-to-cell spread of transformation. The release by transformed cells of a mitogenic factor which can then act on other cells was discussed. The very high frequency of transformation obtained by mixing allogeneic lymphocytes (2 percent for ABG-incompatible rats) was not satisfactorily explained. Opinion on this point was split. The "anticlonalists" were delighted, while the "clonalists" (advocates of Burnets' theory of clonal selection) sought escape by postulating (i) a low binding energy threshold for triggering this type of transformation, or (ii) an abnormally high natural frequency of reactive cells, possibly due to the alloantigens playing a role in tumor surveillance.

Mitchison contrasted the induction of cellular versus humoral immunity. Ideas about this duality of response are dominated by the Burnet-Good theory, which holds that lymphocytes are divided into two populations. One population, precommitted to cellular immunity, is derived from the thymus. The other, precommitted to humoral immunity, is derived from the bursa (in birds) or directly from the marrow (in mammals). The theory has stood up well to recent developments. Thymus-derived cells are now known to be needed for at least some types of humoral response, for example, but their need in this respect is probably as antigen-handling helpers rather than as precursors of antibody-secreting cells. It is not unlikely that this act of cooperation between thymus and marrow-derived lymphocytes may explain many of the classical hapten-carrier effects. Furthermore, studies of the mechanism of action of antiserum to lymphocytes (ALS) have led to postulation of two populations of lymphocytes, one preferentially recirculating and the other preferentially sedentary, and these appear to correspond to the two populations of the Burnet-Good theory.

Two populations of lymphocytes were invoked to account for certain clinical findings. Cellular immunity may be either lacking or defective in infectious disease involving intracellular microbial parasitism (for example, lepromatous leprosy). Cellular immunity appears to be totally absent in DiGeorge's syndrome, as a result of congenital lack of the thymus. The use of Lawrence's transfer factor to treat lepromatous leprosy was suggested. No clear distinction can yet be drawn in man between thymus-dependent and thymus-independent antigens.

The role of thymus-derived cells in immune response in vitro to cellular antigens has not yet been completely clarified. Cell cooperation is evidently needed in this system because populations of cells can be isolated from the mouse spleen either by gradient centrifugation or by surface adherence; these populations have to be combined in order to obtain a full response. Data were quoted which indicate that the adherent population is thymus-dependent. Here again, then, the concept of a distinct thymus-derived population with special immunological reactivity received support.

Lawrence reviewed and interpreted present information on transfer factor. This agent is a dialyzable moiety with a molecular weight less than 10,000, obtained from blood leukocytes of humans with cellular immunity; upon injection into other individuals it transfers the specific immunity in the form either of delayed hypersensitivity to environmental antigens or heightened resistance to skin grafts. Transfer factor can also be applied to populations of nonsensitive lymphocytes in vitro, where it renders a small fraction of the population susceptible to transformation by the antigen to which the donor was sensitive; here, as well, the low-molecular-weight transfer factor is also known to be active. Neither antigen nor antibody quite fit the properties displayed by transfer factor.

In the course of further discussion several points emerged: (i) the existence of transfer factor has been con-

firmed repeatedly; (ii) most of the data was considered compatible with transfer factor being an immunogen; and (iii) developments in vitro, particularly the activation of animal lymphocytes by dialyzable transfer factor of human origin, augur well for a rapid solution of the problem.

Bloom and Granger were the initiators for two separate discussion sessions devoted to the now recognized MIF and lymphotoxin as effector molecules of cellular immunity. Activated lymphocytes have now been shown to liberate factors with the following activities: MIF, LT, skin-reactivity, chemotaxis, mitogenicity, and interferon. Although the interaction of immune lymphocytes with specific antigen is required for the production of these effector molecules, the subsequent action of these effectors is nonspecific with respect to the target cells affected and, moreover, does not require the presence of antigen. With the exception of interferon, all of these agents have molecular weights around 80,000, and work is already under way to determine whether they are separate and discrete entities or reflect a single component.

The physiological role of these factors is not yet fully established. Chemotactic factor and MIF acting in concert could well account for the manifestations in vivo of delayed hypersensitivity, and the observed consequences of MIF injection can be interpreted in this light. Lymphotoxin, the cytotoxic factor, is suspected of playing a role in the homograft reaction, a concept which is supported by known instances of nonspecific spread of the reaction (for example, in the kidney) but contradicted by other instances of a highly selective reaction (such as in tumors and in the skin). Experiments with antiserums to the factors should rapidly resolve the problem.

In the final discussion, Uhr developed the evidence in support of immunoglobulin as the recognition unit in cellular immunity, and the thesis that the difference from humoral immunity probably hinged on a seemingly minor but essential aspect of immunoglobulin retention by thymic cells as compared to its secretion by plasma cells. The consensus was that our understanding of the effector side of the cellular immune response is now progressing rather rapidly, whereas there was less optimism concerning clarification of the induction side.

Publication (Academic Press) of the proceedings of the meeting is scheduled for October. The first volume of the new series was *Immunological Tolerance*, proceedings of a similar meeting in 1968.

N. A. MITCHISON
National Institute for Medical Research, Mill Hill, London, England

Sleep and Biorhythmicity

The relation of sleep research and biological rhythm research was examined in a symposium during the ninth annual meeting of the Association for the Psychophysiological Study of Sleep in Boston, 20–23 March 1969. The estrangement of these two related areas of work was ascribed to the preoccupation of sleep researchers with the psychophysiology of rapid eye movement (REM) sleep since its discovery 15 years ago. Since then a profusion of data, almost all of it involving measurements over time, has appeared.

Variable sleep dimensions in the time domain include latency to onset, total duration, duration of component phases (REM and non-REM), and period length of the cyclic alternation of component phases. Yet, in the post-REM era there has, until very recently, been no critical examination of the rhythmic aspects of sleep despite the fact that a highly sophisticated set of methods exists by which they may be studied. The student of sleep who was familiar with rhythm research could, at the least, define, measure, and control for periodic phenomena in his data.

Halberg showed how rhythms, especially circadian and ultradian ones, could be detected by the use of specialized computer programs whether or not they were apparent in sleep data plotted as a function of time. The parameters of such rhythms, namely, period (τ), amplitude (C), phase (ϕ), and phase difference (Φ), can likewise be estimated. For time series or sections thereof with constant phase angle, a least-squares spectrum and a cosinor display the amplitude and amplitude-weighted phase, respectively.

These measures have been determined for sleep data from diverse sources. Pöppel reviewed the evidence of the Aschoff school for the circadian character of the human sleep-waking cycle. The period (τ) of this rhythm in subjects isolated from time-givers was about 25 hours and such "free-running" individuals showed a change in phase difference (Φ) between the