means constant collaboration with their consultant colleagues and the stimulus to keep abreast with modern developments. The patients soon realize that there is a degree of continuity and that their doctor also has hospital responsibilities. The doctor too is aware that he cannot easily shelve responsibility by moving his patient into hospital. We believe this makes for an increase in mutual respect. It can, however, have strange repercussions for newcomers. On at least one occasion a patient has disagreed with the opinion and advice of a doctor in his surgery and has appeared some hours later in the casualty department asking for another opinion, only to be confronted by the same but wearier and slightly annoyed doctor.

One hospital of the group, however, in a similar position was closed down many years ago for over a year. The local doctors lost interest in hospital work, and valiant attempts to get the hospital running again on its same standards have been in vain. Once general practitioners lose their hospital skills and connexions they need much coaxing to come back into hospital work. It is only fair to add that throughout the years we have had a most understanding hospital management committee and administrative officers who are prepared to understand the problems of a cottage hospital sympathetically, and they have given every support to our endeavours to improve the service.

In the Bonham-Carter Report (Central Health Services Council, 1969) the future of the hospital which we have described comes in for anxious discussion and its future seems to be uncertain. We might ask whether such a satellite hospital has a function in the hospital service of the future. It is apposite at this time to quote an extract from the *General Practitioner and the Hospital* (Oxford Regional Hospital Board, 1969):

"In order to reconcile functional and economic requirements, decisions are required of the order of comparison between needs, for example, for admission to inpatient facilities of 'cold' surgical patients and acute medical 'G.P. type' patients. Great flexibility of attitude is required, but once the resource is made available to the general practitioner, hospital consultants would need to recognize that the patient's needs had competed fairly. Conversely, general practitioners would have to recognize their responsibility to use resources at least as economically and efficiently as consultants. It should be possible in this way to separate 'clinical control' from the management of resources and to bestow both much more flexibly, both in and out of hospital."

We think that in our area we have gone a long way to meeting these requirements and that for a particular type of case as envisaged in the Bonham-Carter Report we can effectively contribute to the medical needs of a community of about 50,000 people separated from a major hospital. In paragraph 34 of that report it is stated that "the essence of such a unit is that it should not attempt to provide a complete hospital service to its community, but only those hospital services which can with reasonable economy of skilled manpower (and of money) be provided locally."

Should medical services be provided with the doctors working as clinical assistants under the guidance of consultants or, alternatively, taking clinical control of the patients? We believe that in the end it is essential that a particular doctor should have clinical control, and at our level of hospital work this should be the local practitioner working along the lines described. But at all times it should be remembered that "there is a tendency for some cottage hospitals to produce a service to satisfy general practitioners and patients in a manner rather unrelated to the requirements of modern medicine or the community concerned" (Oxford Regional Hospital Board, 1969). We believe that in many cases of an intermediate type we can show an improvement in patient care for the community which is distinct from that of the local district hospital. We think that the integration with the general practice service shows an optimum use of medical manpower and that the resulting unification of medical effort should be the fundamental aim of any health service.

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FOR DEBATE . . .

Unified Concept of Cell-mediated Immune Reactions

G. S. PANAYI,* M.B., B.CHIR.

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Reactions of delayed hypersensitivity are thought to be involved in a number of biological phenomena of great interest in clinical medicine, such as acquired cellular resistance to infective and parasitic diseases (Mackaness and Blanden, 1967), the homograft reaction (Brent and Medawar, 1969), certain autoimmune diseases (Pearson and Wood, 1964), and tumour immunity (Bennett, 1965). The central pathogenetic role in these situations is exerted by sensitized lymphoid cells (Gowans and McGregor, 1965), and it is for this reason that the term "cell-mediated immunity" is used in preference to the operationally descriptive term "delayed hypersensitivity."

* Medical Research Council Junior Research Fellow, the Division of Immunology, the Mathilda and Terence Kennedy Institute of Rheumatology, London W.6.

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The mechanism whereby lymphoid cells express immunological reactivity, however, is not clearly understood. This lack of knowledge is especially felt at the biochemical level, and without such information the possibilities of a more rational interference with reactions of cell-mediated immunity become remote. Recently, with the development of more reproducible and more sensitive in-vitro techniques (Symposium on Delayed Hypersensitivity, 1968), these problems have begun to yield some of their secrets to a more systematic and analytical approach. This research has not, as yet, reached a wider clinical audience, and this seems an opportune moment to summarize the results of these researches. Furthermore, the presentation of a unified concept of cell-mediated immunity, based on present knowledge, may help to focus attention on future developments.

Present Research

The introduction of specific antigen into an animal or human being sensitized to that antigen leads to activation of specifically sensitized lymphocytes. Such activation sets in motion a train of immunological events which may be observed as a delayed skin reaction or the rejection of a homograft. Antigen stimulation of sensitized lymphocytes in tissue culture has shown that activated lymphocytes synthesize and release into the culture medium soluble cell-free factors which may be the effector molecules of many aspects of in-vivo cell-mediated reactions. Thus antigen-activation of lymphocytes leads to the release of a pyrogen (Johanovský, 1960; Atkins, Bodel, and Francis, 1967) which produces fever in recipient animals. It is distinct from endotoxin fever and from the endogenous pyrogen liberated by neutrophil granulocytes. This pyrogen may be responsible for immune fever in many clinical situations.

Subsequently, antigen-activated lymphocytes have been shown to generate soluble material which inhibits the migration of non-sensitized peritoneal exudate cells (macrophage inhibiting factor), stimulates non-sensitized recipient lymphocytes to transform (mitogenic factor), is cytotoxic for mouse fibroblasts in monolayer cultures (cytopathic factor), and to possess inflammatory activity in vivo (inflammatory factor). These various activities are generated simultaneously in the same lymphocyte culture, are of molecular weight 80-50,000, and apparently act independently of antigen, classical antibody, and antigen-antibody complexes (Dumonde *et al.*, 1969). The factor(s) has (have) been given the generic term "lymphokines." Other factors which have been described as being released in identical experimental models are a material which is chemotactic for monocytes (Ward and David, 1969) and a material which promotes macrophage phagocytosis (Barnet, Pekárek, and Johanovský, 1968).

Delayed Hypersensitivity Reactions

It is thought that such factors may play a part in the evolution and pathogenesis of delayed hypersensitivity reactions. If one considers the various types of cell-mediated immune responses (the delayed skin reaction, rejection of homografts, tumour resistance, and acquired cellular immunity), these have many points of similarity: inflammation, accumulation of infiltrates of mononuclear cells, and varying degrees of parenchymal tissue damage. If the cutaneous response to a soluble antigen in a sensitized animal be taken as a model of a delayed hypersensitivity lesion, then a unified concept of events taking place can be devised on the basis of release of lymphokine activities by antigen-activated lymphocytes.

In such a model (see fig.), entry of antigen would cause the release of cell-free soluble mediators of delayed hypersen-

Model of delayed hypersensitivity lesion. C.F.=Cytotoxic factor. M.F.=Mitogenic factor. I.F.=Inflammatory factor. M.I.F.=Macrophage inhibiting factor. *=Chemotactic factor.

sitivity. The slow tempo of delayed skin inflammation is the result of two processes: time to produce soluble factors and time for sufficient lymphoid cells to arrive at the site. Accumulation of cells at sites of delayed hypersensitivity reactions would be a consequence of the vascular permeability promoting effect of inflammatory factor and the action of monocyte-chemotactic factor. Grossly, such cellular accumulations would be recognizable as induration, one of the hallmarks of the delayed cutaneous response; and in target tissues, such as the thyroid in experimental autoimmune thyroiditis, as accumulations of mononuclear cells. Furthermore, such a mechanism would explain the results of Hamilton and Chase (1962), Turk (1962), and McCluskey, Benacerraf, and McCluskey (1963), who showed that in passive transfer of the delayed response the accumulating cellular infiltrate was overwhelmingly of host origin.

Cytotoxic effects on target tissue would be dependent on the release of cytopathic factor and the extent to which soluble mediators activate by-stander lymphoid cells to express cytotoxicity, so that tissue damage may occur where there is no antigenic similarity between target tissue and initiating antigen. This may occur in some of the human "auto-immune" diseases, in which case there would be no correlation between antibody titres and the magnitude of the disease; antibodies would be merely secondary indicators of tissue damage releasing sequestered antigen. Furthermore, transport of factors beyond the immediate area of antigen deposition, as a consequence of increased vascular permeability, would allow for spread of the reaction to more distant sites, a situation which apparently occurs in-vivo (Waksman, 1960). Indeed, part of the increased permeability may be a cytotoxic effect of lymphokines on vascular endothelium. In addition, substances released during cell death may have permeability-increasing and chemotactic properties, thus enhancing and amplifying an originally purely immunological response.

Mitogenic factor released would stimulate non-sensitized lymphocytes, leading to their recruitment in the response, possibly by releasing further mediators, and thus may contribute further to the development of the lesion. Concurrently, such stimulation may lead to "sterile inactivation" of participating lymphocytes. Furthermore, the production of lymphocyte inhibitors by the original antigen-stimulated lymphocytes (Dumonde *et al.*, 1969) would tend to result in a feedback diminution of the lymphoid cell response. Lymphokine activation of macrophages by migration-inhibiting factor would lead to their immobilization at the reactive focus. This immobilization, in addition to contributing to cellular accumulation, may be expected to have two consequences: removal of antigen by phagocytosis (Ehrenreich and Cohn, 1969) and processing of antigen into a more immunogenic form (Humphrey and Turk, 1963). Such a sequence of events may explain the potency of the intra-dermal route in the induction of delayed hypersensitivity to protein antigens (Uhr, Salvin, and Pappenheimer, 1957).

Non-production of lymphokine mediators would lead, therefore, to profound disturbances in effector aspects of cell-mediated immunity. Indeed, Childgren, Meuwissen, Quie, Good, and Hong (1969) suggested that the cutaneous anergy of chronic mucocutaneous candidiasis is due to precisely such a defect.

Three Factors

In this scheme, control of cell-mediated reactions would depend on three factors: lymphocytes, macrophages, and vascular permeability changes. Firstly, contribution of lymphocytes would diminish because of the action of lymphocyte inhibitors, "sterile inactivation" by mitogenic factor, and, possibly, functional inadequacy of lymphocyte daughter cells. Secondly, activated macrophages, by phagocytosing and then

metabolically degrading or sequestering antigen (Kölsch and Mitchison, 1968), would remove the primary stimulus. Thirdly, the loss of lymphocyte factors and other cellular products from the lesion by increased vascular permeability would further contribute to cessation of immunopathological changes in the area, by their dilution in the blood vascular compartment or by enzymatic inactivation therein. Such enzymatic inactivation would be taking place, presumably, in the lesion itself.

Thus antigen-activation of sensitized lymphoid cells unleashes a series of major biochemical, biological, and physiological events whose tendency is to restore the *status quo ante* by removing the stimulating agent—antigen. In some situations these events are regarded as beneficial; in others they are a dangerous complication, as in the homograft reaction. In the future, knowledge of the properties of lymphocyte-generated soluble mediators of cellular immunity may allow suppression or enhancement of immunological processes in clinical and experimental practice regularly, satisfactorily, quantitatively, and, hopefully, with few side-effects.

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Reprint requests to: Rheumatic Diseases Unit, Northern General Hospital, Edinburgh EH5 2DQ.

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Review Body's Twelfth Report

The Review Body in its Twelfth Report, dated 31 March 1970, recommends increases of 30% in the pay of practically all doctors in the N.H.S. to start on 1 April 1970 and to run for two years. Rises in fees and allowances are also proposed along with increases in the expenses element of general practitioners' remuneration. The Government announced on 4 June that it will implement the award in full to hospital junior doctors but that 15% "on account" will be paid to consultants, S.H.M.O.s, and general practitioners. The remaining 15% has been referred for a second opinion to the National Board for Prices and Incomes, which has been asked by the Government to report back by 15 July. The Secretary of State for Social Services, Mr. R. H. Crossman, has undertaken to abide by the board's advice. Lord Kindersley and his colleagues on the Review Body resigned in the wake of the Government's announcement. The cost in a full year of the Review Body's proposals, which also cover dentists' remuneration, would be about £85 million. Leading articles appear at pages 615 and 616.

The Review Body's Twelfth Report, which has been sent by the B.M.A. to all N.H.S. doctors, covers the fourth general review of the remuneration of doctors and dentists since the Review Body was established in 1962. In it the Review Body draws attention to the time intervals covered by its various reports. These range from three years for the first report in 1963 to 15 months in the review period up to 31 March 1970 covered by the tenth report. The present review is intended to extend for two years. Twenty-four meetings were held between October 1969 and March 1970.

Introducing the Report the Review Body states: "Our intention in the present general review has been to re-assess doctors' and dentists' remuneration, taking into account particularly any changes since the time of our Seventh Report in the workload and in the manpower situation in the two professions. There has been time since that report to see whether or not its recommendations are beginning to have the effect we aimed at, and there have been no major changes in the pay structure of doctors or dentists in the meantime which would complicate such an appraisal. We have also considered their remuneration in relation both to current earnings in comparable professions and occupations and to movements in salaries and wages since the time of our Seventh Report; in effect trying to make a double check on its consequences."

Workload

The Report states "We have not been able on this occasion, any more than in previous reviews, to find a method of accurately measuring the total workload of doctors or dentists. We can therefore make only a qualitative assessment." It refers to the B.M.A.'s evidence about the increasing pressure of work on all grades of hospital staff. The Review Body thinks "the policy of

quicker discharge from hospital and certain of the advances in medical techniques must be imposing a greater burden of work and responsibility upon many hospital doctors. The increase in the numbers of hospital medical staff is a welcome improvement, but we do not think that this will have put right earlier deficiencies in hospital staffing. There is also the requirement to supervise the work of the increasing number of doctors from overseas. Junior hospital doctors and at least some senior doctors appear to be required regularly to make themselves available for work for especially long periods; this is a symptom either of bad management or more probably of a continuing shortage of the appropriate staff."

Several paragraphs are given to workload in general practice, and mention is made of the B.M.A.'s views on the increase due to certification, the changing age-structure of the population, the policy of early discharge of patients from hospital, and the implications of the permissive society.

The Review Body concludes "that the evidence, including the figures for average list sizes, suggests that the workload of general medical practitioners has been growing in recent years, principally because of the new techniques in medicine and the extra burdens referred to above. The indications are that the workload will increase further in the immediate future."

Manpower

The Review Body takes the estimates of the Todd Report as providing some basis for two tests by which the Review Body assesses the adequacy of medical manpower for the N.H.S.—(1) "the number of 'British resident' graduates each year from British medical schools; and (2) the change in the number of doctors in the general medical service and the hospital service, and in partic-