The Value of Immunological Concepts in Medicine

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In Dr Croone's time Europe was only too familiar with infectious diseases to which those who survived them were subsequently immune. But physicians liked to suppose that recovery was due to their ministrations, and diagnoses were usually vague. So acquired immunity was not so obvious as it might have been. The earliest attempts at prophylactic immunisation, by variolation, were not made in Britain until the early years of the eighteenth century, although two letters to the Royal Society in 1700 described the practice of protection by intranasal installation of smallpox crusts as already prevailing in China.

In 1980 the WHO was able to announce the final conquest of smallpox and its abolition from the face of the earth, with the exception of virus locked up in a few special laboratories. This triumph of preventive medicine was largely achieved by mass immunisation of the populations in endemic areas with vaccinia virus. It cost the WHO less than six hours' worth of current world expenditure on armaments. It was possible because vaccination was cheap, safe and effective; the virus itself was stable; and there are no hosts, other than man, to act as reservoirs.

Dr Edward Jenner, who showed that vaccination with cowpox prevented smallpox, is often referred to as the founder of immunology, but he had no idea how vaccination worked. The real foundations of immunology were laid by Pasteur, Koch, Ehrlich, Buchner, Kitasato, von Behring, Bordet and others around the turn of the nineteenth century. Their work led them to recognise that foreign materials—not only bacteria and toxins but many harmless substances—when introduced into the body caused the production of antibodies that could detectably and specifically interact with the same foreign materials. Portier and Richet, Arthus, von Pirquet, Browning and others also recognised that this interaction was accompanied by an altered state of reaction in the body—allergy—which could produce harmful reactions when the foreign materials were reintroduced.

For 50 years immunology was largely an aspect of bacteriology. In 1937, when I became interested, it was not a discipline in its own right. There were virtually no specialised textbooks and only two international journals with immunology or immunity in their titles. The relatively few interested workers outside bacteriology departments were biochemists, physiologists and pathologists. Considering the impact which prophylactic immunisation had already had on some infectious diseases of man and domestic animals, and the usefulness of serological methods of classification, this lack of interest may seem surprising. However, much of the relevant knowledge was empirical. The nature of antibodies was unknown—they were not shown to occur among the recently identified gamma globulins until 1939—and no one knew which cells made them. Only their exquisite specificity was recognised, and immunochemistry, brought to a fine art by Karl Landsteiner, was the one area in which genuine theoretical advances had been made.

The fact is that much of the practical impact of immunology could be achieved by empirical approaches, without needing to know about antibody structure or the nature and behaviour of the cells responsible for their production. So long as the aim was to imitate the natural processes of immunity, though in a controlled way, enlightened empiricism was adequate for devising immunising agents that were sufficiently non-toxic, and in several instances—e.g. diphtheria, yellow fever and Rift Valley fever—very effective.

Modern immunology dates from about 1960, when the general structure of antibodies was discovered, and the fact that lymphocytes were the cells responsible for their production, and for cellular immunity, was established. Subsequent developments have been enormous and are continuing; a recent market survey identified some 600 journals covering the subject of immunology to a significant extent.

The Lymphocyte

The central themes of immunology are the properties and function of lymphocytes and their products. However, because immunology is also concerned with immunity, and other cells react to and dispose of foreign materials, the umbrella of immunology covers many aspects of the behaviour of monocytes, macrophages and granulocytes, including mast cells. The complement system, which plays a vital part in the effectiveness and pathology of

immunity, was first studied in that connection, and has remained subsumed there. Even the interferons, which were first identified as natural antiviral agents, turn out not only to be produced by macrophages and lymphocytes but to affect their behaviour in important ways, and so are partly within and partly without the immunological literature. Nevertheless, the outlines of immunology are blurred and it overlaps into many other fields mainly because antibodies are useful tools for the identification, isolation, and quantitation of substances that are otherwise difficult to discern or assay. Because of their exquisite specificity, which is greatest with monoclonal antibodies with uniform combining sites specific for a single determinant on a molecule—and the development of very ingenious and sensitive methods for revealing antibody interaction with the substances to be detected—such as immunofluorescence, radioimmunoassays, enzyme-linked antibodies and indicator-linked particles—immunological techniques have become common coin in most biological laboratories.

Lymphocytes form a dispersed organ, sometimes termed the lymphon, whose cells, though in continual circulation round the body, are concentrated in lymphoid tissues (thymus, spleen, lymph nodes, gut-associated lymphoid tissues) in which they come into contact and interact with other cells (macrophages, dendritic cells) in specialised micro-environments that keep some cells apart and bring others together. An adult human has some 2×10^{12} lymphocytes. Some are long-lived, but there is constant death and renewal, throughout life, at a rate of many millions each day. They originate, in adult life, from haemopoietic stem cells concentrated in bone marrow. Their progeny leave there to undergo a series of stages of development, which proceed along two main lines. One line migrates to the thymus, within which several stages of differentiation take place and many cells die, but those which emerge are the thymus-dependent or T-lymphocytes. There are about 10^{12} of these and they continue to live an independent existence and to undergo further maturation in the peripheral lymphoid tissues. The other line also undergoes a series of maturation steps, but solely in the peripheral tissues. These are the B-lymphocytes of which there are also some 10^{12}. As they mature, both T- and B-lymphocytes develop surface receptors, i.e. molecules, a part of which is complementary to and capable of binding with measurable, often very high, affinity to determinants or shapes on a wide variety of other molecules. The molecular structure of the receptors on T- and B-lymphocytes differs. Those on B-lymphocytes are immunoglobulins similar to the antibodies which they can secrete when suitably stimulated. The structure of receptor molecules on T-lymphocytes is still unknown; they are not the same as the immunoglobulins on B-cells though the receptor sites themselves have similar shapes. They may contain molecules, or parts of them, controlled by the Ir locus on the major histocompatibility genes. T-cell receptors certainly interact best, and perhaps exclusively, with molecules associated with other molecules controlled by the major histocompatibility complex (MHC) locus.

The variety of distinct receptors expressed by a population of mature lymphocytes is staggeringly large. Most intelligent guesses arrive at a number around 10^8. No individual lymphocyte has been shown to express more than one or two specificities; this implies that, at some stage during development from the stem cells, each progeny must come to express a very restricted part of the possible repertoire. How such a huge repertoire could be stored in the genome is a puzzle, but for B-cells it has been solved, at least in principle, by the discovery that immunoglobulin molecules are each assembled from the products of seven distinct genes present in the germ line, and that each of these genes has four or more variants. By variable recombination between these genes a very large number of possible structures can be coded for, and the possibilities are increased further by somatic mutation, which is known to occur in some of these genes during the repeated cell divisions which take place during the cells' maturation. The choice of gene product that a B-cell will ultimately express appears to be largely random, since some receptors are more common than others, even in animals subjected to no special stimulation. Thus the frequency of B-cells bearing receptors that can react detectably with molecules unlikely to be met naturally (e.g. keyhole limpet haemocyanin or a special site on β-galactosidase from *E. coli*) has been found to range between 10^{-3} and 10^{-6}.

Much less is known about receptors on T-cells, but they probably show a similar range, although the frequency of receptors that can recognise the MHC of other animals of the same species is much greater, being one per cent or more.

The significance of this is that each of us produces lymphocytes that include some with receptors capable of binding to almost any determinant, synthetic or natural, that can be assembled—and these will include not only foreign molecules but self components, and even the combining sites on other receptors. This applies both to T- and to B-cells. A system able to recognise anything that is not self must inevitably generate the capacity to recognise self.

Before considering how this paradox is resolved I must outline the life-cycle of lymphocytes and the effect of their interaction with the molecules that their receptors recognise. These molecules, which in this context are termed antigens, may be in free solution or—as is commonly the case with foreign materials—may have been ingested by macrophages but partly retained in some way associated with the macrophages' own cell membranes. The most easily detected effect is the stimulation of lymphocytes to multiply and differentiate into functionally active cells. An effect rendering them non-functional would obviously be much harder to discern.

B-Lymphocytes

The earliest recognisable B-cell precursors appear already to have selected which immunoglobulin they will make, but do not express it at their surface; they are therefore unaffected by external contact with antigens. Once immunoglobulin has been expressed on the surface, they are 'early' B-cells. At this stage the cells have the interesting

properties of being arrested, or switched off, by contact with low concentrations of the appropriate antigen in free solution, but of being stimulated by antigen associated with macrophages and factors supplied by T-cells to multiply and differentiate. Differentiation can proceed in two directions, usually concomitantly. One results in B-cells with an increased number of receptors on their surface, which live for a long time but do not actually secrete immunoglobulin unless or until they are re-stimulated; these are referred to as B memory cells. Progress in the other direction involves dividing, and developing the machinery for synthesising and secreting large amounts of immunoglobulin—up to 10,000 molecules a second. Although some B-cells can be stimulated to secrete antibodies without participation of T cells, in most cases—and always when they have passed through the stage of becoming B memory cells—they require 'help' from T-cells. 'Help' is a useful term that makes no pretence to conceal its vagueness. In the absence of 'help' they can still be switched off by contact with free antigens in solution, but to do so a much higher concentration is needed. I should mention that factors that can stimulate B-cells, irrespective of the specificity of their receptors, are produced by macrophages and T-cells *in vivo* all the time, and that there is probably a very low and biologically insignificant background production of immunoglobulins covering the whole range of possible specificities, except those that have been switched off. Each ml of plasma contains some 10^{16} molecules of immunoglobulin, so they could easily not be noticed.

The basic unit of immunoglobulin consists of four polypeptide chains, two light (L) and two heavy (H), each of which contains the antibody combining site at one end and at the other the so-called 'constant' regions which confer other biologically important properties. Any of the constant regions (μ, δ, four kinds of γ, two kinds of α and ϵ) can be linked with the same combining site, and antibody secreting cells can switch from making one kind of constant region to another in the order given. The different biological properties associated with different constant regions include capacity to activate complement, to cross biological barriers such as the placenta and the newborn gut wall, to be concentrated at mucous surfaces, to be secreted in bile or milk, and to bind selectively to mast cells. This ingenious device enables antibodies with a vast variety of specificities to exert their biological effects through a limited number of final common pathways.

T-Lymphocytes

Our knowledge of mature T-lymphocytes that have entered the circulation is derived from much painstaking experimental work, which depended initially on the availability of genetically defined strains of mice and rats, and has been greatly speeded by improved methods for cultivating lymphocytes *in vitro* and by the recent development of specific antibodies able to distinguish subsets of T-cells with functional differences. So it is possible to make some statements with a reasonable degree of confidence of their still being true in a few years' time. The population of T-lymphocytes also includes cells with an enormous range of receptors, though their specificities are not precisely identical with those of B-lymphocytes; in general, they require to recognise a larger part of a molecule than do antibodies. Their range is also affected by the nature of molecules controlled by that part of the MHC complex called the Ir (or immune response) genes, possibly because the receptors include those in their make-up. T-lymphocytes with particular receptors can also probably be switched off at some stage early in their life-cycle by antigens in free solution. Mature circulating T-lymphocytes contain two major populations that arise from a common precursor. These are termed 'helper' and 'suppressor' classes, but each class probably contains more than one functional kind of T-cell. 'Helper' T-cells are stimulated by contact with antigens, but only when these are associated (usually on macrophages) with the same Ir gene product—I-A in mice and DR in man—as they themselves can express. Cells comprised within the 'helper' population do several different things when stimulated. They divide and multiply to increase their representation in the population; they stimulate B-cells with receptors for other parts of the same antigen to secrete antibody; they also stimulate 'suppressor' T-cells; and they themselves secrete a variety of products, 'lymphokines' which include interferon, a macrophage activating factor, a permeability factor, and other less well defined factors responsible for the manifestations of delayed type hypersensitivity reactions.

The population classed as 'suppressor' cells responds to antigens associated with yet another part of the MHC complex—the I-J antigens in mice but not identified in man—and requires T-cell help to become functional. They do at least two important things. One is to act as cytotoxic lymphocytes that recognise antigens on other cells when those antigens are associated with molecules that are part of the MHC expressed on almost all cells—the $H2^D$ and $H2^K$ molecules in mice and the HLA-A, -B and -C molecules in man—and kill those cells. The other is to suppress the stimulation by antigens of B-cells and helper T-cells. They secrete 'suppressor' factors whose structure and mode of action are not yet known. The reason why potentially self-reactive B- and T-cells, which have escaped being switched off during their earlier stages, do not generally respond to self antigens is usually because the appropriate T-helper cells are suppressed or because the antigens are not available in the right form to stimulate them (e.g. not associated with I-A or DR determinants).

The Network Theory

These concepts are rather complex. But there is one additional concept that both unifies and further complicates the story. This is the Network Theory, put forward on theoretical grounds by Niels Jerne eight years ago, but increasingly confirmed by experiment. The theory states that the library of different receptors, whether on T- or B-lymphocytes, is likely to contain some that can recognise each different and unique receptor site on other receptor molecules. The name given to such a unique receptor site

is an 'idiotype'. In an initial random state the concentration of any one idiotype is too low to stimulate lymphocytes bearing the corresponding anti-idiotype. But when the concentration of any given idiotype is increased following stimulation by an antigen, it can stimulate B-cells to secrete anti-idiotype or T-cells which can act on cells expressing that idiotype—either to help or, more usually, to shut them off. In turn, the anti-idiotype molecules stimulate other lymphocytes which express anti-anti-idiotypes, and an infinite network of interactions is potentially set up, which will not only regulate the initial response to antigen but leave the whole balance altered. I will give one striking example. An anti-idiotype must be a good fit with the idiotype with which it can combine, and the antigen to which the idiotype corresponds must be likewise. So the shapes of the anti-idiotype and of the antigen must be very alike. It has been possible in carefully designed experiments to immunise a mouse with anti-idiotype molecules and elicit antibodies against the original antigen, which the mouse had never experienced. This suggests that it is the idiotypes with which specific suppressor T-cells react on helper T-cells or B-cells, and that the way in which specific T-cells stimulate B-cells to secrete involves reacting with the idiotype rather than presenting some modified form of the original antigen. If this is so, the role of antigen could be to start the process but play no direct part thereafter. This must have great relevance to auto-immunity.

I have presented the outline of immunological concepts as though they had been arrived at solely from developments in basic immunology, but this is, of course, far from being the case. In many instances it was observations on patients—what Robert Good termed 'experiments of Nature'—that forced immunologists to recognise phenomena that did not fit in with what they thought they knew, and to design experiments to explain them. Animal models have been discovered that reproduce human diseases more or less accurately, and, from studying them, it has been possible to assess the relevance of immunological concepts to the pathogenesis and the devising of rational treatments. I am also well aware that I have left out those non-specific mechanisms of immunity which are independent of lymphocytes and their products, and which constitute the first line of defence before the latter come into play—the integument, mucins, enzyme inhibitors, iron-binding proteins, direct activation of complement, non-specific opsonisation, and so on.

Immunological Concepts in Medicine

How far are these concepts important for medicine? Let me take some examples.

Prophylactic Immunisation

No basic understanding of immunology is needed to imitate natural infections, but it certainly helps to understand that preformed antibodies can neutralise microbial toxins, prevent microbes from attaching to sites of entry into the body or into target cells, and can destroy many microbes with the help of complement or by opsonisation and phagocytosis. At one time it was reckoned that antibodies were all that was needed for protection, but it is now recognised that once microbes capable of intracellular multiplication have become established, cellular immunity (cytotoxic lymphocytes or activated macrophages) is required to destroy them along with the infected cells. Recognition that both are needed has greatly altered the strategy of prophylactic immunisation, especially against viruses and intracellular bacteria such as salmonella. Much current effort is being put into the use of highly purified or even synthetic microbial antigens, but the lesson has been learned that acceptable adjuvants will also have to be devised to ensure that the correct responses will be made and that they will endure. Furthermore, the discovery that, during infections with some important parasites, effective immunity is often circumvented by changes in the surface antigens of the parasites and also by the development of profound immunosuppression, has clarified the aspects of the interplay between host and parasite which must be understood better before immunisation is likely to be effective.

Immunodeficiency Diseases

These diseases due to defects in the lymphon are now intelligible in that we can ascertain what is defective (though often not why) and know in principle how to correct it. Rational treatment often proves gratifyingly effective.

Proliferative Disorders of the Lymphoid System

These disorders—i.e. leukaemias and lymphomas—are more intelligible. At any stage in their development from stem cells a clone of lymphocytes may undergo malignant transformation, with uncontrolled proliferation of the transformed clone. Now that markers are available to permit identification of the stage at which transformation took place, classification and prognosis are much improved. Treatment with cytotoxic drugs and radiation remains empirical, but increasing understanding of what controls normal differentiation may eventually produce means of bypassing the maturation arrest or of devising chemotherapy specific to the arrested stage. The prospects of doing this seem to be particularly good if there is an associated chromosome abnormality of known function.

Cancers of various kinds express surface antigens peculiar to the tumour cells—though more often than not there is loss rather than gain of antigens. In principle, tumour specific antigens should evoke an immune response against them—and in experimental animals (in which the antigens are often coded for by viruses) they do so. Even in man circulating immune complexes, which indicate that an antibody response must be taking place, are often present. But effective cellular immunity sufficient to prevent tumour growth is rarely detectable, and cellular immunity in general may be depressed. This is perhaps because tumour cell products actually inhibit cellular immune mechanisms or perhaps because they fail

to evoke them. Much effort is being expended on devising means of stimulating effective anti-tumour immunity that can be done in laboratory animals.

Auto-immunity

Auto-immunity, or the production of damaging amounts of antibody or cellular immunity against constituents of one's own body, was demonstrated as a cause of disease long before it became explicable theoretically. It proved remarkably easy to provoke tissue specific auto-immune diseases in animals, more or less resembling those in man, by immunisation with the appropriate tissues combined with an adjuvant containing dead tubercle bacilli, which is a potent evoker of T-cell help. The experimental diseases are nearly always transient, probably because suppressor cells eventually become predominant. A generally accepted explanation for the development of tissue specific auto-immunity is that although potentially reactive B-cells are present, appropriate helper T-cells able to co-operate with them are normally absent or suppressed. They can be substituted for by helper T-cells evoked by the tissue antigen that is altered in some way, such as by association with viral antigens. Since in some animal models such as obese strains of fowls or rats which develop spontaneous thyroiditis, there is a notable deficiency of suppressor T-cells, such deficiency may have a similar result.

Another mechanism is the development of antibodies against self-components which are normally not expressed or not available to interact with lymphocytes. The most important example is rheumatoid factors, which are antibodies against normal immunoglobulin molecules distorted by interaction with antigens. Rheumatoid factors are regularly produced when antigenic stimulation is prolonged, and immune complexes are formed, but their appearance is transient. In rheumatoid arthritis there must be some additional factor which maintains both the production of antibodies and the distortion of immunoglobulins to create a vicious circle; one possibility is that this is the inflammatory reaction set up by rheumatoid factors interacting with normal immunoglobulins and with themselves. Less common examples are auto-antibodies to sperm antigens following spermatic cord ligation or mumps, and to uveal tract pigment following damage to one eye, thus leading to sympathetic ophthalmia in the other.

Systemic lupus erythematosus (SLE) and its congeners, which are characterised by auto-antibodies against a variety of nuclear constituents, remain a puzzle. There are now several animal models which develop spontaneous auto-antibodies of the same sort, some presenting a disease picture with a sex incidence very like that in man. In all these models the disease is genetically determined, but none of the proposed explanations for SLE—such as early loss of suppressor cells—is common to all the models. The only common feature is heavy infection with a C-type virus, which has not been found in the human disease.

We have to acknowledge that clones of auto-reactive cells, which we know to be normally present, can be stimulated for reasons which we do not know, though there is clearly a strong genetic predisposition for this happening. Prolonged administration of certain drugs is sometimes a provocative factor—e.g. hydrallazine leading to antibodies similar to those in SLE, and methyldopa to auto-antibodies against erythrocytes (usually involving Rh antigens). But these effects are reversible when the drug is stopped, and we do not know why or how the effects are caused. It has been claimed that methyldopa specifically inhibits suppressor T-cells, but this hardly explains why the auto-antibodies should be confined to erythrocytes. One of the greatest puzzles is why the auto-immune response in different diseases is confined to particular antigens.

There are several auto-immune diseases in which the patients are apparently cured if their auto-antibody levels are permanently reduced by plasmapheresis, or by long-term treatment with immunosuppressive drugs. Examples are Goodpasture's disease caused by antibody against glomerular basement membranes, and some forms of myasthenia gravis, caused by antibodies against acetylcholine receptors. One possibility is that the clones of antibody-producing cells have become exhausted, but a more interesting possibility—supported by evidence in experimental animals—is that the balance of the idiotype/anti-idiotype network has been altered and suppressor cells have become dominant. This is an area which deserves much further exploration.

Immune Complex Diseases and Glomerulonephritis

Immunological concepts have had a profound influence on our understanding of this group of diseases. The series of events is complicated but the concepts are simple. Antigen-antibody complexes which appear in the circulation (having failed to be removed and catabolised by the reticulo-endothelial system) are liable to become deposited on the basement membrane of renal glomeruli and/or in the walls of arteries, particularly small arteries outside the kidney. When complement is activated by the complexes, fragments that increase vascular permeability are released, platelets are activated, granulocytes are attracted and release their lysosomal enzymes, and the result is an acute local inflammatory response in and around the vessel wall. In the kidney, from which there is a continuous flow of small molecules into the urine, any acute inflammatory response is shortlived, but complexes and complement components continue to accumulate, causing thickening of the glomerular basement membrane, disruption of the epithelial foot processes and leaky glomeruli, which are eventually destroyed.

The concept of antigen-antibody complexes, which are present in the circulation more than transiently and above some threshold concentration, being liable to cause vasculitis and especially damage to the kidney, has been enormously important in understanding the pathology and guiding the treatment. Immunological concepts have also proved essential in the fields of allergy and organ transplantation.

Allergy

The immunological basis of allergy has long been recognised, but distinction between immediate type acute and delayed type allergic reactions was essential for their understanding, even though the two may co-exist. So far as immediate type reactions are concerned the basic concept is that IgE binds to specific receptors on mast cells, cross-linking of which allows rapid entry of calcium ions and activates a series of reactions leading to extrusion of the mast cell granules. What happens thereafter is fascinating, but belongs in the realm of pharmacology. Delayed type hypersensitivity reactions are conceptually more complex, involving interaction between antigens and part of the circulating helper T-cell population. The visible effects are mediated by activated macrophages and the other lymphokines that I mentioned, but may be modulated to a variable extent by concomitant stimulation of cytotoxic and suppressor T-cells which are also present. This means that the duration and intensity of effect depends greatly on the balance achieved.

Organ or Tissue Transplantation

Except between identical twins, organ or tissue transplantation involves the body's permanent acceptance of an organised tissue composed of cells carrying at least some foreign antigens of the sort that are particularly effective at stimulating an immune reaction and causing rejection of the graft by the host. In the case of bone marrow transplantation, there is the possible added complication of the donor lymphocytes reacting against and destroying the host. In both these procedures success depends upon having sufficient understanding of immunological concepts to minimise the stimuli that cause rejection, and damp down by immunosuppression the severity of the immune response until a state of tolerance has been achieved. This state is now reckoned to be due to induction of suppressor mechanisms rather than to elimination of lymphocytes that may potentially react against the graft or the host.

Therapeutic Measures

Several cytotoxic drugs are both useful in suppressing unwanted immune responses by lymphocytes and selective enough to avoid serious damage to other cells. They succeed because they act on dividing lymphocytes, which are especially sensitive to them, if the right drug or combination of drugs is used. Although other useful responses to microbes, which are going on simultaneously, are also suppressed, it is hoped that the responses already established (and not requiring cell division at the time when the drugs are administered), will suffice to protect the patient from microbial invasion. Besides selectively inhibiting lymphocytes, corticosteroids have the added advantage of inhibiting other activities, such as those of macrophages, involved in inflammatory reactions. I have to admit that none of these drugs, even though they may have selective actions on T- or B-cells, was developed with immunological concepts in mind and we do not really know how corticosteroids cause their effects. Nevertheless, certain special properties have been discovered because they were actually looked for. One is that a metabolite of cyclophosphamide makes mature B-cells behave like 'early' B-cells and become particularly susceptible to switching off by low concentrations of free antigens; another is that cyclosporin-A has a selective action on the multiplication of T-helper cells.

Plasmapheresis, the removal of unwanted circulating antibodies or immune complexes, is the therapeutic measure that springs directly from immunological concepts, as does the use of anti-lymphocytic antiserum—unselective as it is at present. Between them, the existing measures, judiciously used, can, in many immunologically-based diseases, effectively tide patients over until the cause of the disease has been eliminated or the balance within the immune system has become stabilised.

There are also drugs that are claimed to act positively to increase one or another arm of the immune response, such as thymopoietin, interferon, the mysterious leucocyte extract 'Transfer Factor', levamisole and several other compounds up the manufacturers' sleeves. Convincing controlled therapeutic trials are needed to prove their worth.

We are now in a position to know (more or less) what to aim for. For instance, in experimental bone marrow transplantation it has been shown that if all mature T-cells are removed (by specific antibodies and complement or other devices) and only haemopoietic stem cells are left in a viable state, such cells can completely reconstitute lethally irradiated animals, even across a major histocompatibility barrier, without causing any graft-versus-host disease. If monoclonal antibodies able to selectively remove mature T-cells from human marrow can be developed, and if man proves to resemble the rat, the ease and available range of bone marrow transplantations would be greatly increased.

Although I have given no more than a bare outline of immunological concepts, I have tried to demonstrate their relevance to clinical conditions. Immunology is becoming quite a popular subject nowadays and has a fascination all its own. Much remains to be discovered, and ideas and possibilities are changing all the time, both at fundamental and applied levels. Immunology has also helped greatly in our understanding of many disease processes, and has simplified rather than complicated such understanding. As a guide to clinical management its current virtue may be to indicate what not to attempt, but it undoubtedly saves lives. When applied in active or passive immunisation it has freed much of the world, at low cost, from several diseases which once were terrors—but the price of this freedom remains eternal vigilance.