Immunology in Clinical Medicine

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Foreword

It has always appeared a strange paradox to me that the word immunology, derived as it is from a Latin word which means exempt, should be associated for the most part with hypersensitivity reactions and have little to do with exemption from anything. Immunology, however, is a science full of paradoxes yet one that grows daily in its importance for the clinician.

It is because immunology is so important to all of us in the medical profession today and because it is such an odd discipline, full of paradoxes, that I welcome this introduction to it by Dr. John Turk. He has that fortunate gift of clear, simple exposition, which is only found in those with complete mastery of their subject, and not always with them.

I bear some responsibility for the pattern of this book as I discussed it at length with Dr. Turk before he wrote it and I was delighted when he let me read the finished manuscript as it seemed to me just what most of us are now looking for. Its title explains precisely what it is all about; "Immunology in Clinical Medicine." I commend it to all who want a good introduction to the subject, Dr. Turk is a splendid guide.

The bibliography is highly selective and well suited to a book of this kind. If I can prophesy there will soon be a demand for a second edition. Certainly the speed with which this new subject is developing will call for it.

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Preface to the First Edition

Advances in medical science have progressed so rapidly in the past twenty years that most physicians and surgeons find it very difficult to keep up with changes in the basic concepts of disease which underly the practice of medicine. Although Immunology is one of the oldest branches of pathology, the relation of immunological processes to the causation of diseases other than those initiated by infectious agents, has been little appreciated until recent years. It is now realized that immunological concepts apply to a diverse number of medical conditions ranging at one extreme from the appearance of a simple furuncle in the skin to, at the other extreme, the means whereby the body controls the spread of cancer. Naturally throughout this period of rapid advance in knowledge, there has been a wealth of books, reviews and scientific articles each contributing to our understanding of these processes. Books written at the beginning of the period of rapid expansion of knowledge have been found to be out of date and have been revised. However, as soon as they are revised they appear to double their content to the extent that they cease to be books which can be read by the non-specialist and become encyclopaedias into which one might dig for information on a small aspect of the subject or how to perform a laboratory technique. As these volumes increase in size and scope they leave the practising physician far behind and become incomprehensible to all but the specialist in that particular field.

This is not only so with standard texts on the subject but also with books which were originally written with the medical student in mind. Such is the breadth of the subject that many of these books have now reached the same size as the standard medical student's textbooks of internal medicine and pathology. They have in fact become the textbooks for those taking specialized courses in immunology, rather than being books which can be taken up and read by medical students and practitioners who wish only to be acquainted with the way in which this subject impinges on the practice of clinical medicine.

The purpose of this "small" book is to describe current concepts of immunology and how they affect our understanding of disease processes, for an audience which has been left behind by the advances.

As an immunologist with a wide circle of clinical friends and colleagues I have been impressed by the need for such a book which discusses the immunological concepts underlying disease processes rather than the principles behind laboratory tests. Such a book should I felt be written by one author rather than being, as most of the available texts on the subject, a multi-author book. It should express the opinion of one immunologist on how he thinks diseases are affected by immunological processes, rather than present a confusion of opinions.

It is now known that cell-mediated immunological processes are as important, in disease mechanisms, as those processes involving circulating antibody, both in their initiation and in their control. Most textbooks of immunology tend to place a greater emphasis on circulating antibodies as these are easier to investigate in the laboratory and more knowledge has accumulated about antibodies in disease rather than about cell-mediated immune processes. As far as is possible the present volume attempts to provide a more balanced approach and wherever the knowledge is available cell-mediated immune processes are given full emphasis in proportion to their importance. However, there has been a noticeable movement towards calling any disease process in which an immunological component is suspected, but circulating antibody involvement cannot be proved, cell-mediated. It is hoped that this will not develop in the same way as the recent trend to call diseases "autoimmune", where, for technical reasons, an extraneous antigen cannot be demonstrated.

With these points in mind, this book has been written to present immunology to students and practitioners of clinical medicine. I have started with an exposition of basic immunological concepts as they impinge on disease and then taken a tour through a number of diseases or disease processes in which we know or suspect that immunological processes play a part. These include not only those diseases which result from a heightened immunological activity but also those which develop as a result of a depression of these processes. Throughout the effect of drugs known to suppress immunological processes are considered especially in relation to whether they operate by really suppressing immunological processes or whether they have other actions.

No references are included in the text, but a bibliography is provided at the end of each chapter. This has three parts. The first is a collection of books which would bring the reader, if he so desired, deeper into the subject. The second and third parts consist of two types of references, review articles and actual references to recent scientific or medical publications. The former have been chosen to supplement the books and the latter are only included where the subject is not covered by the books or review articles, and are mainly publications which have occurred within the last two years. These are intended to give a lead to anyone wanting to delve deeper into the subject. References are thus kept to a minimum and are intended only to give material which might help the reader get started, and are intentionally not comprehensive. This book can be used either to give an outline of the subject to those for whom time is at a premium or as an introduction to those clinicians who wish to dig deeper into the subject.

I should like to take this opportunity of thanking Mr Frank Price for drawing the figures for me. I need to emphasize that these by no means depict what is going on accurately, but are intended to give an idea

what we think may be going on in as simple a way as is possible, in relation to the information available at the present time. Finally I should like to thank and dedicate this book to my closest clinical colleague, my wife, who has continually indicated the direction in which this book has been written.

J. L. T.

London
March 1969

Preface to the Second Edition

Since the publication of the first edition of this book, there have been a number of major advances in Clinical Immunology. Perhaps the most important of these is the recognition of Clinical Immunology as an independent medical speciality. With this in mind I have prepared a further chapter for this book on "The role of the Clinical Immunologist". An increasing number of medical schools throughout the world are having clinical immunology departments. I am not sure whether this is a good idea. At the present time, I think that such departments should remain more as divisions or sub-departments within a department of internal medicine. Although many clinical immunologists have started within pathology departments, immunology plays such a role in the day-to-day care of patients with "immunological" disorders, that there is more and more need for the presence of the clinical immunologist at the bedside. It is particularly important that he does not hide himself any longer completely in the laboratory. However, as research is the life-blood of clinical immunology, he will need the most up-to-date laboratory facilities for patient investigation.

From the scientific point of view major advances have occurred in the recognition that clinical manifestation of disease due to a particular aetiological agent can vary considerably depending on the patient's immunological response. Thus specific deficiency of cell-mediated immunity may be associated with hyper-reactivity of humoral antibodies and increased cellular immunity with low levels of antibody. A whole range of clinical disorders due to such agents may depend on a spectrum of intensity of immunological response. Such features have recently been recognized as the causation of the wide range of clinical appearances in chronic infectious diseases such as leprosy, tuberculosis and leishmaniasis, as well as certain chronic viral diseases. An assessment of the status of the host's immune response is now considered an important part of the investigation of patients with neoplastic disease and is in many cases mandatory, before initiating specific therapy, as many tumours have now been recognized to cause a non-specific failure of cell-mediated immunity.

The interaction between cell-mediated immunity and humoral antibody which was emphasized in the previous edition of this book has been particularly highlighted by recent work on the phenomenon known as "immunological enhancement". Although this phenomenon has been known for many years, it is only recently that its full significance has been appreciated and attempts have been made in clinical practice to suppress a cell-mediated immune reaction with "enhancing antibody". There is also an increased awareness that "enhancing antibody" could be one of the factors behind defects in cell-mediated immunity in infectious diseases, as well as in cancer.

J.L.T.

London
April 1972

Contents

	Foreword	vii
	Preface	ix
Chapter I	**The Nature of the Immune Response**	1
Chapter II	**Reactions in the Tissues Mediated by Humoral Antibodies**	24
Chapter III	**Reactions in the Tissues Caused by the Cell-Mediated Immune Response**	44
Chapter IV	**Immunological Processes in Infective Diseases**	60
Chapter V	**Immunological Deficiency Diseases—Abnormalities in Immunoglobulin Synthesis**	78
Chapter VI	**The Concept of Autoimmunity and its Relation to Disease**	91
Chapter VII	**Immunosuppressive Agents**	104
Chapter VIII	**Transplantation of Tissues and Organs**	120
Chapter IX	**Connective Tissue Diseases**	135
Chapter X	**Immunological Processes in Diseases of the Kidney**	149
Chapter XI	**Skin Diseases**	159
Chapter XII	**Related Organ-Specific Immunological Diseases—Thyroid, Adrenals, Parathyroids and Stomach**	173
Chapter XIII	**Diseases of the Intestinal Tract, Respiratory Tract, Liver, and Amyloidosis**	182
Chapter XIV	**Haemolytic Diseases and Thrombocytopenic Purpura**	196
Chapter XV	**Immunological Processes Affecting the Eye and Nervous System**	209
Chapter XVI	**The Immunology of Cancer**	225
Chapter XVII	**The Role of the Clinical Immunologist**	242
	Index	253

Chapter I

The Nature of the Immune Response

1. Introduction

The science of immunology began with a study of immunity to infection and can be reckoned to have started with Jenner's classical study in 1798 of the role of vaccination in protection against the virus infection smallpox. The study of immunity was coupled with that of bacteriology throughout the latter part of the nineteenth century. However, a number of observations made about the time of the beginning of this century indicated that similar mechanisms to those involved in protection from microbial infection could produce tissue damage. The terms "hypersensitivity" and "allergy" were introduced at this time to describe the increased reactivity of the body to a foreign substance, after there had been a previous contact with the agent, as compared with the first reaction when the body made its initial contact with this material. Hypersensitivity reactions were first described to foreign serum proteins or bacterial extracts. Eventually such reactions were discovered to occur after contact with a wide range of substances of both plant and animal origin as well as contact of the skin to certain molecules with a very simple chemical structure. Hay fever, asthma, urticaria, anaphylaxis and serum sickness were among the first conditions attributed to allergic or immunological mechanisms. However, it was probably the syndrome of "serum sickness", which developed as a result of repeated treatment of bacterial infections with sera prepared in animals, which first alerted pathologists to the wide range of tissues which could be damaged by immunological reactions.

Throughout the first half of this century research into diseases involving immunological mechanisms was restricted to a study of those involving classical allergic phenomena. Within the last thirty years, however, there has been an increasing awareness that immunological mechanisms in disease were not restricted to those phenomena which had previously been accepted as being "allergic", but were involved in a much wider range of pathological conditions. Perhaps the greatest stimulus to this widening of the scope of immunology was the enormous steps made during and after the second world war in the study of the nature of the homograft reaction. Much of this work was done under the stimulus from practising surgeons who envisaged the need for more knowledge of the nature of this reaction, so that eventually the transplantation of organs and tissues might become a feasible surgical procedure. The demonstration that the rejection of tissue homografts was an immunological phenomenon led to a study of those conditions

under which an immune response might be inhibited. The stimulus for research along these lines developed because of the obvious value that an inhibition of the immune response would have in allowing grafts of foreign tissues or organs to "take". Two approaches to this problem were discovered almost simultaneously, one was the production of a specific state of immunological tolerance to a single antigen and the other was the demonstration of the immunosuppressive effect of a wide range of drugs which had been demonstrated both clinically and experimentally to be cancer chemotherapeutic agents. At the same time paediatricians were becoming aware of the fact that in rare cases neonatal death was being caused by a deficiency of immunological mechanisms. It was from a study of these immunological deficiency diseases coupled with an interest in the mechanisms of rejection of tissue homografts that it soon became apparent that the thymus, an organ whose function was until then wrapped in mystery, played an important role in the control of immunological processes.

Another line of investigation occurring again at about the same time was the demonstration of immunological processes directed against the body's own tissues in certain diseased states. Ehrlich at the turn of the century had postulated that although the body would react immunologically against foreign substances, it could not react against components of its own tissues. He thus introduced the concept of *Horror autotoxicus*. This was confirmed as a general principle by the demonstration of blood group *iso-antibodies* in the blood which were always the opposite of and did not react with the individual's own blood group antigens on his red cells. However, it is now known that under certain disease conditions the body can overcome this *Horror autotoxicus* and develops *autoantibodies* against its own tissues. Almost simultaneously it was demonstrated that disease of the thyroid gland could be produced in experimental animals, associated with the presence of *autoantibodies* in the serum directed against the body's own thyroid tissue and that similar *autoantibodies* could be demonstrated in the serum of humans with Hashimoto's thyroiditis, directed against thyroid tissue. Since then autoimmune phenomena have been found to be associated in some way or another with a wide range of tissue disorders.

Another group of disorders in which immunological processes have been implicated or associated are the so-called connective tissue diseases. Of these probably the most important group are those of a rheumatic or rheumatoid nature. Research over the past twenty years into this group of diseases has revealed a complex pattern in which the damaging effects of both infective and immunological processes are intimately interwoven and are often difficult to dissociate. From a study of these and other diseases it has become apparent that tissue damage can result as readily from proximity to an immunological reaction of the body

directed against the infective agent, as from the direct toxic effect of the infective agent itself. It is also apparent that the body can react against its own tissues damaged either by an infective agent or by physical or chemical means as though it were a completely foreign tissue.

Perhaps one of the most exciting fields of modern immunology is recent evidence of the role of immunological processes in controlling cancer. It appears that the body recognizes cancer cells as being foreign. In this way an immunological reaction is started in an attempt to control the growth and spread of the malignant cells. In most cases of clinical cancer a fine balance is set up with the scales weighted very slightly in favour of the malignant cells so that the cancer progresses but in a slow but sure manner. It is, however, suspected that malignant clones (colonies) of cells are produced continuously throughout life but are eliminated rapidly by the body's immune processes and it is only in those cases where the immune response is in some way slightly deficient that the cancer can spread throughout the body. The importance of this concept is that a new approach is now being made for the treatment of cancer by attempting to develop means by which it might be possible to enhance the immunological response of the body against cancer and tip the fine balance between the immune reaction and the malignant cells in a more favourable direction.

2. The Nature of Antigens

It can thus be seen that the immunological reaction of the body is concerned with firstly the recognition and secondly the rejection of foreign material. The body has an inborn mechanism for recognizing what is "self" and what is "not self". Damage to tissue can result during the process of rejecting what is "not self" and also on rare occasions from a failure to recognize what is "self" and treat it as "not self". This capacity to recognize "self" and reject "not self" develops at some early stage during foetal life because it is known that certain mammalian foetuses can develop the property of rejecting homografts and of producing circulating antibodies before parturition.

Most immunologists agree that, to become antigenic or be able to immunize, a foreign substance must be of a relatively high molecular weight. However, the actual size the molecule need be to make it antigenic will vary on its chemical nature. Lipids alone are not antigenic, proteins and polysaccharides are and so are lipo-proteins and lipo-polysaccharides. Polysaccharides need to be of a higher molecular weight than proteins to become antigenic. Proteins of molecular weight as low as 5,000 can be found to be antigenic. An example of a low molecular weight protein of clinical importance which is antigenic is insulin (molecular weight approximately 6,000). Polysaccharides need to be far larger to be antigenic. Thus dextran of molecular weight 100,000 is not antigenic, whereas dextrans of molecular weight 600,000

or more are antigenic. (The dextrans used as plasma volume expanders are of molecular weight between 40,000 and 150,000 and are not believed to be antigenic.)

Small chemical molecules such as dinitrochlorobenzene (molecular weight 203) or primulin the active sensitizer from the plant *primula obconica* (molecular weight 210) which bind immediately to protein carriers can convert the body's own proteins into antigens and the specificity of the immunological reaction is directed against these small chemicals themselves. Such small molecular weight chemicals are called *haptens*. However, a small molecular weight chemical can only become haptenic if it binds onto protein spontaneously or if it is bound to a macromolecular carrier artificially in the laboratory. Haptens such as dinitrochlorobenzene and primulin can convert the body's own protein into an antigen which the body will fail to recognize as "self" by virtue of the addition of the small chemical grouping. An immunological response will then be launched directed against proteins carrying this small molecular weight group. This subject will be discussed much more fully in relation to chemical contact sensitivity which is an important cause of industrial dermatitis.

The ability of the body to distinguish between different antigens is remarkably specific. Immunological mechanisms can recognize small molecular weight substances such as aniline and amino-benzoic acid and even distinguish the three stereoisomers of tartaric acid when bound to protein. It can recognize different spatial configurations of the same chemical structure, as well as discriminate between a wide range of simple organic molecules. Study of contact dermatitis has shown moreover that people can develop immunological reactions and become hypersensitive to a number of simple inorganic metal radicals containing nickel, chromium, beryllium and mercury when attached to the body's own proteins, and can thus distinguish between one metal ion and another.

3. The Nature of the Immune Response

The immune response can be divided into two different but fundamentally similar mechanisms (Fig. 1). Rejection of foreign antigen can be produced by means of the action of humoral antibodies (serum proteins—immunoglobulins) or by direct interaction with specifically sensitized lymphocytes producing what is called the cell-mediated immune response (CMI). Cell-mediated immune reactions are responsible for phenomena such as tissue homograft rejection and delayed hypersensitivity. Humoral antibodies are synthesized by plasma cells which are themselves derived from lymphocytes. Lymphocyte precursors of the specifically sensitized lymphocytes of CMI and of plasma cells which synthesize CMI are found in the liver in foetal life and later on in development in the bone marrow. Lymphocytes involved in CMI come

under the influence of the thymus in late foetal or early neonatal life and are therefore generally referred to as T-lymphocytes. Lymphocytes which become plasma cell precursors are independent of the thymus. In birds they come under the influence of the bursa of Fabricius in late foetal or neonatal life. In mammalia it has been postulated that the bursal equivalent is provided by lymphoid tissue lining the intestinal

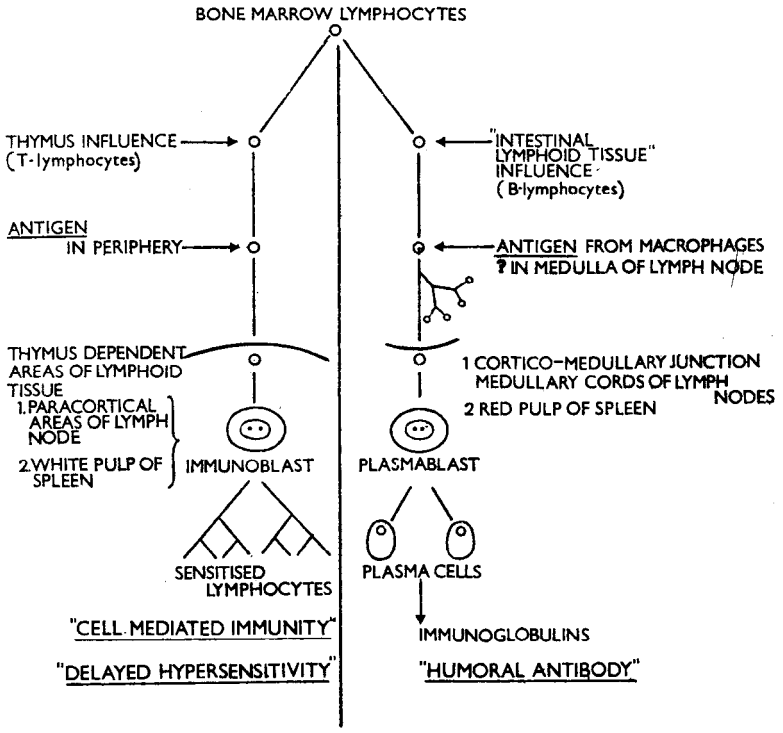

FIG. 1. Diagrams of the two forms of immune response.

tract—the Peyer's patches and the appendix. Lymphocytes of this pool are therefore often referred to as B-lymphocytes. Lymphocytes in the body may be static or mobile. They may also be long lived or short lived. T-lymphocytes are usually long lived and mobile. They are found circulating in the blood, lymph and through certain areas of the lymphoid tissue referred to as thymus-dependent areas (Figs. 5b, c). In lymph nodes these are the paracortical areas. B-lymphocytes are found in the lymph follicles and at the cortico-medullary junction of lymph nodes as well as in the non-thymus-dependent area of the spleen. They tend to be far less mobile than T-lymphocytes. T-lymphocytes may differ

from B-lymphocytes in having an extra antigen on their cell membrane, by which they can be identified.

(*a*) *Humoral antibody response*

Antibodies are serum proteins which run electrophoretically mainly as γ-globulins and react directly with antigens. Often, if they are in sufficient concentrations and if they have a strong enough binding power, they will specifically precipitate a solution of the macromolecular antigen. If the antigen is on the surface of cells, such as erythrocytes or bacteria, these can be agglutinated by sera containing antibodies specifically directed against the particular antigen. Antibodies belong to the class of serum proteins now known as immunoglobulins, because it is thought that this class of proteins all have an immunological function: Immunoglobulins are made by cells of the plasma cell series. One cell is thought to make only one type of globulin. Plasma cells have all the apparatus within them for synthesizing and secreting proteins. Plasma cells are found under normal circumstances in the medulla of lymph nodes and the red pulp of the spleen. Plasma cells are thought to develop from B-lymphocytes derived originally from the bone marrow, influenced in some way by the lymphoid tissue lining the intestinal tract. How these cells are influenced to become plasma cell precursors is not known, but the process is thought to be analogous to a similar mechanism by which the thymus is thought to influence the same bone marrow lymphocytes to become able to be sensitized to proliferate under an antigenic stimulus which will produce cell-mediated immunity (see below) (Fig. 1). To date, immunoglobulins in the human have been divided into five groups known as IgG, IgA, IgD, IgE and IgM. IgG, IgA and IgD have a molecular weight in the range of 150,000, IgE is of molecular weight approximately 200,000. IgM is a macroglobulin of molecular weight of 900,000 and consists of five subunits each similar in structure to that of the lower molecular weight immunoglobulin. The structure of the IgG molecule has been studied extensively and is thought to consist of four polypeptide chains, two of molecular weight approximately 25,000 and two of molecular weight 50,000, which are called the light and heavy chains respectively. These polypeptide chains are joined by disulphide bonds (Fig. 2). The whole immunoglobulin molecule can be split by enzymes into two fragments containing a light chain and the adjacent part of the heavy chain (Fab fragment: ab = antigen binding) and a third fragment consisting of the rest of the heavy chains which can be crystallized (Fc fragment: c = crystallizable). The heavy chains when separated from the light chains can be split into two fragments, the part adjacent to the light chain is known as the Fd fragment. There are two antibody-combining sites on a simple immunoglobulin molecule each on the Fab fragment, involving a light chain and the adjacent Fd fragment of the heavy chain. It has, however, been

demonstrated under the electron microscope that when antibodies react with antigens the angle between the Fab fragments widens so that the molecule can react with two antigens and in the same process the Fc fragment contracts (Fig. 3). The specificity of the different antibodies is

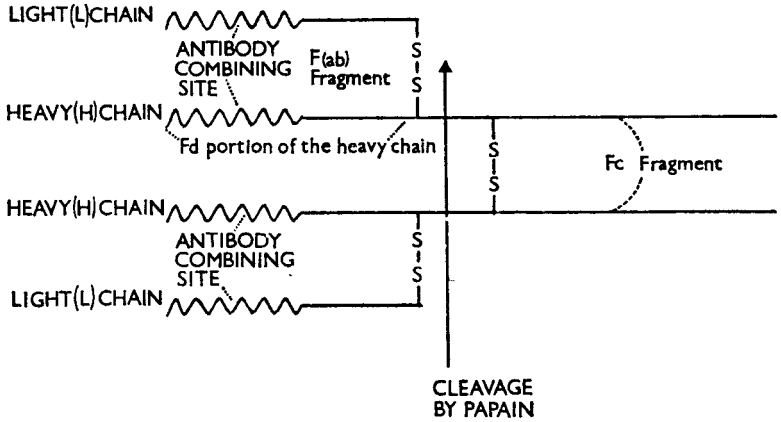

FIG. 2. Diagram of the polypeptide chains of the immunoglobulin molecule. The two antibody combining sites are formed by the end portions of the light chain and the Fd fragment of the heavy chain.

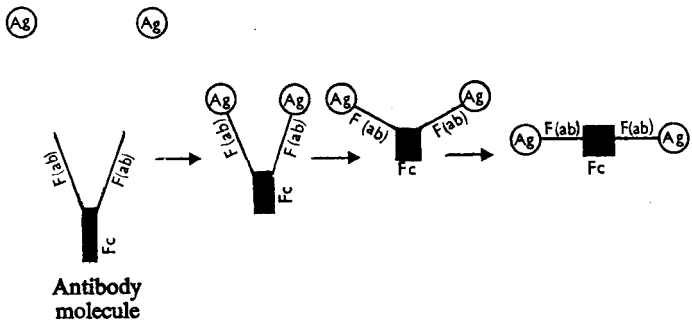

FIG. 3. Behaviour of immunoglobulin molecule after binding antigen. [After Feinstein and Rowe (1965), *Nature*, **205**, 147.]

thought to be due to differences in the sequence of amino-acids in those parts of the polypeptide chains which form the antibody-combining site. Immunoglobulins differ from all other proteins in that the terminal half of the light chain and the terminal quarter of the heavy chain in the antibody-combining site vary from one protein to another in their amino-acid sequence. In these "variable" regions, 80% of the amino-acids may vary. However, the position of the glycine components is

always constant. It has been considered that the glycines can function as a pivot on which the variable regions of the molecule can move to provide a better fit for the antigen. Most antibodies belong to the class of immunoglobulins IgG, only a small fraction of serum antibodies belong to the class IgA. IgA antibodies form, however, most of the antibodies in saliva and the intestinal secretions. They appear to be derived from plasma cells in the mucous membranes and around the exocrine glands. They immunize the individual against antigens found on the surface of mucous membranes and are involved in local immunity. IgA antibodies are found against ABO blood group antigens because these develop as a result of cross reaction with the intestinal flora. However, they are not found against Rhesus antigens as immunization against these antigens is caused by transfusion or leakage of foetal red cells across the placenta. Antibodies of the IgD class are not commonly found. However, IgD antibodies have been described against insulin, bovine proteins and diphtheria toxoid as well as autoimmune antinuclear antibodies. The IgM fraction contains some of the ABO red cell isoantibodies and the saline agglutinating anti-Rhesus red cell antibodies (although incomplete Rh antibodies are IgG). Cold agglutinins directed against red cells are also IgM. Among antibacterial antibodies which belong to the IgM class are antibodies directed against the somatic antigen of Salmonella. The rheumatoid factor is also a macroglobulin antibody.

Reagins. the skin sensitizing antibodies, associated with anaphylactic phenomena such as hay fever and asthma have been classed as IgE antibodies. They have a number of different physico-chemical properties which distinguish them from other low molecular weight antibodies and account for their marked difference in behaviour. These antibodies will be discussed more fully in the chapter on immediate-type hypersensitivity reactions.

Multiple myeloma is a disease where the growth and development of a colony of plasma cells of one particular type gets out of control and becomes neoplastic forming tumour-like aggregations consisting mainly of plasma cells and occurring mainly in bones. These tumours as they are formed of plasma cells make immunoglobulins which are all of one type (either IgG, IgA, IgD or IgE). Until recently it was thought that these cells were programmed to make immunoglobulins without antibody specificity. However, in a few cases it has been shown that these myeloma proteins have antibody-like specificity. This activity has been discovered against streptococcal and staphylococcal antigens, and even against the dinitrophenol group acting as a hapten. In experimental animals, the incidence of antibody-like specificity in myeloma proteins is as high as 5–10%. Many of the antigens with which these proteins react can be shown to be produced by organisms in the gastrointestinal and respiratory microbial flora. Thus it appears that