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Clinical Immunology

Report of a WHO Scientific Group

A Scientific Group on Clinical Immunology met in Geneva from 25 to 30 October 1971. Dr. T. A. LAMBO, Assistant Director-General, opened the meeting on behalf of the Director-General.

1. Introduction

Clinical immunology is emerging as a distinct specialty encompassing the diseases characterized by abnormal function of the lymphoid tissues and those in which the immune response plays a major role. This has come about as a result of the great advances made by immunologists during the past two decades. Thanks to their research, an understanding has been gained of thymic function, the nature of cell collaboration in the immune response, the mechanism of antibody formation, and the biological functions and abnormalities of the various immunoglobulins. The scope of clinical immunology, its past achievements, and possible future activities are examined in greater detail in Annex 1, which is based on a draft prepared by a group of experts convened by WHO in October 1970.

Much of this knowledge was derived from clinical observations that have influenced the experimental work and theoretical concepts of specialists in immunology. For example, the discovery of new classes of immunoglobulins and knowledge of the structure of immunoglobulins arose out of the study of myeloma proteins, and the relationships between various lymphoid organs were elucidated by the study of immunodeficiency diseases.

Many of the conceptual and methodological advances made in basic immunology, especially during the last decade, have clear implications for diagnosis and therapy. In the past, clinicians have frequently consulted immunologists on an *ad hoc* basis, but the full potential of clinical immunology was not realized.

The main fields in which basic immunology can be applied clinically are: immunodeficiency diseases, immunoproliferative disorders, infectious diseases, autoimmune diseases, allergy, haematological diseases, transplantation, and cancer. Only where immunological investigations are made is the role of the immune response appreciated. To be fully effective, a clinical immunology unit should be able to assess the role of immune phenomena in disease, to make immunological tests available to a medical centre for diagnostic purposes, and to develop new diagnostic tests and new approaches to the management of immunological disorders.

There is an urgent need to create a suitable organization with staff and facilities for applying immunological knowledge to clinical problems. The Scientific Group, after having assessed the situation and considered ways of ensuring the optimum utilization of this knowledge, developed guidelines for organizing effective programmes in clinical immunology.

2. Organization of Clinical Immunology Departments¹ in Academic Institutions

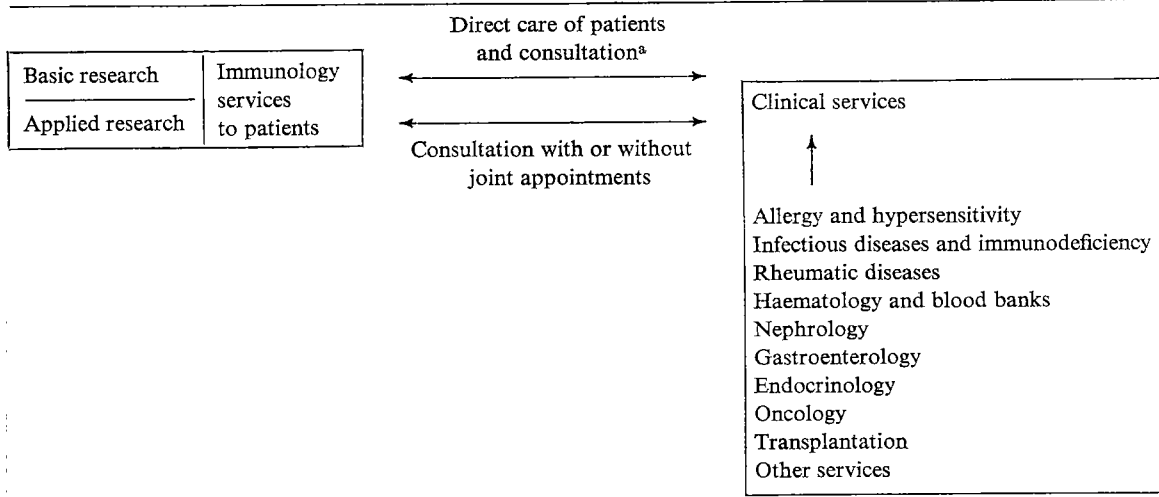
2.1 Functions and Aims

Basic immunology should be used for the benefit of patients by: (a) applying the expert knowledge of the immunologist to the various clinical specialties; (b) providing tests for diagnosis and for assessing disease activity in persons with immunological disorders; (c) establishing programmes of basic and clinical research that could lead to the development of new diagnostic tests and of new approaches to the management of immunological disorders; and (d) providing facilities for teaching and training.

2.2 Organization

Ways of organizing a clinical immunology department are shown in figure 1. Whatever the size and scope of such a department, its core should be a group of dedicated individuals working full time. The basis

¹ The Group used the term 'department' to denote an autonomous administrative unit.



^a Clinical immunology service integrated into a clinical immunology department.

Fig. 1. Organization of a clinical immunology department.

of the department would be a complex of laboratories equipped for serological, immunochemical, cellular-immunological, and immunopathological investigations.

A clinical immunology department organized in this way would be actively engaged in research programmes designed to ensure an effective link between advances in basic immunology and the clinical investigation of immunological disorders.

It is essential that a clinical immunology department should maintain effective contact with patients, e. g., through a consultation service or the direct care of patients within the department.

2.2.1 Contact with Patients

In the past, investigators interested in clinical immunology held appointments in departments of general internal medicine, paediatrics, rheumatology, dermatology, pathology, microbiology or other departments, as well as in blood banks. Clinicians working within normal department limits rarely had an opportunity of developing the required laboratory skills and had little time for making a proper clinical investigation of patients with immunological disorders, frequently because

of conflicting departmental interests. As a result, immunological advances of clinical importance have been brought to the patient chiefly in the following ways.

a) Several centres now have clinical immunology departments that provide direct care to patients, usually only for one or two categories of immunological disease, e.g., autoimmune diseases or clinical allergies. An essential feature of such a department is its responsibility for the care and investigation of certain classes of patient. Ideally, the staff of the department would be entirely responsible for a number of beds and associated out-patient facilities. Patients with immunological disorders, particularly those relevant to the research programme of the department, would be admitted to these beds, which should be located close to the laboratories of the department. Since clinical immunology embraces various branches of medicine, the clinical facilities of the department would not usually deal with all aspects of immunology. However, the department should be able to provide specialized laboratory services and the latest information on all immunological disorders.

b) In various other centres, clinical immunology departments have developed out of basic science departments and function autonomously as central laboratories studying the immunological problems of patients already in the care of clinical departments. A useful way of meeting the immunological requirements of modern medical practice, under these circumstances, is through joint appointments, i. e., the appointment of senior and junior medical staff to posts with both laboratory and clinical responsibilities. In addition, as stated in paragraph (a) above, physicians should be able to consult immunologists working in the laboratory.

These two main ways in which clinical immunology departments can be organized are not mutually exclusive. An important advantage of placing some categories of patient with immunological disorders under the direct responsibility of the clinical immunology department is that such a structure favours continuous commitment to thorough clinical investigation. To achieve the same advantages under the system described in paragraph (b), it is imperative that the joint appointments carry full clinical responsibility. Furthermore, close contact with clinical problems will cause laboratory workers in the field of basic research to become interested in the practical application of immunology.

The main advantage of organizing the clinical immunology department as a complex of laboratories with consultative responsibilities but no facilities for the care of patients would be to allow a full range of im-

munological resources to be developed. As a result, patients cared for in other clinical departments can also benefit from comprehensive immunological services. With either form of organization, adequate immunological services will be available to the medical community only if the clinical immunology department is of sufficient size.

In many instances, clinical immunology is developing within other disciplines, e. g., a nephrologist may study basic immunology for a time before returning to his own clinical specialty to concentrate on its immunological aspects. It is essential that such extra study should receive the full support of the clinical immunology department and not require the establishment of a small separate laboratory, draining resources that may be more effectively concentrated within a central immunology department.

2.2.2 Immunological Services

Immunological services constitute a broad field with important clinical implications for the diagnosis, classification, and evaluation of diseases and for the control of immunological therapy.

Clinical immunology consists in much more than the application of a few immunological tests to patients. For this reason immunological tests and services are most effectively carried out in centralized immunology departments having direct contact with patients.

Laboratory organization and economic assessment may be facilitated by dividing immunological investigations into the four stages shown in table I.

2.3 Research

Many of the current tests used in immunology are complex and so require a degree of expertise that is likely to be available only in a laboratory keeping pace with the latest developments and pursuing active research. Applied research will often be directed towards the improvement of existing tests and the development of new ones such as the radio-immunoassay for carcinoembryonic antigen as a marker of intestinal tumours. In addition, the investigation of the role of immunological processes in the pathogenesis of diseases such as rheumatoid arthritis, and new approaches to the design and evaluation of treatment (e. g., the grafting of bone marrow in immunodeficiency, manipulation of the immune response in atopic allergy), are likely to figure prominently in applied research programmes.

Table I. Immunological investigations

Stage	Investigation	Examples
I ¹	Serological	tests for antinuclear antibodies, cold agglutinins, or rheumatoid factors
	Immunochemical	immunoglobulin quantification and electrophoresis, hepatitis-associated antigen (HAA) determination
II ²	Tissue biopsy	detection of immunoglobulin and complement deposits in kidney or skin
	Cellular immunity	lymphocyte stimulation <i>in vitro</i> by phytohaemagglutinin, mixed lymphocyte culture, or migration inhibitory factor determinants
	Elaborate serological	tests for anti-DNA, anti-adrenal antibodies
	Elaborate immunochemical	complement components determination, IgE determination
III ³	Evaluation of immune function in patients	performance of skin tests, specific immunization
IV ⁴	Applied research	detection of immune complexes, development of new diagnostic techniques
	Basic research	detection of lymphocyte receptors, manipulation of the immune response

¹ Essential initial serological and immunochemical investigations using well-established techniques (automated where possible) that can be carried out by technical staff.

² More elaborate or expensive techniques, which have to be evaluated by the professional staff of the department, should not be performed without prior consultation with a senior member of the department.

³ Includes such *in vivo* procedures as skin tests for allergic diseases, and the evaluation of humoral and cellular immune responsiveness.

⁴ Research, as discussed in section 2.3, is essential for maintaining high standards and progress in clinical immunology.

Immunological services need to be supported not only by applied research but also by basic research, since immunology is constantly evolving and there is fruitful interaction between basic immunology and clinical

cal medicine. For example, present knowledge of the central and peripheral lymphoid tissues and of the major lymphocyte populations have resulted both from animal experiments involving ablation of the thymus or bursa of Fabricius and from the study of patients with selective immunodeficiencies. The discovery of 'paraproteins' in patients prompted the investigation of immunoglobulin structure, and it was through animal models of kidney disease that immune complex glomerulonephritis and Goodpasture's syndrome were recognized and understood. In general there is a continuous spectrum from applied to basic research; the larger the department, the greater is the possibility of covering both ends of the spectrum actively.

2.3.1 Standardization

The Scientific Group recognized the need for standardization in clinical immunology, and urged the active development of appropriate standards and specifications for reagents.

International standards have been developed for many materials². Most of them are available primarily for the calibration of national standards and, because supplies are limited, they are distributed sparingly. Other reagents, more generally available, include preparations for the quantification of human serum immunoglobulin IgG, IgA, and IgM of known content in international units³, and preparations for IgD⁴ and IgE⁵. Other reference materials for use in clinical immunology laboratories are available from national reference laboratories and national research council laboratories.

Recognizing the need for reagents of good quality, the International Union of Immunological Societies has established a Standardization Committee, to be responsible for developing standards for reagents and drawing up specifications for reagents used in immunology. This new committee will operate through a number of specialized subcommittees to develop the required reagents and specifications. Until standard reagents are developed, some of the WHO reference centres listed in Annex 2 will continue to provide useful samples of sera, etc., although these materials may not meet the criteria for acceptance as international standards or reference reagents.

² Wld Hlth Org. techn. Rep. Ser., No. 463 (1971).

³ Bull. Wld Hlth Org. 42: 535-552 (1970).

⁴ Bull. Wld Hlth Org. 43: 607-609 (1970).

⁵ Bull. Wld Hlth Org. 43: 609-611 (1970).

2.4 Staff

The composition of the staff in clinical immunology departments should reflect an appropriate balance between laboratory and clinical disciplines.

There should be at least three senior staff members, experienced in basic research and immunological services. One of them at least should be a medical graduate with appropriate postgraduate qualifications – e. g., board certification or the equivalent – as well as substantial experience in clinical or basic immunology. Appropriate clinical experience will naturally be a prerequisite for conducting clinical investigations directly involving patients. The other senior staff members would be trained scientists with a doctorate in either medicine or basic science, and a minimum of two years' postgraduate experience in immunology.

The junior staff – whose number would depend on the size of the immunology department and medical centre served – would assist their senior colleagues in these tasks. Furthermore, research fellows and residents intending to specialize in clinical immunology should serve for a time in a clinical immunology department.

In addition, joint appointments (see page 8) would appear to be desirable at all levels. Members from other basic science and clinical departments may greatly contribute to the vigour and efficiency of an immunology department. Clinical and research fellows are valuable as intermediaries between the clinical and immunology departments. Such fellows may be engaged in laboratory work in immunology while working in the clinical departments to which they belong. Joint appointments and fellowships will improve the care of patients, especially through the application of new knowledge on immunology.

3. Organization of Clinical Immunology in Community Medicine and Public Health

Immunology departments capable of providing clinical and laboratory services of high quality are required to serve community hospitals and major public health programmes.

Minimum requirements of efficiency should be laid down for all clinical immunology departments, whether they form part of an affluent medical service or of one with limited resources. Such minimum require-

ments are: a laboratory giving clinical immunology services to patients, an immunological research and development programme, and a division with a number of beds for the direct care of patients. In addition to their clinical functions, members of such departments should participate in community health and teaching activities.

3.1 Immunological Service Programme

Services should cover as wide a range of tests as possible depending on local needs. Simple and multipurpose techniques are to be preferred. If the laboratory is equipped for immunochemistry, serology, cellular immunology, and immunohistology, it should be able to carry out most if not all of the tests required.

It is better for one clinical immunology department to serve as a reference and service centre for a whole region than for a multiplicity of small laboratories to be established. In some situations, it may be necessary to set up peripheral laboratories to provide clinical immunology services, but if possible these laboratories should be autonomous, using local resources in manpower and money. In that case, however, it is imperative that they keep in close contact with the reference centre in order to ensure that the quality of their services is maintained.

The central clinical immunology department should perform the tests corresponding to stages I to IV (table I). The branch laboratories, on the other hand, would primarily concentrate on the procedures included in stage I and part of stage II, as well as preparing and distributing immunological reagents according to local needs.

The laboratory of clinical diagnostic immunology should be closely linked with laboratories for pathology, clinical microbiology, and immuno-haematology (unless the latter is included in clinical immunology) so that resources can be shared.

The clinical immunology department may provide direct care to patients, or it may operate through joint appointments or consultation, as outlined in figure 1 and discussed in section 2.2.1.

3.2 Research Programme

Research is considered to be a necessary part of clinical immunology, mainly because without it teaching would be poor and progress unlikely.

Regardless of its size, a peripheral clinical immunology laboratory must carry out research, if only in collaboration with the central clinical immunology department. Such research may be applied to clinical and epidemiological problems. A certain number of full-time immunologists is essential to represent the main disciplines of immunology.

3.3 Public Health

The activities of the clinical immunology department must extend beyond the confines of the hospital. They will depend on the problems to be solved, which may include: the search for hepatitis-associated antigen in blood donors and patients; the prevention of haemolytic disease of the newborn; the detection of *in utero* infections; the correlation with environmental factors of diseases with immunological components; the early detection of neoplastic diseases, and the evaluation of the population at risk in relation to the infectious diseases.

3.4 Teaching

Teaching is essential in order to make the medical profession aware of the value of immunology; to lower the threshold of detection of immunological diseases; to increase career opportunities for specialists in clinical and basic immunology; and to encourage trainees to undertake further study in this field.

Specific teaching requirements are discussed in section 5.

4. Outline of Immunology Programmes in Developing Countries

In general the organization of clinical immunology in developing countries should follow the same pattern as that in more advanced countries. Each developing country should organize the type of training and research programme that suits its own medical and public health problems. In particular, immunology programmes in such countries should be directed towards solving important public health problems, such as the control of epidemic and endemic infectious diseases and the interrelationships between hygiene, malnutrition, and immune responsiveness.

The organization of such programmes should also take into consideration the following special problems faced by developing countries:

- a) The shortage of trained manpower (both academic and nonacademic) and funds (generated locally or received from outside sources).
- b) Poor communications owing to geographical isolation from areas of intense scientific activity and immunology centres in other developing countries, as a result of which the exchange of ideas and discussion of research and training problems are impeded.
- c) As existing immunology centres have to service large geographical areas, existing facilities require rapid expansion.
- d) The need for economic and political stability.
- e) The difficulty of providing adequate servicing and repair facilities for equipment.

4.1 Organization of an Immunology Centre

Emphasis is placed in this section on the minimum requirements for immunology centres in developing countries. The clinical immunology department itself should act as a centre from which immunology programmes would be organized. This centre should be located within or closely related to a medical centre (medical school and/or teaching hospital) and be administratively autonomous.

4.2 Staffing

The staff should be composed of three or four senior members with a keen interest in basic immunological research, supported by adequate personnel. If possible, their background and interests should cover different fields (e. g., immunochemistry, immunobiology, immunopathology). Senior members may be doctors of medicine with clinical responsibilities or limited (consultative) clinical activity; or they may be qualified in basic medical sciences (e.g., PhD in immunology or related branches).

4.3 Training Functions

Training programmes, though varying in detail according to local circumstances, should attempt to meet the following general needs:

a) The introduction of immunological thinking and technology to medical and paramedical personnel by means of broad-based courses, such as the 2-4-month courses held at WHO Immunology Research and Training Centres.

b) Intensive short-term training (2-3 weeks) in specific aspects of immunology for more specialized (qualified) groups by means of seminars or workshops.

c) Postgraduate training (2-4 years) for potential immunologists.

d) Programmes of various durations designed to train technical personnel in the methodology and techniques used in immunology.

e) Undergraduate teaching in immunology in the medical school curriculum.

4.4 Research

The teaching staff should (a) be competent to conduct research in basic and applied immunology in their fields; (b) collaborate with members of other departments in clinical research in immunology; and (c) advise members of other departments in matters relating to immunological aspects of research projects.

4.5 Services

The services rendered by an immunology centre should include:

a) The development and standardization of immunological tests useful in clinical practice. Some of these (particularly the specialized tests) should be performed in the laboratory of the centre and some may be performed in other clinical laboratories or departments.

b) The preparation and standardization of reagents for distribution to other departments or investigators.

c) Advice on the diagnosis and management of immunological disorders.

4.6 Relations with Other Departments

An immunology department may maintain relations with clinical, pre-clinical, and other departments, as well as with laboratories, by means of joint appointments (including interfaculty appointments); consultations; and participation in grand rounds, clinicopathological conferences, and interdepartmental meetings.

4.7 Relations with National and International Agencies

Such agencies can play an important role in reducing the isolation of immunology centres by providing opportunities for the exchange of scientific ideas and data (e.g., with centres that are more active and specialized, particularly in immunological research on locally prevalent infections and parasitic diseases), by making training grants available to junior and technical staff members of the centre, and by establishing co-operative studies and research programmes.

The formation of national and regional immunological societies is a further way of fostering co-operation and the exchange of ideas between immunologists.

5. Education and Training

A clinical immunology department as described would exercise a variety of training and teaching functions.

5.1 Medical Students

All students of medicine should follow a course in the principles of immunology. Subsequent clinical instruction in immunology can take the form of detailed investigations of selected patients in whom there is evidence of immunological disorders, with the participation of the students⁶.

5.2 Postgraduate Education

5.2.1 Graduates

This group could be taught immunology by means of tutorial sessions and participation in the courses and research activities of the department. Members of the clinical immunology department could assume responsibility for supervising the research activities of candidates for doctorates (e. g., PhD).

5.2.2 Postdoctoral Fellows and Residents of the Clinical Immunology Department

Holders of a PhD or medical degree wishing to specialize in immunology should receive at least two years' formal training, with emphasis

⁶ Wld Hlth Org. techn. Rep. Ser., No. 358 (1967).

on the clinical application of fundamental immunology and on the performance and interpretation of immunological tests. Qualified physicians would also be concerned with patients with immunological disorders. Research would be an essential component of this training programme.

5.2.3 Hospital Staff and Residents of Clinical Departments

The expert knowledge of the staff of the clinical immunology department should be made widely available to their colleagues in the various clinical departments and to the medical community as a whole. The staff of the department would participate in the general educational programmes – seminars and grand rounds – that characterize the activities of centres of academic medicine.

5.2.4 Practitioners

This group can be reached through periodic postgraduate courses. Informal contacts and collaboration on individual patients problems are also important mechanisms for imparting new immunological concepts.

5.3 Courses in the Techniques and Concepts of Clinical Immunology

Short courses (1–3 weeks) in the techniques and concepts of specific fields of clinical immunology (e. g., autoimmune serology), such as those organized by WHO Immunology Research and Training Centres, may provide valuable training. It is recommended that more of such courses be organized, at the national as well as at the regional level.

5.4 Technical Staff

Intramural specialized training is required for technicians and laboratory workers, but training outside the department is equally important. Workshops and short courses can be used to train senior laboratory staff of neighbouring community hospitals and public health institutions in the current methods of immunology.

5.5 Certification

An important improvement in the status of clinical immunology would result from certification by nationally recognized agencies. The

requirements for certification in the laboratory and clinical aspects of immunology are likely to differ from country to country.

Annex 1

*Immunology in Human Disease*⁷

The material in this annex is intended to show the scope and achievement of clinical immunology and to indicate its possible future pathways. Paragraphs relating to subjects that fall under the headings of specialist or future activities are printed in smaller type. A list of the tests that are currently used in six clinical immunology centres is available on request from the World Health Organization, Geneva.

1. Immune Responsiveness

1.1 Heterogeneity of Immunologically Active Cells

Lymphoid stem cells appearing first in the fetal liver and later in the bone marrow mature into at least two major lymphocyte populations, both of which show antigen sensitivity:

⁷ The final version of this annex adopted by the Scientific Group was based on a draft prepared by a group of experts composed of: Dr. A. C. ALLISON, Clinical Research Centre, Northwick Park Hospital, Harrow, Middlesex, England; Dr. J.-F. BACH, Clinique néphrologique, Hôpital Necker, Paris, France; Dr. DEBORAH DONIACH, Department of Immunology, Middlesex Hospital Medical School, London, England; Dr. G. EDSALL, State Laboratory Institute, Massachusetts Department of Public Health, Boston, Mass., USA; Prof. ASTRID FAGRAEUS, National Bacteriological Laboratory, Stockholm, Sweden; Dr. J. L. FAHEY, Chief, Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Md., USA; Dr. W. P. FAULK, Medical Officer, Immunology, WHO, Geneva, Switzerland; Prof. J. PEPYS, Department of Clinical Immunology, Institute of Diseases of the Chest, Brompton Hospital, London, England; Prof. I. M. ROITT, Department of Immunology, Middlesex Hospital Medical School, London, England (Chairman); Prof. N. R. ROSE, The Centre of Immunology, State University of New York at Buffalo, USA; Dr. D. S. ROWE, Director, WHO International Reference Centre for Immunoglobulins, Institut de Biochimie, University of Lausanne, Switzerland; Dr. M. SELIGMANN, Hôpital St-Louis, Paris, France; Prof. J. F. SOOTHILL, Department of Immunology, Institute of Child Health, London, England; Dr. A. SZENBERG, Medical Officer, Immunology, WHO, Geneva, Switzerland; Dr. R. A. THOMPSON, Consultant Immunologist, East Birmingham Hospital, Birmingham, England; and Prof. J. L. TURK, Department of Pathology, Royal College of Surgeons, London, England.

a) thymus-dependent (T) lymphocytes, which are responsible for cell-mediated immunity and are recognizable by their blastogenic response to phytohaemagglutinin (PHA) and histoincompatible lymphocytes (mixed lymphocyte reaction); and

b) thymus-independent (B) lymphocytes, which are responsible for the secretion of humoral antibody. These mature in birds under the influence of the bursa of Fabricius and a 'bursa-equivalent' has been postulated in mammals. Further work may show that subpopulations exist.

The two systems are linked through the ability of T cells to co-operate with B cells in the production of some antibodies by the latter. The ability of T cells to give cell-mediated hypersensitivity reactions and to co-operate in antibody production accounts for the association often seen between the two phenomena. The assessment and treatment of patients with immunological disorders should take into account the existence of these two major populations and their differing responsiveness as well as the role of the phagocytic system.

1.2 Immunodeficiency

Immunodeficiency should be suspected when a patient experiences repeated infections, has a known family history of immunodeficiency, or has certain other characteristic syndromes – e. g., diarrhoea and failure to thrive in infancy. Defects, quantitative or qualitative, of specific immunity mechanisms (cellular and humoral), as well as non-specific mechanisms, must be tested.

In cases of repeated bacterial infections, adequate examination for local causes and generalized systemic diseases must be undertaken.

When these are insufficient to explain the syndrome, humoral immunity should be assessed. Immunochemical quantification by single radial immunodiffusion is the method of choice for measuring serum immunoglobulin concentration, the interpretation depending on the age of the patient.

When there is a strong clinical suspicion of immunodeficiency, tests of humoral immunity should be performed unless the three main serum immunoglobulin classes are grossly reduced. They should include tests for isohaemagglutinins, antistreptolysin titres, and antibodies to diphtheria or tetanus toxoid, flagellin, and polio, after stimulation or boosting by vaccination if necessary. Live vaccines should always be avoided.

In future, response to standardized bacterial polysaccharide antigens should also be evaluated in selected patients, and adequate methods of assessing the secretory antibody response should be devised.

The cellular immune response should be assessed, particularly in patients with chronic fungus or virus infections, *Pneumocystis carinii* infections, or infantile failure to thrive.

The first test consists in repeated blood lymphocyte counts. Then delayed hypersensitivity skin reactions to common antigens such as candida, purified protein derivative (PPD), streptokinase-streptodornase, and mumps should be tested for. Where no evidence of pre-existing immunity is found, sensitization and subsequent testing with dinitrochlorobenzene (DNCB) may be done. Furthermore, *in vitro* lymphocyte culture following stimulation with phytohaemagglutinin (PHA), or antigens will be required.

The interaction of sensitized lymphocytes with antigen releases a number of factors including migration inhibitory factor (MIF). MIF release appears to be a good *in vitro* indicator of cell-mediated immunity. It is hoped that reliable and convenient techniques will be devised and applied to the study of these factors.

It is also desirable that methods be devised for isolating a sufficient number of macrophages (blood monocytes) in order to allow *in vitro* evaluation of their phagocytic as well as enzymatic capacities.

Tests for the early diagnosis of severe combined immunodeficiency or thymic hypoplasia in infants are important because treatment by graft or by transfer factor is possible. These tests should be instituted before severe infection has occurred, because transfusion and vaccination with live vaccine are to be avoided. The serum IgG is not useful for diagnosis. The lymphocyte count may be low but not consistently so. Low IgM concentrations after the first few days of life may facilitate diagnosis. Lymphocyte uptake of tritiated thymidine on PHA stimulation is mature at birth in normal infants. Such a normal response in cord blood or venous blood helps to exclude severe combined immunodeficiency. In infants with little or no response, the full range of immunity function tests, listed above, should be undertaken. Transient hypoglobulinaemia may occur in families where one member has been shown to have severe combined immunodeficiency – presumably as a manifestation of heterozygosity for an abnormal autosomal gene. Repeated immunoglobulin estimations in infants in such families with normal PHA re-

sponse may detect a potentially dangerous, but transient and treatable, IgG deficiency.

Immunodeficiency can arise secondarily to other conditions, e. g., loss of immunoglobulin and lymphocytes in the gut or urine, which may require radical treatment.

Among the defects of non-specific defence mechanisms, chronic granulomatous diseases should be considered first. The nitroblue tetrazolium test is an important screening procedure for such diseases.

Other rare functional deficiencies of polymorphs have been described (Chediak-Higashi syndrome and myeloperoxidase deficiency) and it is to be hoped that further tests of polymorph function will be developed.

Deficiencies of the complement system giving rise to immunodeficiency may not be uncommon, since conventional complement tests fail to detect the underlying abnormality. It is important that the study of these deficiencies be undertaken in special centres.

1.2.1 Complications of Immunodeficiency

Direct complications of immunodeficiency include a high incidence of infection – often by organisms that are otherwise relatively non-pathogenic – and an increased incidence of malignant tumours. Autoimmune features such as autoimmune haemolytic anaemia and pernicious anaemia are sometimes found in patients with immunodeficiency, as well as in members of their families.

The investigation of complications of immunodeficiency requires the full range of laboratory and clinical skills of the immunologist. To the procedures previously outlined for the diagnosis of immunodeficiency disease must be added the measures for the demonstration and control of neoplasms, infections, and immunological disease. A proper understanding of genetics and of genetic counselling is also necessary. Therefore the management of immunodeficiency disorders will illustrate the important role of the clinical immunologist, acting as a consultant to the physician giving direct care to patients, in establishing the association of certain diseases with an underlying immunodeficiency and in avoiding natural or iatrogenic hazards.

Certain centres will concentrate on the study of immunodeficiency disease. A patient with an identified immunodeficiency ought to be referred to such a centre at some point during his illness, even if he is later cared for at a local institution. Periodic visits to or communication with the reference centre are needed when complications become manifest. At the reference centre certain more detailed tests of immunological function will be undertaken, as previously described in connex-

ion with immunodeficiency disease itself. Next, steps to avoid or prevent complications will be initiated, including measures of passive or active immunization and a surveillance programme for associated diseases. Finally, the reference centre will gather information of a genetic and epidemiological nature that will aid in understanding the origin of this group of diseases.

A fuller account of the immunodeficiency disorders is given in a memorandum published in the Bulletin of the World Health Organization⁸.

1.3 Immunoglobulins in Disease

The diagnosis of 'myeloma-type proteins'. There is a need for a satisfactory terminology with respect to these proteins. The term 'homogeneous immunoglobulin' or 'uniform immunoglobulin' is considered more appropriate than others previously used. Zone electrophoresis is a useful screening procedure. Immunoelectrophoresis is considered to be the method of choice in the diagnosis of these proteins, in order to avoid confusion arising from artefacts (e. g., in aged serum, confusion with other proteins such as high transferrin in serum and lysozyme in urine), and situations in which the zone electrophoresis pattern is not distinctive (e. g., in heavy-chain diseases with electrophoretic heterogeneity of the anomalous protein) or where a small amount of homogeneous immunoglobulin coexists with diffuse hypergammaglobulinaemia.

The identification of the heavy-chain class is essential, and the use of specific and suitable light-chain reagents is necessary for: (a) the detection of Bence-Jones protein; and (b) as part of the diagnostic tests for heavy-chain diseases.

Light-chain and heavy-chain subclass typing is at present of little value but may be carried out in specialized laboratories.

The finding of a homogeneous protein necessitates further careful haematological and radiological investigations. Where there is no evidence of overt myelomatosis or macroglobulinaemia, the diagnosis of myeloma is made more probable by: (a) gross elevation of the homogeneous protein; (b) depression of other serum immunoglobulin levels; and (c) the presence of an appreciable amount of Bence-Jones protein in the urine.

Patients with homogeneous immunoglobulin and without overt macroglobulinaemia or myelomatosis should be carefully investigated for

⁸ Bull. Wld Hlth Org. 45: 125-142 (1971).

other conditions of lymphoreticular proliferation, autoimmune diseases (including cold autoagglutinin syndrome), immunodeficiencies, and rare diseases such as lichen myxoedematosus. Furthermore, such patients should be followed up.

Screening for cryoglobulins in clinically appropriate conditions is indicated. When these are present, it is important to identify the proteins of the cryoprecipitate in order to distinguish mixed cryoglobulins from single-class homogeneous cryoprecipitating immunoglobulins.

The measurement of serum viscosity is also recommended when the clinical situation warrants it.

Quantification of serum immunoglobulin. This is imperative in suspected immunodeficiency and in patients affected with or suspected of having myelomatosis.

The value of quantifying serum immunoglobulins for other clinical purposes has been established in only a few instances such as the determination of IgE levels in atopic diseases, and IgM levels in infants suspected of congenital infections, and as an aid in the diagnosis of trypanosomiasis.

Immunoglobulin estimations in other biological fluids such as the urine and cerebrospinal fluid are useful in some conditions, and the estimation of concentration ratios (fluid/plasma) of IgG and albumin may indicate vessel-wall damage or increased local production of the immunoglobulin.

Immunoglobulin studies in the families of patients with immunodeficiency or homogenous immunoglobulins may clarify the role of genetic factors and may prove useful in preventive medicine.

1.4 The Role of Non-Specific Factors

Complement. In serum and biological fluids, complement can be estimated either as 50% haemolytic units, or by an immunochemical method using specific antisera to individual components. The latter is frequently more useful in practice since it does not require fresh sera, and immunochemical estimations of C3, or preferably C3 and C4, are useful in the diagnosis and management of certain diseases and systemic lupus erythematosus.

Evidence of increased complement utilization is provided by the demonstration of altered complement components by immunoelectrophoretic analysis of fresh

EDTA plasma or joint fluid, especially if the antiserum to the a2D antigen of C3 is available.

Localization of bound C3 by immunofluorescence is also useful in biopsy material, such as the kidney in renal disease and the skin in lupus erythematosus.

Of the rare deficiency diseases, the most important is familial angioneurotic oedema, in which the inhibitor to the first component esterase is lacking. The typical clinical picture accompanied by a low haemolytic complement and by low C4 and normal C3 levels is suggestive of the condition. Such cases should be referred to a special centre, as should other rare familial complement deficiencies, some though not all of which may be accompanied by the syndrome of immunodeficiency (see Annex 1, section 1.2).

Phagocytosis. Tests of phagocytic activity must distinguish between the ability of phagocytes to: (a) move along a chemotactic gradient; (b) ingest particles; and (c) kill ingested organisms or degrade ingested material.

Most tests of these functions are still likely to be mainly research investigations. The nitroblue tetrazolium test is an established measure of the bactericidal function of phagocytes.

2. Infection

2.1 Infectious Disease and Immunization

Many immunological procedures applicable to the diagnosis of infectious diseases and the recognition of infectious agents were developed in the time of EHRLICH and WRIGHT but are still in general use. The same applies to some of the procedures employed in evaluating the response to immunizing agents. In general these procedures serve a useful purpose, although their significance is too rarely examined critically, uniform standards for their performance are generally non-existent, and present-day immunological knowledge in some cases offers simpler, faster, more economical, and more reproducible substitutes. Thus in this general field, the expertise of clinical immunology is required primarily in consultation regarding the mechanisms, interpretation, and possible improvements applicable to serology as it is currently practised.

Serological tests for responses to infections, or for the identification of infectious agents, form a large proportion of all immunological tests

regularly performed. In addition, a number of tests based on newer procedures, such as those used in the diagnosis of rabies, the identification of rubella antibodies, and the identification of group A streptococci by immunofluorescence, are regularly performed. However, such techniques offer technical and conceptual difficulties best overcome with the assistance and guidance of the immunologist.

Other purposes for which immunological techniques are frequently used are the detection and quantification of individual immunoglobulin types, e. g., IgM antirubella, anticytomegalovirus, antitreponemal, and antitoxoplasma antibodies in the newborn infant. If these procedures are performed by technicians, they must be supervised by persons trained in the immunological principles and techniques involved and able to interpret ambiguous or aberrant results of such tests. A need exists in many laboratories for the preparation and standardization of diagnostic reagents of high and uniform quality. (However, many of the problems in the procurement, standardization, and evaluation of such reagents can be resolved only if the work is sponsored and preferably directed by an international organization such as WHO.) Any clinical immunological laboratory should be able to perform various types of agar-gel test, immunoelectrophoresis and starch electrophoresis, prepare and use antigen-coated red cells or other particles, and carry out other familiar immunological procedures as required. The laboratory should also be prepared to carry out studies on patients suspected of hypersensitivity reactions to immunizing agents – e. g., blast transformation – as well as properly performed, observed, and interpreted skin tests. It will offer advice on problems arising in the interpretation of familiar test procedures.

In some cases, the central or reference immunological laboratory will perform research on the evaluation of immune responses; the testing of antigens for immunogenicity; the application of new and more precise or sensitive techniques for the detection and measurement of antibodies; the detection and characterization of specific Ig levels; the production or localization of special immunoglobulins such as secretory IgA in relation to surface infections and immunization; and problems relating to the immunological patterns of the gastrointestinal and respiratory tracts, the eye, etc. It may also be required to investigate the role of cell-mediated immunity in chronic intracellular infections; of persisting antigen in the maintenance of immunity; of humoral or cell-mediated immunity in infections of undetermined immunological dynamics (e.g., does antibody in brucellosis protect or enhance, or is it without effect?); and of macrophage activation in immunological surveillance (e. g., does the eradication of tuberculous infection entail risks as well as benefits?). The laboratory may also undertake to characterize antigens as well as antibodies involved in infection-immunity system; to solve problems – such as

the aggravation of disease following immunization against respiratory syncytial virus, mycoplasma, trachoma, and other infections – raised by the complications of antigen-antibody complexes (e. g., in the haemorrhagic fevers); and to identify individuals who are susceptible to infection for various reasons.

The central laboratory may also be actively engaged in studies on the identification and management of patients suspected of being or known to be at risk of adverse immunological reactions to vaccines or infectious agents; the immunology of infectious oncogenic agents and of latent infections, such as subacute sclerosing panencephalitis of circulating antigen-antibody complexes (as found in some cryoglobulin precipitates); and the immunological problems that may result from sequential immunization or infection with cross-related antigens.

2.2 Hepatitis-Associated Antigens

A good example of the practical value of applying immunological procedures to clinical problems is provided by recent investigations on antigens associated with hepatitis. The serum antigen now called HAA (hepatitis-associated antigen) is thought to be associated in some way with the virus.

In view of the unresolved role of viral hepatitis in causing chronic liver disease and cirrhosis, the importance of looking for HAA in all liver disorders cannot be overestimated. The original precipitin test is insensitive though still of great value for detecting infected blood and hepatitis carriers, especially when using countercurrent electrophoresis to improve the sensitivity of precipitation. Complement fixation is 10 to 50 times more sensitive but is technically more difficult and requires more antiserum. Radioimmunoassay is reported to be 10,000 times more sensitive than precipitation.

All centres providing blood or blood products for transfusion should apply a test for HAA and its antibody. At the moment, the most practical procedure seems to be a micromethod of countercurrent electrophoresis. High-voltage electrophoresis is particularly recommended, since it is reported to split the antibody antigen complexes that may be present in some sera. An intensive search must continue for other sensitive methods that are sufficiently simple and cheap.

In addition to pretransfusion testing, diagnostic procedures should be available for both serum and infectious hepatitis. These tests may be important in certain chronic diseases of the liver. The frequent occurrence of hepatitis in patients receiving long-term dialysis requires that the

personnel of dialysis units be tested for HAA or its antibody. Reference centres are developing more sensitive tests for this antigen and its antibodies, which will allow them to undertake more complicated immunological, epidemiological, and clinical studies. For example, antibodies of at least three different specificities have already been reported. This question of serological specificity is especially relevant to the proper selection of diagnostic antisera. A related problem is the preparation of animal antisera as diagnostic reagents to replace the human sera that are in short supply. The presence of HAA infection, as revealed by a sensitive test for antibody, should be studied in various population groups especially those with some genetic or acquired defect in immunological response or with suspected hypersusceptibility to this group of viruses. The value of anti-HAA immunoglobulin preparations in the prevention of hepatitis in individuals exposed to the virus should be determined.

2.3 Hypersensitivity to Viruses, Bacteria, Fungi, and Parasites

Viral, bacterial, fungal, and parasitic antigens may induce anaphylactic immune complex (Arthus-type) and delayed hypersensitivity reactions in the host. Some of these are part of the characteristics of the disease produced by the particular agent. In many cases such allergic reactions may account for the well-known clinical manifestations of the infections. The immunological basis of these reactions has been well defined in only a few cases; in others it may be inferred from symptom complexes typical of the particular immune reaction. Examples of these are: (a) anaphylactic – asthma, urticaria, etc. in fungal and helminthic infections; (b) immune complex or Arthus reactions – immune complexes responsible for several diseases in man, such as extrinsic allergic alveolitis, some forms of glomerulonephritis, and malarial nephrosis; and (c) delayed hypersensitivity.

A hypersensitivity state due to circulating immune complexes should be suspected in any postinfective state in which the symptom complex of skin rash, arthritis, iridocyclitis, and proteinuria is observed. Efforts should be made to demonstrate the immune complexes in the skin, glomeruli, or circulation. However, difficulty may be encountered (a) because complexes may be scanty and thus difficult to demonstrate; (b) immune complexes in the Arthus reaction in the skin cannot be demonstrated until 12 h after the induction of the reaction; (c) the conditions

in which immune complexes have been demonstrated so far are those associated with severe tissue damage. Another process thought to result from immune complex deposition is granuloma formation – e. g., around the eggs of *Schistosoma*. In addition to demonstrating the immune complex in the tissues, it would be useful to demonstrate Arthus reactivity to the antigen in the skin. Recommended procedures are skin tests, immunofluorescence, and complement studies. Organisms or antigens should be detected in tissue fluids. Cryoglobulins could be investigated for possible microbial or parasitic antigen content.

Delayed hypersensitivity reactions are usually inferred rather than proved. The association of a positive delayed hypersensitivity reaction in the skin with a predominantly mononuclear infiltrate in a subacute or chronic lesion in the tissues is generally taken to indicate the possibility that delayed hypersensitivity is the cause of the tissue damage – e. g., the skin and nerves in tuberculoid leprosy, the skin in lupus vulgaris and dermal leishmaniasis. Tissue damage associated with cell-mediated immune processes should be suspected in every infective condition in which the patient has a chronic lesion with mononuclear cell infiltrate associated with a strong state of delayed hypersensitivity demonstrable by skin test.

3. Hypersensitivity to Extrinsic Antigens

3.1 Atopic Allergy

The 'atopic state' may be considered as an inherited unusual propensity to become sensitized by inhalation or ingestion of minute amounts of ubiquitous allergens. Atopic diseases usually comprise allergic asthma, hay fever, allergic rhinitis, atopic dermatitis, and certain forms of urticaria. However, uncertainties arise from the fact that it is frequently difficult to distinguish between atopic and non-atopic individuals, since all possible grades and transitions in genetic background, degree and type of clinical manifestations, age at onset, and scope of hypersensitivities are encountered.

Highly atopic individuals have a tendency to develop hypersensitivities of varying specificity early in life, those with a low atopic status develop more limited hypersensitivity later in life, and those with no atopic background may possibly be sensitized only by an injection of allergens.

Whether the atopic status influences only the dose and utilization of allergens required for sensitization or also the type of immunoglobulin formed (e. g., IgE) is not yet settled. In principle, atopic diseases are associated with immediate-type skin hypersensitivity to ubiquitous allergens.

Disorders regarded as 'atopic', especially allergic asthma, have a high incidence and wide disabling – and hence economic – consequences. In developed countries, it is estimated that 4–5% of the population suffers from allergic asthma. There is an evident need for clinical and laboratory services to deal with this problem. The demonstration of skin-sensitizing reaginic antibody, mainly IgE, is the chief object of investigation at present, but tests for other antibodies and for cellular hypersensitivity are also important. Investigations on the pathophysiological mechanisms of atopic diseases and hyposensitization procedures as well as on the role of genetic factors should be encouraged.

3.1.1 Diagnostic Tests in Current Use

a) Skin tests, in particular prick tests that show a good correlation with the presence of specific IgE against some allergens, are an essential part of etiological diagnosis. The intracutaneous tests are to be interpreted with caution for some allergens primarily toxic for the skin. Intracutaneous tests, however, are usually required for the detection of immune complex allergy and delayed-type hypersensitivity.

b) Provocation tests by nasal, bronchial, and ingestion challenge are useful for the confirmation of other tests or when these tests are not informative (e. g., when there is no correlation between the result of the skin test and the history of allergy).

c) Precipitin and haemagglutination tests are essential for the demonstration of antibodies, for example against fungal antigens such as *Aspergillus fumigatus* and *Micropolyspora faeni* (in farmers) or other organic antigens such as those of avian sera. Precipitin-mediated reactions may complicate 'atopic' disease and also attempts at hyposensitization.

d) Radio-immunodiffusion (RID) tests or tests with red-cell-linked allergens show the presence of allergen-specific IgE and other types of specific antibody in sera, secretions, and excreta.

e) Lymphocyte transformation tests may be useful for etiological diagnosis and for assessing the effects of hyposensitization.

The following developments may be expected:

a) Serological tests for allergen-specific IgE (in addition to (a) above)

will play an increasingly important part in the diagnosis of 'atopic' diseases and it should soon be possible to perform them at stage I (table I). These include the tests of radioallergosorption (RAST) and radioimmunosorption (RIST) for demonstrating by radioisotopic methods the fixation of allergen-specific IgE to allergen-coupled particles. Total IgE measurements are also likely to be of some clinical use.

b) Allergen-induced release of histamine from leucocytes may prove to be useful for standardizing allergens and assessing the effects of hypo-sensitization therapy.

c) Basophil degranulation tests might be further developed and may be useful for etiological diagnosis.

d) Passive transfer tests to monkeys or baboons will be used for demonstrating IgE antibodies and, more particularly, specific IgG 'short-term' or 'short-latency' antibody, which also sensitizes mast cells. Passive sensitization of the lungs and smooth muscles in human and non-human primates will also be performed. Passive transfer tests in man will therefore not be essential.

e) Allergen-specific antibodies of different classes may be correlated with the clinical findings and their measurement may help in the control and assessment of 'hypersensitization' procedures by the injection of allergens.

f) Further investigations will be made of other methods of decreasing sensitivity – e. g., by blocking the sensitization of mast cells with non-allergen specific IgE or its components or by using monovalent allergen fragments to block specific antibodies and/or to induce specific tolerance.

3.1.2 Immunological Reagents

a) Standardized or reference allergens for skin and other tests are urgently needed to ensure the comparability of tests in and between laboratories. Progress in this field of medicine will be retarded until appropriate standardization of the most common allergens has been achieved.

b) The provision of coupled allergens, standardized if possible, for the RAST and RIST is desirable.

c) Standard specific serological reagents such as anti-IgE and other anti-immunoglobulin sera are required for the RAST, RIST, and RID test. Standard human and animal allergen-specific antisera possessing antibodies of all the immunoglobulin classes are needed as positive controls.

3.2 Immune Complex or Arthus-Like Phenomena

Sensitization to ubiquitous allergens may also involve the participation of non-skin-sensitizing antibodies, mostly of the IgG and IgM types, capable of forming tissue-damaging complexes with the participation of the complement system.

One condition in this group that has gained wide recognition recently is acute interstitial pneumonitis with chronic pulmonary fibrosis due to inhaled antigens, such as *Thermoactinomyces* (causing farmers' lung), weevils in wheat flour, serum proteins in the faeces of birds (causing disease in bird fanciers), bovine and porcine pituitary and serum protein antigens in pituitary snuff taken by patients with diabetes insipidus, and various fungi and organic antigens in air conditioners. Other conditions that are being investigated are skin rashes (e.g., those occurring in serum sickness, and erythema multiforme), arthritis, iridocyclitis, glomerulonephritis, polyarteritis nodosa associated with HAA (see Annex 1, section 2.2), infectious diseases, and the side effects of long-term chemotherapy (e.g., with sulfonamides or hydantoins), as well as certain types of vasculitis.

3.2.1 Pulmonary Reactions to Inhaled Organic Antigens (Diagnosis)

- a) Precipitin, haemagglutinin, and immunoelectrophoretic tests to establish exposure and sensitization.
- b) Skin and provocation tests to demonstrate hypersensitivity; these should be evaluated not only after 20 min but also 6–12 h after challenge.

3.2.2 Detection of Immune Complexes

- a) Complement: Estimation of C3 and recognition of complement breakdown products by immunoelectrophoresis. Immunofluorescent studies of tissues for immunoglobulins, immune complexes and complement.
- b) Circulating complexes: Demonstration of cryoprecipitates and of 'intermediate complexes' by ultracentrifugation. Precipitation of aggregates by Clq.

3.3 Direct Cellular Damage by Circulation Antibodies

Circulating antibodies can underly haemolytic anaemia, thrombocytopenic purpura, and agranulocytosis associated with drugs. Either im-

immune complexes reacting with complement may directly damage the cell or the antibody may be directed against a hapten bound to the cell membrane of red cells, platelets, or leucocytes (e. g., haemolytic anaemia to penicillin, quinidine purpura).

a) Antibodies specific for the hapten and/or hapten-cell wall conjugates may be sought.

b) The serum of patients should be investigated for the presence of cytotoxic antibodies against formed elements of the blood.

c) Transfusion of ^{51}Cr -labelled red cells or platelets should be carried out.

3.4 Delayed Hypersensitivity

Delayed hypersensitivity reactions can occur following the direct topical application or injection of antigens into the skin – e. g., the attachment of a simple chemical hapten to epidermal and dermal proteins, as in contact hypersensitivity; or by insect bites. Contact-sensitizing haptens may be simple metals, e.g., nickel, dichromate, or organic compounds such as dinitrochlorobenzene (DNCB), paraphenylenediamine, and a wide range of chemicals currently used in daily life. Contact dermatitis may also be produced by the epicutaneous application of drugs – e. g., penicillin and neomycin.

Delayed hypersensitivity reactions involving both microbial and non-microbial antigens can act synergistically with immune complexes to cause tissue damage. The role of delayed hypersensitivity mechanisms in allergic pulmonary disease, such as asthma and interstitial pneumonitis, has not been sufficiently investigated. The same applies to several types of skin rash in allergy to ubiquitous allergens, to drugs, and in infectious diseases.

Erythema nodosum, for example, has been considered to be allergic in nature as it is associated with the ingestion of certain drugs or occurs in relation to streptococcal, mycobacterial, or fungal (histoplasmosis, coccidioidomycosis, etc.) infections. It has not yet been determined whether this condition is due to immune-complex deposition, delayed hypersensitivity, or a synergism between these two types of reaction.

3.4.1 Diagnostic Tests in Contact Dermatitis

Patch tests are universally used and are very reliable in the diagnosis of chemical contact sensitivity. However, care must be taken to ensure

that the concentration of agent used is not so high as to cause irritation of the skin. 'Prophetic' patch tests on people at risk from a contact agent in an industrial environment are not advisable as they may result in sensitization of individuals who might not normally have become sensitized. No desensitization procedure is available at the present time in such cases.

There is a risk that a patch test on a highly sensitive individual may induce generalized dermatitis. The development of an *in vitro* test for contact hypersensitivity would permit further investigations and possibly the development of hyposensitization procedures.

3.4.2 Diagnostic Tests in Delayed Hypersensitivity to Allergens

a) Skin tests are at present the only practical means available to the physician for detecting delayed-type hypersensitivity to allergens. Techniques of intracutaneous testing (as standardized for tuberculin allergy) should be established and the clinically important allergens standardized.

b) Lymphocyte transformation tests may be used and are usually positive in cases of delayed-type hypersensitivity. However, they are not specific for delayed-type allergy and may also be positive in immediate-type hypersensitivity (e.g., allergy to pollen and penicillin).

c) The macrophage migration inhibition factor (MIF) test seems at present to correlate best with delayed-type hypersensitivity *in vivo*. There, too, efforts to standardize the techniques and allergens used for clinical purposes should be undertaken.

Other tests based on biological or immunochemical analysis of mediators produced *in vitro* during the interaction of sensitized lymphocytes with allergens should be developed. Such tests would be very valuable for the diagnosis and assessment of therapeutic procedures.

3.5 Drug Allergy

Allergic reactions to drugs are an important hazard in modern clinical medicine. It has been estimated that 10% of hospitalized patients suffer from one or another form of iatrogenic, drug-induced, untoward reaction. Allergic reactions to drugs may take various clinical forms (e.g., anaphylaxis, urticaria, serum sickness type of syndrome, exanthemas, fever, and haematological disorders). Their mechanism may involve reaginic antibodies, direct cytotoxic effects, immune complexes, delayed-type hypersensitivity, or any combination of these. Some mani-

festations of drug reactions may closely mimic allergic symptoms but are not due to immunological mechanisms. Penicillin, sulphonamides, and salicylate derivatives appear to be the drugs most frequently causing allergic symptoms.

3.5.1 Diagnostic Tests in Drug Allergy

The development of satisfactory and reliable diagnostic tests requires knowledge of the immunochemical reactivity of the drug, its metabolites, and its degradation products. It also requires the use of immunological tests capable of detecting the various types of immunoglobulin and sensitized lymphocytes involved. The study of drug allergy would benefit greatly from group research, as the number of clinically certain cases of hypersensitivity to a given drug available to a single investigator is usually limited. With the exception of penicillin allergy, where fairly reliable tests are now available, the development of diagnostic tests is urgently required and could proceed along the following lines:

- a) Skin test reagents, including polyvalent non-immunogenic drug-peptide conjugates (e. g., penicilloyl-polylysine).
- b) Drug-coupled particles for the detection of various immunoglobulin classes (e. g., for the RAST) or radioactive-labelled drugs and metabolites for direct antibody assays.
- c) Drug-bacteriophage preparations allowing very sensitive detection of anti-drug antibodies (these are usually present at a very low level).
- d) Cellular techniques (lymphocyte transformation, MIF test, rosette test) to detect cellular hypersensitivity to drugs. With some drugs, such tests may already be considered to be quite useful and reliable; with others, methods to improve reliability and sensitivity should be devised.

4. Immunohaematology

Standard haematological tests for the recognition of autoimmunization and isoimmunization are usually performed in blood banks and haematological laboratories. An advantage is the close relation with other branches of haematology – e.g., blood morphology, blood-cell survival studies (red cells, platelets), red-cell chemistry, and blood clotting. However, immunohaematology may be considered to be a substantial part of clinical immunology, and refined immunological methods are often necessary to analyse the various types of isoantibody and autoantibody, to determine subclasses of immunoglobulin, and to study complement components involved in the reactions between cells and antibodies.

Among the major tasks are blood grouping, cross-match procedures, and antibody identification with regard to blood transfusion and pregnancy immunization. HL-A typing is of importance for organ transplantation as well as for the preparation of compatible platelet suspensions and possibly also of white-cell suspensions for patients with blood cell diseases. The different serological entities of autoimmune haemolytic anaemias and drug-induced blood cell dyscrasias require further study.

Besides agglutination, complement fixation, and haemolysin tests used for the recognition of blood cell antigens and antibodies, other methods – e. g., immune adherence, opsonic adherence, cell-culture techniques, migration inhibition tests – are often applied. Therefore it seems advisable to have such tests performed by well trained immunologists.

Another reason might be that autoimmune diseases of the blood are often associated with other autoimmune disorders, paraproteinaemias, and immunodeficiencies, and the diagnostic methods for these disease states are routinely carried out in a clinical immunological laboratory.

A close working association of the clinical immunologist and the immunohaematologist will be to their mutual advantage. Many principles of blood grouping have general application throughout immunology. For example, lymphocyte typing is basically similar to blood grouping, especially of the Rh system. Conversely, the clinical immunologist can play a useful role in the management of immunohaematological problems. The recent introduction of Rh immune globulin for the prevention of haemolytic disease of the newborn exemplifies this fruitful collaboration.

5. Diseases associated with Autoimmunity

5.1 Etiology and Pathogenesis

Autoimmune manifestations can be of 3 categories: (a) low-titre auto-antibodies found in normal subjects; (b) temporary autoimmunization following injury (e.g., cardiomy syndrome); and (c) autoimmune diseases associated with a chronic persistent immunization to body constituents and in which no external agent has yet been identified.

Genetic factors are involved in abnormalities of the immune responses leading to autoimmune diseases, as shown by family studies. It is thought that chemical and physical agents, drugs, or micro-organisms

may be important in starting autoimmunization in predisposed individuals.

Current and future studies will include:

1. An extension of family studies, including twin studies, and evaluation of the incidence of antibodies in isolated or inbred populations. Studies of antibodies in chromosome aberrations (e. g., Down's syndrome, Turner's syndrome).

2. The investigation of autoimmune reactions to drugs (e. g., Coombs' positive haemolytic anaemia after methyl dopa, lupus-like disorders following hydralazine or procainamide).

3. The search for micro-organism including co-cultivation (slow-virus disease group). The examination of affected tissues by immunofluorescence and electron microscopy. In this context, organisms of low virulence are expected to be of greater importance; genetically determined increased tolerance to certain organisms or selective immunodeficiencies could be involved.

Micro-organisms may be concerned in the following ways: (a) by containing cross-reacting antigens – e.g., group A, streptococcus, *Mycoplasma pneumoniae*; (b) by incorporating host material – e. g., myxoviruses; (c) by modifying the cell membranes – e. g., neuramidase; (d) by binding to cells and acting as carriers; and (e) by a cytopathogenic effect and the release of hidden antigens.

Epidemiological studies could include the correlation of autoimmune reactions with various infections.

Three pathogenic mechanisms can be recognized in autoimmune diseases: (1) cytotoxic effects of humoral antibody; (2) the formation of antigen-antibody complexes; and (3) the cytotoxic action of sensitized lymphocytes. Each of these mechanisms is immunologically specific, but may lead to secondary, non-specific effects such as fixation of complement, complement-mediated lysis, attraction of leucocytes, phagocytosis, or activation of other lymphocytes or monocytes. These secondary mechanisms may greatly magnify the original reaction. In any particular disease, it is likely that more than one pathogenetic mechanism may be called into play. Thus, it seems that acquired haemolytic anaemia may be taken as an instance of humoral antibody effects, and lupus nephritis as an antigen-antibody complex disease. There is no unequivocal evidence as yet of a human autoimmune disease process mediated by sensitized lymphocytes; however, this evidence is being sought.

5.2 Diagnostic Tests

5.2.1 Immunohaematological Test (see section 4)

5.2.2 Rheumatoid Factors and other Antiglobulin Tests

It is recommended that at least two specificities be looked for: anti-human globulin is estimated by Latex FH II agglutination, and anti-rabbit globulin by sheep cell agglutination tests. Rheumatoid factors are found in many conditions but are of diagnostic importance in rheumatoid arthritis and allied disorders.

5.2.3 Anti-Nuclear Antibodies

The LE cell test is most relevant for systemic lupus and is usually performed in haematology departments. The immunofluorescence test is more sensitive and, therefore, low titres are found in many other diseases and in healthy subjects, especially women. The absence of anti-nuclear antibodies almost excludes systemic lupus, but positive sera must be titrated and the results assessed in conjunction with the clinical condition. The fluorescence pattern of anti-nuclear antibodies may be of some diagnostic significance but should be studied further. Since DNA antibody is present in active systemic lupus, it is particularly important to use complement fixation with native and denatured DNA, to confirm the presence of the antibodies. In specialized laboratories it might soon become possible to estimate anti-DNA by radioimmunoassay.

5.2.4 Mitochondrial Antibodies

Mitochondrial immunofluorescence found in primary biliary cirrhosis patients has proved to be of diagnostic significance since the test is rarely positive in other forms of obstructive jaundice and in normal subjects. This test has also made it possible to separate a subgroup in cryptogenic cirrhosis.

5.2.5 Smooth Muscle Antibodies

The antibody is found in most cases of infective hepatitis regardless of the nature of the infectious agent, but high titres are seen in the three chronic liver diseases associated with other autoimmune phenomena.

5.2.6 Thyroid

Immunofluorescence is the method of choice for screening tests used to distinguish the organ-specific group of diseases. Cytoplasmic fluorescence obtained with microsomal antibodies and thyroglobulin antibodies determined by tanned red-cell agglutination are of value for the differen-

tial diagnosis between Hashimoto's thyroiditis, colloid goitre, and thyroid cancer. The tests should be performed in every case where subtotal thyroidectomy is contemplated.

Some thyrotoxic patients have moderate or high titres of thyroid antibodies and those with positive complement fixation are liable to develop postoperative myxoedema. This group of cases can be selected by antibody tests and given prolonged courses of antithyroid drugs if control of the disease proves possible. In some circumstances, assay for long-acting thyroid stimulation (LATS) may be performed.

5.2.7 Stomach

Gastric parietal cell antibodies detected by indirect fluorescence are present in the serum of most patients suffering from pernicious anaemia but also in some individuals with chronic atrophic gastritis. The test is of particular help in assessing anaemic patients who have received vitamin B₁₂ injections and in the differential diagnosis of megaloblastic anaemias.

Antibodies for gastric intrinsic factor are generally detected by the charcoal test of ARDEMAN and CHANARIN and by several other procedures using ⁵⁰Co-labelled vitamin B₁₂. The charcoal test is of value for distinguishing between latent pernicious anaemia and simple gastritis.

5.2.8 Adrenal

Idiopathic adrenal atrophy is associated with circulating cytoplasmic antibodies to adrenal cortex. These tests may be of some help in deciding for or against antituberculosis therapy in persons with Addison's disease.

A second adrenal microsomal antibody reacts with ovarian, placental, and testicular interstitial cells and is present in patients having both Addison's disease and premature menopause.

5.2.9 Striated Muscle Antibodies

These are found in the serum of patients with myasthenia gravis and are useful in deciding whether the disease is associated with thymoma, in which case the tests are practically always positive.

5.2.10 Skin Antibodies

These are of diagnostic help in pemphigus vulgaris and pemphigoid, the two diseases being associated with distinct fluorescent patterns. Skin

antibodies associated with burns have been studied in specialized centres.

5.2.11 Sperm Agglutinins

A small proportion of infertile males have these antibodies.

5.2.12 Deposits of Immunoglobulins and Complement

Immunoglobulin and complement can be detected in tissues by immunofluorescence in those diseases – e.g., in lupus erythematosus – in which damage is caused by deposits of immune complexes. The tissues usually studied by this method are those from biopsies obtained for diagnostic purposes – e.g., kidney and skin.

5.2.13 Complement Quantification

Quantification of complement activity and certain complement components has become an important means of evaluating diagnosis and disease activity in certain autoimmune disorders.

6. Transplantation

Transplantation immunology is now a significant component of clinical immunology. A specific field of immunogenetics and typing technology has developed about the HL-A antigen system – a major histocompatibility system in man. Tissue transplantation, in addition, requires immune suppression and, in the case of bone-marrow transplantation, immune serological techniques to identify and quantify the function of donor and recipient cells after bone-marrow grafting.

Although the final role of HL-A testing in tissue transplantation has not yet been determined, the significance of these antigens in tissue rejection reactions and the present requirement for complete HL-A matching for successful bone-marrow transplantation without disastrous graft-versus-host disease are well established. The large number of HL-A antigens, the rarity and complexity of certain typing reagents, the inability of most laboratories to do complete typing, and the research nature of HL-A typing suggest that at the present time HL-A typing is probably best done in a limited number of centres. However, the clinical immunological group without HL-A typing capacity may well wish to establish a working relationship with an HL-A typing centre.

HL-A antigens, as components of the cell surface, may be found to have significance in relation to disease. The clinical immunologist may wish to conduct HL-A typing for purposes other than transplantation. But research in this field has only just begun.

The mixed lymphocyte culture (MLC) test, especially one-way lymphocyte stimulation, provides a guide to HL-A identity and non-identity between individuals in a family. The test is used in evaluating family donors for bone-marrow and kidney transplantation and its value in other areas of tissue transplantation is being investigated.

Additional histocompatibility systems are likely to exist in man, and their identification can be expected. Their relationship to donor-recipient selection and to disease will, of course, have to be established. Advances in this field will be of interest to clinical immunologists, and a capacity to work in it may be important to a strong clinical immunology programme.

Schedules for immunosuppression in patients have been rather empirically determined, the usual end-point being graft survival. Measurements of individual immune functions (cell-mediated and humoral factor) specifically involved in homograft (or graft-versus-host) reactions may prove to be of considerable significance in evaluating the type and dosage of immunosuppression needed for successful tissue transplantation. If such measurements are of clinical value, it is likely that similar immunological techniques would be used for all types of tissue transplantation. Therefore immunological testing can be performed more economically and efficiently if it is centralized in one laboratory. As prompt testing of fresh tissue and serum may be important for methodological and clinical reasons, such an immunological laboratory would be needed in a clinical centre with an active transplantation programme.

7. Suppression of Immunopathological Effects

The suppression of immunopathological effects may be classified as:

- a) Antigen-specific: antigen avoidance, antigen administration, and antibody administration.
- b) Immunosuppressive and anti-inflammatory: corticosteroids (e.g., prednisolone), alkylating agents (e.g., cyclophosphamide, chlorambucil), antimetabolites (e.g., azathioprine), and antilymphocyte globulins (ALG).

- c) Reduction of lymphoid tissue by surgery or X-irradiation.
- d) Suppression of the effects of the reaction: antihistamines (e.g., pir-
iton), anti-inflammatory agents (e.g., indomethacin), anticoagulants, and
anti-complement (ϵ -aminocaproic acid).

7.1 Antigen-Specific Treatment

a) Antigen Avoidance

This measure, when possible, is highly effective in reagenic allergy, contact sensitivity, and drug reactions – three of the most frequent immunopathological diseases. It requires precise identification of the antigen.

b) Antigen Administration

Hyposensitization is sometimes effective in atopic disease and in some forms of contact dermatitis (presumably cell-mediated). In view of the complexities of interactions between the different systems, the administration of antigen alone or combined with short courses of immunosuppressive treatment, is likely to be valuable. The dangers of exacerbation of symptoms must be considered.

c) Antibody Administration

The suppression of antibody response to fetal cells by antibody administered to mothers with rhesus-incompatible babies has been very effective. This approach is likely to be applied more widely and preliminary attempts have been made in certain transplant situations.

7.2 Immunosuppression

Some substances that are used in immunopathological disease and in suppressing graft rejection and have been shown experimentally to have an immunosuppressive effect have been listed above. As all of them have anti-inflammatory effects, any detectable therapeutic benefit is not necessarily achieved by immunosuppression. The immunosuppressive action of such agents differs from species to species. Any drug needs to be tested in monkeys and, as far as possible, in man. ALG is a particularly difficult problem since each serum is unique and *in vivo* monkey testing,

though useful, is expensive. *In vitro* tests that correlate with the prevention of skin graft rejection include the rosette test, opsonization, and mixed lymphocyte culture.

Clinical control of the use of immunosuppressive agents depends on tests of the following effects:

a) Therapeutic Effect

This is measured by function tests of the diseased or transplanted organ. Controlled trials based on these tests are badly needed over the wide range of possible applications in order to assess the effect and dosage of these treatments. The present trend is to use such toxic drugs too widely in situations where the evidence of effect has not been substantiated. A therapeutic effect can sometimes be achieved with a low, non-toxic dose, and the lowest dose of each drug in each circumstance should be established.

b) Toxicity

Tests for unacceptable toxicity rest on the effects of each individual drug and should be carried out according to protocol. Polymorphonuclear and platelet counts are, therefore, necessary for controlling the dose.

c) Drug Concentration

It is desirable to measure variations in absorption, activation, and metabolism of drugs in patients by determining the levels of the active drug in the plasma. The rosette inhibition test makes this possible for antimetabolites. This test will be particularly valuable in liver or kidney failure. Patients with slow metabolism of a certain drug run a high risk of bone-marrow toxicity.

d) Tests of Immunological Function of the Recipient

A number of research groups have attempted to correlate the observed therapeutic effect of the treatment with its effect on the results of immunological function tests, but they have met with only limited success. More work on these tests is therefore needed.

A full range of function tests of cellular and humoral immunity is available. Some of the more promising are (1) uptake of thymidine by lymphocytes in culture, on stimulus with PHA, antigen, or allogeneic lymphocytes; (2) leucocyte migration; (3) cytotoxic effects of lymphocytes; (4) rosette formation; and (5) antibody levels.

The tests under (a) and (b) should be performed in all centres where immunosuppressive treatment is used, but those under (c) and (d) can be undertaken only at special centres.

7.3 Reduction of Immunologically Competent Tissue

Surgical ablation of immunologically competent tissue (e.g., thymectomy, splenectomy, or thoracic duct drainage) is effective in certain experimental diseases, and has been tried in human beings. The beneficial effect of splenectomy in haemolytic anaemia may well not be immunosuppressive. X-irradiation of tissue or of circulating lymphoid cells may also play a role in immunosuppressive treatment.

7.4 Suppression of Effects of the Reaction

Antihistamines, corticosteroids, and disodium cromoglicate are of value for the symptomatic treatment of reaginic disease and some other forms of immunopathological disease. The use of other agents is less clearly established, but has given promising results. Such drugs may produce only transient suppression of symptoms while they are given; lasting improvement – as sometimes happens with steroids or cyclophosphamide in the steroid-sensitive nephrotic syndrome – may result from breaking a vicious circle of disease.

8. *Tumour Immunity*

Three aspects of this field of study are relevant to clinical immunology. The first is the use of immunological techniques as aids to tumour diagnosis and possibly as guides to prognosis and therapy; the second is the use of immunotherapy as an adjunct to other forms of treatment; and the third is assessment of the role of immunological surveillance against tumours in man. In all these, the collaboration of a clinical immunologist with medical personnel responsible for cancer therapy, or with epidemiologists, is desirable. The immunologist can ensure that investigations are soundly based and controlled, which is especially necessary in this field, where poorly controlled reports have appeared.

8.1 Diagnosis of Malignancy

8.1.1 Abnormalities of Immunoglobulin Production

These are important signs of lymphoreticular malignancy, as discussed above.

8.1.2 α -Fetoprotein

This is a protein, produced by the human fetal liver, which is found in the serum of most patients with primary carcinoma of the liver or teratoma of the ovary, testis, or occasionally other sites. The protein is also found, sometimes in low concentrations, in the serum of pregnant women. Primary hepatomas are common in certain populations – e.g., Africans. The International Agency for Research on Cancer, Lyon, already provides antibody suitable for the detection of α -fetoprotein, and technical improvements to increase the sensitivity and reliability of the methods are being made. It seems likely that radioimmunoassays for this antigen will be performed in a few specialized laboratories in many countries within a few years.

8.1.3 Carcinoembryonic Antigen

This is an antigen found in the fetal colon and in tumours of the large bowel. Many patients with gastrointestinal carcinomas have antigen in the circulation, detectable by immunoassay. If a reliable sensitive test for this antigen were available, it would be very useful clinically.

8.1.4 Other Tumour-Associated Antigens

Studies of several tumours – e.g., neuroblastoma, kidney tumour, osteocarcinoma, melanoma, and bladder carcinoma – have recently revealed the presence of antigens common to each type of tumour in different patients. Methods of recognizing these antigens in tumour biopsies or sera, or of identifying the nature of the tumours from the immune responses of patients, may be developed.

8.1.5 Specific or Aberrant Secretions by Tumours

Radioimmunoassays for peptide hormones have already proved useful for identifying secretions from tumours, including chorionic gonadotrophins from choriocarcinomas, calcitonin from thyroid carcinomas, gastrin from pancreatic tumours associated with the Zollinger-Ellison syndrome, and insulin or ACTH from pancreatic, pituitary, or lung tumours. As these methods come into routine use, they will be of considerable help in cancer diagnosis. Again, they will be performed in a few specialized laboratories.

8.2 Assessment of Prognosis and Treatment

One of the most important recent developments has been the application of *in vitro* lymphocyte cytotoxicity tests to demonstrate that most human patients have cell-mediated immune responses against their own tumours. Many patients have in their sera antibodies that can block the expression of cell-mediated anti-tumour immunity. The presence of blocking antibodies may come to be used as a guide to prognosis and treatment. Thus, it is possible that, if a patient with carcinoma of the breast were to have no blocking antibodies, it might be wise to do a simple mastectomy, leaving the lymph nodes in which a cell-mediated immune response could be mounted. In patients with blocking antibodies, radical mastectomy might be advisable, removing the lymph nodes that produce blocking antibodies and possibly contain metastatic tumour cells. Systematic work is needed before these tests can be accepted as clinically useful. Among other investigations, histological examination of the lymph nodes to ascertain whether reactivity is primarily in thymus-dependent areas or in germinal centres may be helpful.

It is important in cancer therapy to have some measure of the number of viable tumour cells present at any time. Measurement of a product in the serum by a sensitive immunological technique (e. g., a tumour-associated antigen or hormone such as chorionic gonadotrophin) may be useful, although factors other than the tumour size, such as blood flow to the tumour, may also be relevant.

8.3 Immunotherapy

This is intended to increase the effectiveness of the host's response against his own tumour. Certain conclusions are generally acceptable, others are more tenuous. Among the well-established points are the following:

a) Immunotherapy is likely to succeed only when the mass of tumour is small i. e., the bulk of the tumour cells should be eliminated first by some other treatment.

b) Immunotherapy is most likely to succeed when the tumour antigens are strong. Examples in which immunity probably acts synergistically with chemotherapy to give excellent results in most patients are chorionepitheliomas (with a histocompatibility difference between tumour and host cells) and Burkitt's lymphoma (in which virus antigen is present).

c) The immune responses of the host may be severely suppressed by the cancer chemotherapy. There is a need for good tests for the capacity of treated cancer patients to mount immune responses. These tests should be performed serially. Primary responses to small doses of viral antigens – e. g., polio virus or bacteriophage X – might be considered. These are transient IgM responses and disappear without immunological memory. Some of the recently developed *in vitro* tests for cell-mediated immunity should be applied after standard challenges with appropriate antigens.

d) Usually the immune response most effective against the tumour is cell-mediated, whereas antibody tends to enhance tumour growth. There is a need for simple and reliable tests for blocking antibodies. Possibly the recognition of anti-

tumour antibodies attached to cells by means of a radioactive anti-globulin reagent or mixed-cell agglutination will be helpful. Immunotherapy should be designed to increase the effectiveness of cell-mediated immunity without stimulating the production of blocking antibodies. There is at present no reliable way of doing this after the appearance of tumours.

The following are lines of research that have so far yielded inconclusive results and merit further investigation:

a) The use of stimulation with agents like BCG to prolong the remissions after treatment of acute leukaemia in children.

b) The potentiation of anti-tumour immunity by *Corynebacterium parvum*. The results so far obtained in different laboratories have been variable and no information is yet available for human patients.

c) In experimental animal tumours, double-stranded polyribonucleotides (poly rI; poly rC and poly rA; poly rU) have anti-tumour activity. These agents have many effects, including interferon production, macrophage activation, potentiation of immune reactions, or even immunosuppression, depending on dosage regimens. Preliminary trials in human patients with Hodgkin's disease have not been encouraging, and toxicity has been encountered.

d) Viruses can potentiate anti-tumour immunity. It might be expected that tumour cells with viral antigens would be more immunogenic than those without them: by stimulating the immune response, the strong viral antigen would potentiate the host's response against the weaker tumour-specific antigens. Animal experiments, notably those of LINDENMANN and KLEIN on the induction of immunity against uninfected tumour cells by tumour cells superinfected with influenza virus show that such potentiation, which is an important component of virus 'oncolysis' can be achieved. Attempts to reproduce this effect in human cancer patients have been disappointing, but further efforts should be made.

e) Injections of tumour cells coupled with haptens of foreign proteins may increase anti-tumour immunity. The experimental evidence on this is incomplete and results in human patients are equivocal.

f) Contact sensitivity increases anti-tumour effects in human skin tumours. Although these observations have been uncontrolled, they are sufficiently interesting to warrant thorough investigation. The underlying mechanism may be complex.

8.4 Immunological Surveillance against Neoplasms in Man

The high incidence of tumours observed in patients given immunosuppressive treatment after renal transplantation and in patients with immunodeficiency syndromes parallels the high incidence of virus-induced tumours in experimental animals in which immunosuppression has been induced and could be interpreted as a loss of immunological surveillance. The suggestion that non-specific immunostimulation – e.g., by BCG administration – may heighten the immunological surveillance against neoplasms in man needs further exploration.

Annex 2

WHO Reference Centres for Immunology and Related Fields

Immunology

Immunoglobulins

International Reference Centre for Immunoglobulins, Institut de Biochimie, University of Lausanne, Switzerland

Regional Reference Centre for Immunoglobulins, National Cancer Institute, National Institutes of Health, Bethesda, Md., USA

Genetic Factors of Human Immunoglobulins

International Reference Centre for Genetic Factors of Human Immunoglobulins, Centre départemental de Transfusion sanguine et de Génétique humaine, Bois-Guillaume, Seine-Maritime, France

Regional Reference Centre for Genetic Factors of Human Immunoglobulins, Department of Medical Microbiology, University of Lund, Sweden

Regional Reference Centre for Genetic Factors of Human Immunoglobulins, Department of Biology, Western Reserve University, Cleveland, Ohio, USA

Serology of Autoimmune Disorders

International Reference Centre for the Serology of Autoimmune Disorders, Department of Immunology, Middlesex Hospital Medical School, London, England

Regional Reference Centre for the Serology of Autoimmune Disorders, The Center for Immunology, State University of New York at Buffalo, N. Y., USA

Regional Reference Centre for the Serology of Autoimmune Disorders, The Walter and Eliza Hall Institute of Medical Research, Melbourne University, Australia

Tumour-Specific Antigens

International Reference Centre for Tumour-Specific Antigens, Division of Immunology and Oncology, Gamaleja Institute of Epidemiology and Microbiology, Moscow, USSR

Testing of Natural Resistance Factors

International Reference Centre for Testing of Natural Resistance Factors, Department of Immunology, Institute of Microbiology, Prague, Czechoslovakia

Use of Immunoglobulin Anti-D in the Prevention of Rh Sensitization

International Reference Centre for the Use of Immunoglobulin Anti-D in the Prevention of Rh Sensitization, Medical Research Council Experimental Haematology Research Unit, St. Mary's Hospital Medical School, London, England

Human Genetics

Glucose-6-Phosphate Dehydrogenase

International Reference Centre for Glucose-6-Phosphate Dehydrogenase, Department of Medicine, University of Washington, Seattle, Wash., USA

Regional Reference Centre for Glucose-6-Phosphate Dehydrogenase, Sub-Department of Haematology, University College Hospital, Ibadan, Nigeria

Regional Reference Centre for Glucose-6-Phosphate Dehydrogenase, Department of Haematology, Tel-Hashomer Government Hospital, Israel

Abnormal Haemoglobins

International Reference Centre for Abnormal Haemoglobins, Medical Research Council Abnormal Haemoglobin Research Unit, University of Cambridge, England

Serum Protein Groups

International Reference Centre for Serum Protein Groups, Zoology Department, University of Texas, Austin, Tex., USA

Health Laboratory Services

Blood Groups

International Blood Group Reference Laboratory, Medical Research Council Blood Group Reference Laboratory, London, England

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