BRITISH MEDICAL JOURNAL

LONDON SATURDAY JULY 24 1954

THE NEWER APPROACH TO IMMUNITY IN ITS BEARING ON MEDICINE AND BIOLOGY*

BY

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In recent years my primary interest has been in the behaviour of viruses, but from the very beginning of my scientific work the nature and significance of immunity has been a necessary and abiding interest. Immunity, however, is to-day a rather unfashionable topic in comparison, for example, with adrenal hormones or viruses, but I believe that it might be of interest and perhaps even of value to speak of the modern approach to immunity in its bearing particularly on medical problems. For the most part I shall speak in rather general terms, and I cannot avoid introducing some consideration of immunity as a general biological phenomenon. Some may feel that such a discussion of immunity might have been more appropriate forty to fifty years ago in the great days of Ehrlich, Bordet, and Almroth Wright. On the contrary, I should like to show that new facets are emerging that may modify importantly the understanding of several types of human ills.

The Biological Approach

Immunity from one point of view is so advantageous a physiological attribute that one might almost say from the biological angle that its existence is self-explanatory. In a world that is full of micro-organisms capable of infecting living tissues, it is a positive necessity for survival that most experiences of infection by any given microbe should be followed first by recovery and secondly by a persisting insusceptibility to an attack of the same disease. On other occasions I have given reasons for thinking that perhaps the important factor in the development of the particular types of immune reaction with which we are familiar in man was the evolution of his mammalian ancestors for the most part as relatively solitary arboreal animals in tropical jungles. In such environments it seems likely that the major type of pathogen that would be encountered would be those protozoa and viruses spread by insect—especially mosquito—vectors. It is not improbable that the type of immunity characteristic of human beings is essentially something evolved to deal effectively with infection by mosquito-borne viruses of the yellow-fever type.

They may represent an unnecessary refinement, but at least we can be sure that immunity is a mechanism that has been evolved to deal with the entry of foreign

micro-organisms into the body, and that it has been perfected by the normal process of selective survival.

Medical immunology, however, deals with a wider range of phenomena than those concerned simply with immunity to infectious disease. With the modern development of blood transfusion as a therapeutic measure, a very important set of new clinical conditions has been uncovered—conditions in which the immune mechanism has been constrained by circumstances to give rise to a harmful or fatal set of reactions. I am concerned here mainly with the significance of conditions in which this abnormal or harmful functioning of the immunity mechanism occurs, and I should at once like to introduce the two central concepts of *antibody*, its nature and production on the one hand, and of the contrast between *self* and *not-self* on the other. These are basic to any understanding of immunity.

A Concept of Antibody

The nature of antibody is now reasonably familiar to everyone with some knowledge of medicine or biology, but there are still many aspects of the nature and production of antibodies that are obscure. Simplifying the situation so far as is legitimate, we can describe antibody as a modified soluble protein (present in highest concentration in the blood), the individual molecules of which have properties causing them to stick firmly to those types of molecules or micro-organisms against which the antibody was developed. When a patient is convalescent from an attack of yellow fever we may find that as much as 1 to 2% of the serum protein is yellow-fever antibody. The amount will fall gradually, but in most instances quite significant quantities will be present throughout the whole subsequent life of the individual, and this antibody is the agent responsible for his concomitant immunity against yellow fever. If yellow-fever virus re-enters the body as a result of the bite of a mosquito carrying the virus, the virus particles are immediately coated with the specifically patterned antibody molecules, whose presence effectively prevents the virus from initiating an attack of disease.

Whenever foreign organic material enters the body tissues—in the vast majority of natural instances as a result of invasion by one or other pathogenic micro-organisms—processes are set in motion which have been evolved to rid the body of the foreign element and to ensure that effective invasion by the same type of alien

*The fifth Frederick Price Lecture, delivered at the Royal College of Physicians, Edinburgh, May 3, 1954.

will not occur again. The essential feature is that the cells producing the serum protein gamma globulin change the pattern of the molecules to the extent that is required to allow their specific attachment to micro-organisms of the infecting type. Much work has been done on the physical nature of antibodies and on the cells responsible for their production, but from our present point of view the essential point to recognize is that blood proteins can be produced in a probably unlimited number of *patterns* without more than trivial changes in their physical qualities.

This characteristic reaction to the entry of foreign organic material is apparently the responsibility of that system of mesenchymal cells, including reticulo-endothelial cells, lymphocytes, and plasma cells, which is conspicuous in spleen and lymph nodes and may be conveniently referred to as the scavenging cells of the body. But here we come on a very important difficulty. This is that the cells which deal with foreign organic material are the same cells that are concerned with the disposal of damaged and effete body cells. It is well known that approximately 1% of our red cells are taken from the circulation and broken down in spleen macrophages and elsewhere each day. A corresponding new production keeps the system in equilibrium. Lymphocytes seem to have a very rapid rate of turnover, and probably most cells other than those of the central nervous system are replaced at longer or shorter intervals. It is clearly important that the removal of worn-out erythrocytes or other body cells should *not* provoke an antibody response.

From the literature on transfusion reactions and on haemolytic disease of the newborn we know very clearly what may happen if red cells do provoke an antibody response. If by artificial or natural processes alien red cells enter the organism, antibody production may occur and highly undesirable results ensue. There are several other types of evidence to show that the expendable cells of the body will be treated essentially like foreign micro-organisms if they are inoculated into other species or into genetically dissimilar individuals of the same species. In their own body, of course, they are tolerated and finally disposed of without any immunological response.

"Self" and "Not-self"

The essence of the problem can now be stated. How do the scavenging cells that are responsible for dealing both with bacteria and other foreign organic material on the one hand, and with the body's worn-out expendable cells on the other, distinguish between the two groups, between what is "self" and what is "not-self." The fact that foreign material is eliminated or destroyed *with* antibody production while effete cells of the body's own pattern are broken down *without* antibody production must mean that in one way or another the scavenging cells can *recognize* whether the material they are dealing with is of the body's own pattern or something else, that they can recognize the difference between self and not-self. Such a statement might well be regarded as merely a truism incapable of verification or elaboration by experimental methods. If the capacity to recognize self-structure were built into the body wholly by the processes of inheritance and development then there would be very little more to say. On the other hand, if this recognition of self and not-self is "learnt," as it were, during the process of embryonic development, there are implications which can be observed or experimentally tested.

In our monograph on the production of antibodies (Burnet and Fenner, 1949) we pointed out that there were two sets of natural phenomena which were strongly in favour of

the second alternative—that recognition of material as self is something that needs to be learnt and is not an inherent genetic quality of the organism. The first came from the study of the blood groups of cattle by Irwin and others at the University of Wisconsin. Cattle do not possess blood groups equivalent to the ABO human groups, but by appropriate iso-immunization procedures the existence of several genetically determined types can be demonstrated. With a set of properly produced and differentially absorbed antisera any sample of bovine red cells can be typed. The procedure is often of practical value in cases where the paternity of a calf is in doubt.

The normal rules of inheritance of blood groups, however, appeared to break down when twin calves were concerned. If the twins were non-identical, derived from two separate fertilized ova, it was common to find that both had two blood groups, perhaps 60% of the red cells being of one type and 40% of another. This character persisted through life. The probable explanation is that the two embryos, differing from one another in various details of their inheritance, developed a common placental circulation early in embryonic life. Suppose we assume that one has cells of blood group P, the other of group Q, the difference being genetically determined so that we can speak of one embryo as of P type and the other Q. The common circulation will ensure that many cells, including haematoblasts of P type, will pass into and lodge in Q, and vice versa. In all probability there are other and perhaps more subtle interchanges of antigenic patterns between the two, but we can concentrate simply on the blood cells. If P cells lodged in an animal genetically Q during adult life they would be recognized as foreign, and as part of the process of their removal antibody would be formed. But when this happens in embryonic life, not only are the foreign stem cells accepted but a tolerance is developed which allows their retention and the continuing production of descendant red cells of the "wrong" genetic type. It seems from this that if a foreign organic pattern is introduced at the appropriate stage of development, and if it persists in large enough amounts and for the necessary period of time, it may be accepted as "self." The mechanism for the recognition of self seems to be laid down, at least in cattle, at some period before birth.

Our second example came from a virus disease of mice, lymphocytic choriomeningitis (L.C.M.) which was studied extensively by Traub (1936, 1938, 1939) at the Rockefeller Institute. He followed the development of infection in a mouse colony over these years and ended up with a population almost literally saturated with the virus. Infection took place *in utero*, and, although there were deaths of embryos, many were born apparently healthy, and in these the virus persisted through life. None of these developed antibody; neither neutralizing nor complement-fixation reactions could be demonstrated in their sera. Relatively large amounts of virus could be extracted from any organ. L.C.M. virus injected into normal mice provokes disease of variable intensity and a rather low-grade immunity in which complement-fixing antibodies are demonstrable but not neutralizing ones. With recovery the virus is eliminated from the body. Here again we see a condition in which a persisting foreign entity introduced in embryonic life induces a tolerance to its presence which persists through development and adult life.

Since we published the monograph, another example of great interest has been observed by Dunsford *et al.* (1953). This concerns a woman blood donor of 25 whose blood was found to contain nearly equal amounts of A and O cells. By separating the two types of cell it could be shown that they also differed in respect of two minor antigens as well. The only reasonable inference was that the woman in question had a twin and that the two placental circulations had fused during foetal life. The foreign haematoblasts had been implanted, and, as in the bovine twins, they and their descendants had persisted. It is recorded that when the donor was asked whether she was a twin she

replied in some surprise that she was, but that her twin brother had died at the age of 3 months, 25 years before.

Here, then, are three observations of natural occurrences that point to the likelihood that foreign organic pattern introduced during embryonic life and persisting thereafter can be accepted by the body as if it were "self" material. Last year a direct experimental attack on the analogous problem of skin-grafting by a group headed by Medawar gave strong evidence in support of this conclusion. It is well known to every surgeon that skin grafts, if they are to take, must be from some area of skin on the patient himself. Homografts from another person persist for a few days only before provoking an immune reaction that leads to their rejection and necrosis.

In experimental skin-grafting in mice, however, there are possibilities beyond anything in human surgery. When a closely inbred homozygous strain of mice is available, transfer of skin from one individual to another is possible owing to the genetic uniformity of the strain. Skin from any other strain of mice is rejected just as human homografts are.

In Billingham, Brent, and Medawar's work (1953) three genetically uniform strains of mice were used which may be called A, B, and C. Pregnant females of A were taken about one week before term and each embryo was injected *in utero* with an emulsion of spleen and kidney cells of mice of strain B. Most of the young concerned were born alive, and, when 4 to 6 weeks old, were tested for their capacity to accept grafts of skin from A, B, and C mice. Untreated A mice of the same age were similarly tested as controls. The results were clear-cut in showing that the mice treated *in utero*, unlike the normal controls, accepted the heterologous B graft without immune reaction. This acquired tolerance was specific.

If instead of inoculating mice *in utero* they are injected with heterologous cells or grafted with heterologous skin in adult life, subsequent grafts of the same heterologous skin are rejected much more rapidly. This accelerated reaction represents an acquired and specific intolerance of the foreign cells. We have in the mouse, therefore, the interesting situation that, before a certain point in development approximately at the time of birth, the entry of foreign cells provokes a specific tolerance in later life, while after that point a similar entry gives rise to specific intolerance (or immunity). Probably this holds for other mammals as well as for the mouse, though it does not necessarily follow that the critical point of development is the same for each species. In fact, there is some positive evidence for animals such as guinea-pigs and sheep, which reach a high stage of development *in utero*, that immune reactions can be provoked before birth. In man the critical point is perhaps one to two months before birth, but there is as yet no direct evidence on the matter.

The Nature of Antibody Production

Any theory of antibody production has nowadays to do more than present hypotheses of how antibodies are produced in adult life. It must also take note of the existence of this critical point before which foreign material provokes a specific inability to produce the corresponding antibody in later life. In what has been called the self-marker hypothesis, Fenner and I made an attempt to do this (Burnet and Fenner, 1949). The following outline presents the essentials of this attempt.

The "scavenger" cells of the reticulo-endothelial system are assumed to contain subcellular structures which are or can be developed into "recognition units." These correspond to a fairly limited range of "self-markers," protein or polysaccharide configurations typical of the expendable cells of the body. As in other fields of biochemistry, recognition means simply the existence of a complementary pattern relationship between two complex chemical structures. Ehrlich introduced the simile of a lock-and-key relationship for the antigen-antibody reaction, and we must ascribe some similar relationship to enzyme and substrate or hormone and target substance. So in the present instance,

when specific contact is made between self-marker and recognition unit, the process of disintegrating and disposing the material is set going along the path of tolerance without antibody production. By the time the critical point of development has been reached these recognition units have been laid down and moulded to the self-markers of expendable body cells and to any equivalent foreign patterns that may have been present by some accident of infection, development, or experimental device. Once the critical point is passed no subsequent modification of recognition units can occur.

A new type of response now becomes the rule. On the self-marker hypothesis, antigens—those substances capable of provoking antibody production—are molecular patterns differing from any of those of the body's self-markers but having sufficient resemblance to be capable of partial reaction with one or other of the recognition units of the scavenging cells into which they may find their way. Partial reaction leads to active modification of the recognition unit pattern so that it will be complementary to the antigen, but a new feature emerges. The reshaping of the unit so that it will "recognize" the specific antigen sets in train a process almost equivalent to the entry of a virus into the cell. The modified recognition units multiply, reproducing their new specific pattern and allowing their transfer to the stem cells of the lymphoid series, which can, as it were, act as foster parents for the modified units.

In these stem cells the pattern persists as an inheritable character, sometimes for life, though probably in all cases there is a slower or faster drift back toward the normal pattern complementary to one of the self-markers. Under a new antigenic stimulus of the same type the stem cells produce descendant cells specialized to produce incomplete copies of the modified recognition units and liberate them in large numbers into the blood as antibody molecules. The cells responsible for such active production are necessarily in a state of active protein synthesis. They are the immature plasma cells of the histologist characterized by the pyronine staining of cytoplasm and nucleolus which is indicative of protein synthesis. As the antigenic stimulus wanes, antibody production continues, though on a lower level, and the cells involved in the later stages are almost certainly lymphocytes. There is still controversy on the matter, but it seems legitimate to regard the primary function of the lymphocytes as the production, transport, and liberation of antibody.

By the use of appropriate radio isotopes it can be shown that antibody, like other blood proteins, is constantly being used up and renewed. The "half life" of antibody is about 14 days in man, less in the small laboratory animals. It is a sound rule, therefore, that so long as any antibody is detectable in the blood it is still being actively produced. For any long-lasting immunity we must therefore postulate a perpetual growth and replication of the cells in which the modified pattern is stored and a constant production and breakdown of the lymphocytes that are the actual producers of antibody.

This outline of the self-marker theory of antibody production is condensed and perhaps difficult to follow. It is also a theory that is by no means acceptable to many immunologists. We can still claim, however, that it is as yet the only one which attempts to face the implications of acquired specific tolerance, and, as I hope to show, it has some important ideas to offer for clinical medicine.

Pattern in Biology

Perhaps it would not be out of place to introduce here a parenthesis, as it were, on the significance of pattern in biological reactions. My own interests have been in the field of antibodies, viruses, enzymes, and genes, all potent agents of specific pattern, but now, and perhaps indefinitely, beyond the scope of classical organic and physical chemistry. Perhaps an alternative approach is beginning to open out in the concept of organic pattern as a carrier of "information" or "instructions" from one part of the

organism or the cell to another—a communication theory, as it were, of the living organism. Such a theory has not yet been developed, although Delbrück recently made some important suggestions in this direction about nucleic acids. In our particular instance we can restate the position somewhat as follows. The pattern of foreign cells entering the body before the critical point establishes an information mechanism and a set of instructions on how to deal with such information when it is subsequently received. After the critical point, the same type of information will convey very different instructions.

It is orthodox to regard the aim of the biological sciences as to express phenomena in terms that become progressively more and more those of classical chemistry and physics. It may be more realistic to believe that an approach in terms of the replication of organic pattern, and of a developing communications theory of the organism, may be adequate to allow the full utilization of all the potentialities of controlling biological processes.

Clinical Applications

This, then, is a theoretical picture of the biological significance of antibody production as it appears at the present time. It will be noted that I have said very little about what I have described as the primary function of antibody production—protection against infectious disease. This is simply because I am primarily interested in the newer approach to immunology with its emphasis on the self-not-self relationships.

Similarly, in the concluding sections of this lecture which deal with some of the clinical implications of immunity, I shall say nothing in regard to infectious disease in the ordinary sense. The three topics that I shall briefly discuss in the light of the previous theoretical approach are tissue transplantation, serum hepatitis, and the possible part played by auto-antibodies, so-called, in disease.

Tissue Transplantation

The experiments by Billingham and Medawar that I have mentioned lead naturally to the problems of organ-grafting in surgery, either to repair physical damage as in skin and bone grafting, or with the objective of providing a functioning source of hormone after the usual producer has been eliminated by disease or surgery. So far as one can attempt a generalization from the not always consistent literature, attempts to graft expendable vascularized tissues will succeed only when the grafts are autologous or come from an identical twin of the subject receiving the graft. All plastic surgeons now accept the inevitability of a foreign skin graft failing to "take." At most it can provide a transient "dressing" in the period before the immunological response induces its rejection. In the same way, bone and arterial grafts provide only frameworks on which the recipient's own cells can eventually build up new tissues of the body's own kind.

The interesting possibilities at the present time centre in the cornea and some of the endocrine tissues. Corneal grafting is an accepted surgical procedure and is often successful. I have not been in a position to gain any wide acquaintance with the literature or any experience in this field, but one gathers that the important requirement for success is that union should take place between the non-vascular tissues without the development of new inflammatory vascularization. It seems that foreign tissue can be tolerated if it is not, as it were, brought to the notice of the body. The immunological situation of the tissues of the eye may be more subtle than this. The older literature indicates, for instance, that the lens has none of the normal "self-markers" of the other body tissues, and a thorough-going immunological analysis of the antigenicity of eye tissues and of the reaction of other antigens introduced into the eye might be a very rewarding study at the present time.

Endocrine transplants have been attempted for many years, often with apparent success. At the experimental

level I am most familiar with the work of Woodruff and Woodruff (1950) on the transplantation of guinea-pig thyroid to the anterior chamber of the eye in other individuals of the same species. There are two outstanding points that emerge from this work. The first is that the graft survives only when there is a positive need for thyroid tissue—that is, in thyroidectomized recipients only. The second is that in a successful take there is a phase of almost complete histological disorganization of the tissue which may well be interpretable as a replacement of the interstitial tissues (expendable cells) by cells of the recipient, with subsequent reorganization of the needed thyroid cells within the stroma provided by the new host. Simply as a working hypothesis it would seem reasonable to believe that there are cells of the body which are not expendable in the usual sense of the word: if they decrease in number their disappearance is mediated by some mechanism other than the action of the scavenger cells. For these cells different rules may apply; they flourish or dwindle in response to the hormonal balance of the body. I do not want to elaborate these ideas—they are no more than indications of the way in which the basic idea of the differentiation between self and not-self can be applied to the understanding of problems of practical importance.

Serum Hepatitis

There may be phenomena of clinical importance that are related to the pre-natal phase in which the reciprocal patterns of self-markers and recognition units are adjusted. The very rare existence of two blood groups in a person who was born as one of a non-identical twin pair has been mentioned. A region where similar phenomena may be at work is in regard to the origin of serum hepatitis, perhaps the most puzzling and important of all to-day's virus diseases. It is puzzling precisely because it has no natural history and its importance to the clinician is obvious. It is not right that we should have to undertake life-saving measures like blood transfusion always with the fear that with the blood we may be giving a disease that two to three months later may provoke serious or fatal illness. As a virologist I think that nothing could make me happier than to discover a practical means of determining whether or not a given sample of blood or serum contained the virus of hepatitis.

The nearest relative of serum hepatitis (S.H.) virus is clearly the virus of infectious hepatitis (I.H.), which differs from S.H. virus, (a) in having a shorter (30 days) incubation period, and (b) in being immunologically distinguishable in tests on human volunteers. I do not know any way in which a differential diagnosis can be made on purely clinical grounds. If we are dealing with a virus, as I think we must accept, then we have to find some way in which a reasonable explanation of the presence of the S.H. virus in one person's blood and not in another's can be given. In the absence of any test for the virus, other than human inoculation, facts on which to base any speculation are few and unsystematic. There are one or two cases in which a given donor has been shown to carry the virus for years (3 years at least in one instance: Stokes *et al.*, 1954), and cases of congenital hepatitis in newborn infants are on record. On this very slender evidence we may consider the possibility that serum hepatitis is a variant of infectious hepatitis with two special qualities—(a) it has a diminished antigenicity so that it does not provoke antibody against I.H. virus and is not influenced significantly by I.H. antibody. The question of whether it can in some people provoke effective antibody against S.H. virus itself is not yet clear; and (b) in some instances S.H. virus infects the foetus *in utero* without gross damage in most instances, and such infants may become lifelong carriers of the virus in a fashion analogous to Traub's mice with L.C.M. virus infection.

This hypothesis must remain a sterile one until some laboratory test is available for the S.H. virus. I am still optimistic that such a test will eventually become available, and as soon as it does the hypothesis of uterine transmission

will become susceptible to test. In that sense at least it is a legitimate working hypothesis. Until then its only virtue is that it does provide a possible account of the survival of the virus in nature that is in reasonable accord with the available facts.

Auto-antibodies in Relation to Disease

Almost since the first recognition of allergic disease, there have been speculations about the possible role of antibodies produced against some of the body's own tissues as agents of chronic disease. The loose group of rheumatic diseases, especially rheumatic fever and acute nephritis, have been particularly considered from this point of view. In general, speculation has taken the form that a micro-organismal product reacts with some body component modifying its antigenicity (or, in our terminology, changing one of its self-markers) so that it provokes antibody production. The reaction of this antibody with either the modified or the unmodified body component results in localized damage in certain organs.

It is probably correct to say that there is no decisive evidence against this type of hypothesis but equally no direct evidence in its favour. When anyone can demonstrate a well-defined circulating antibody of the type postulated in every case of rheumatic fever tested at the appropriate period, then there will be a real opportunity for investigation.

Some of the findings that provide indications for the reality of such disease processes may be mentioned briefly.

(1) Perhaps the most important is the occurrence of acute allergic encephalomyelitis in monkeys and other animals when they are inoculated with emulsions of nerve tissue plus adjuvants in the form of killed tubercle bacilli, paraffin, and an emulsifying agent. Even homologous nerve tissue will serve, and one must postulate damaging interaction of actively produced antibody with a normal component of the body. It will be of particular interest to find whether this potential antigenicity belongs only to some components of non-expendable cells not directly concerned in the self-not-self recognition mechanism.

(2) Anti-organ sera, for example, against lymphocytes or kidney tissue produced in another species and injected into the species supplying the antigen can produce well-marked pathological changes resembling those for which auto-antibodies are postulated. This, however, is only indirect evidence, since another species produces the antibody.

(3) There are large numbers of skin-sensitizing agents—formalin, picryl chloride, etc.—which in some animals or individuals appear to combine with body proteins to give new specific antigens regarded as foreign by the body. There is some evidence that the specificity of the new antigen includes an element of specificity for the tissue involved. In guinea-pigs sensitized by painting with picryl chloride the sensitivity can be much better demonstrated in the skin than elsewhere. This supports the suggestion that if a body component is changed so as to become antigenic the antibody produced may react to some extent with the normal component.

(4) In at least one instance the action of a virus on a mammalian cell produces or uncovers a new antigen. Human red cells treated with influenza virus or an equivalent enzyme are agglutinated by a natural agglutinin without action on normal cells and provoke a new specific antibody when injected into rabbits. So far this has not been shown to have any bearing on pathological conditions associated with influenza, but again it offers a model of what might result from virus action on appropriate cells.

Conclusion

The main function of any lecture of this type must be to attempt a summary of current knowledge in such a fashion as may provide a stimulus to thought or action in those not directly and professionally involved in the study of the chosen subject. I am very much aware that

I have adopted a highly theoretical approach and that where I have touched on clinical matters it has been merely to propose a set of questions and speculations. I have provided nothing that will answer any problem of diagnosis or treatment, but I do hope that in what I have said there is a germ of something that may, in time, become important to medicine. In recent years I have become increasingly convinced of the importance of finding new approaches to the science and art of medicine. We have been wonderfully successful in dealing with infectious disease and with traumatic and mechanical injury or disability, but the deeper problems of inherited weakness and chronic functional disease have, on the whole, been approached only in superficial fashion. Advance in those fields will come from two directions: on the one hand, from an understanding of the impact of the human environment, the psycho-social impact on the functioning of the body, and, on the other hand, from a deeper understanding of the processes of inheritance and development—that sequence of replications and interactions among patterned macromolecules—one aspect of which is illustrated by the immunological phenomena with which I have been concerned.

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BONE MARROW*

BY

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In this lecture I propose to give a short account of the quantitative studies of the bone-marrow cells, upon which my colleagues and I have been engaged for the past few years. Since our attention was first directed to the bone marrow by our studies on lymphocyte production, a brief review of these earlier studies may not be out of place, both as an introduction to our bone-marrow work and as an indication of the way in which our ideas have developed.

Lymphocyte Production

Lymphocytes are being continually produced in the lymphoid tissues and thence entering the blood stream. They may obtain access to the blood either indirectly by first of all entering the lymph, in which they are finally discharged into the blood through the thoracic and right lymph ducts, or they may reach the blood directly by passing through the endothelium of the blood capillaries in lymphoid tissue. It is probable that the overwhelming majority of the lymphocytes reach the blood indirectly via the lymph stream, for in the few experiments in which complete lymphatic obstruction has been brought about (Blalock *et al.*, 1937) the blood lymphocytes fall practically to zero. If the lymphocytes were entering the blood directly in large numbers, one would not expect this to be the case. At any rate, whatever may be the number of lymphocytes which enter the blood stream directly, we have no simple way of measuring them. The lymph-borne lymphocytes, on the other hand, can be readily estimated by cannulating the thoracic and right lymph ducts, immediately before they enter the blood. In actual practice, it should be added, most observers have cannulated the thoracic duct only.

*A postgraduate lecture delivered at Dundee on February 25, 1954.