INFECTIOUS AGENTS AND HOST REACTIONS

Edited by

STUART MUDD

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Preface

Investigation of infectious agents and host reactions during the past half century has undergone a rapid evolution, with emergence and growth of numerous and flourishing subspecies of research interest and teaching emphasis. Some observers of the changing scene have expressed concern lest intense preoccupation with specialized aspects, however essential for advancing frontiers through research, should limit the knowledge and insight of our young scientists and medical practitioners into diseases as holistic phenomena. It is with such a concern that the Editor of this volume has appealed to colleagues whose professional lifework has been investigation of infectious diseases in depth. The response of these colleagues has been magnificent, as a close study of the chapters of this volume will make clear.

My hope for this book is that it may help to bring into focus the ecology of parasitic disease in its great breadth and depth: that one may imagine with Sir Macfarlane Burnet and Robert Good the origin of adaptive immunity in the surveillance of inimical somatic mutations; that one may perceive as an integrated whole the mechanisms of immunity through activated cells of the lymphocytic system and through circulating antibodies, mechanisms subtle and complex, yet exquisitely coordinated in the total defense of the macroorganism; that one may follow the diverse adaptations of microparasites toward coexistence in the ecosystem of the host, from those of free-living bacteria to those of the viruses which can subvert and exploit the synthetic machinery of host cells.

This hope must be tempered with realism, however. For it would, indeed, be naïve to suppose that one book could deal adequately with all aspects of parasite-host interaction. The present volume, for instance, gives inadequate attention to genetic factors of either parasite or host in relation to resistance to disease.

Another significant modulating influence on resistance to which little attention has been directed in the present volume is the homeostatic influence of the endocrine system on the reticuloendothelial apparatus, which is of such critical importance in resistance. A long series of studies of modulation of reticuloendothelial function by endocrine action has been published by Pro-

fessor T. Nicol and his collaborators at the University of London (Nicol, T., et al., J. Endocr. 1964, *30*:277–291; 1965, *33*:365–383; 1966, *34*:163–178, 377–386).

Nicol, Vernon-Roberts, and Quantock have written (Nicol, T., B. Vernon-Roberts, and D. C. Quantock. 1966. Effect of orchidectomy and ovariectomy on survival against lethal infections in mice. Nature *211*:1091–1092): "The present results provide additional evidence in support of our earlier postulate that oestrogen is the principal natural stimulant of bodily defence in both the male and female, and further that oestrogen treatment would seem to be of clinical value in the treatment of acute bacterial infections." Broad though present horizons are in relation to the ecology of disease, obviously the horizons open to future exploration are far broader.

Editing this volume has, indeed, been a learning experience. Certainly the most striking lesson to me has been to appreciate that resistance to infectious disease is a far more inclusive complex of interrelated factors than ordinarily realized. Explicitly I, and obviously many others of my generation of teachers and investigators, have tended to think of resistance as *essentially* a function either of circulating antibodies or of activated reticuloendothelial cells. Examples of the former are pneumococcal pneumonia, in which the "crisis" occurred, at least in preantibiotic days, when measurable anticapsular antibodies appeared in the circulation, or measles, in which the clinical disease can be ameliorated or aborted by injection of gamma globulin. The prime example of essentially cellular immunity has been tuberculosis (although less orthodox views about tuberculosis are expressed in Chapter 10 by Dr. Gardner Middlebrook). A modern integration of mechanisms of host resistance is of course presented in the opening chapters of this volume.

Consideration of the chapter by two eminent investigators of streptococcal infection, Drs. Ann G. Kuttner and Rebecca C. Lancefield, is illuminating. In their chapter, "Unsolved Problems of the Nonsuppurative Complications of Group A Streptococcal Infections," two clinical diseases are dealt with: rheumatic fever and acute glomerulonephritis. With respect to the pathogenesis of acute glomerulonephritis the following pertinent facts are brought out.

Outbreaks of acute glomerulonephritis in many parts of the world have been found to be due to specific nephritogenic serotypes of Group A streptococci. These nephritogenic strains fall into five serotypes of the known 55 serotypes of Group A streptococci. Antibodies of the specific nephritogenic type have been found "bound to electron-dense deposits in the glomerular tissue of nephritic patients, but no binding was noted in the glomerular tissues obtained from normal individuals or from patients with other types of renal disease." The reaction with the glomerular basement membrane "is accompanied by marked decrease in serum complement and an accumulation of polymorphonuclear leukocytes which conjointly may be responsible for the disease and is considered to be the cause of the renal lesion." The attack of acute glomerulonephritis is preceded from 7 to 21 days by infection of pharynx or skin by a nephritogenic strain of Group A streptococcus, but, in contrast to rheumatic fever, prior sensitization of the patient is not required. There is complete recovery.

These facts, in the minds of the authors (and the Editor), clearly lead to the conclusion that acute glomerulonephritis is caused by reactions of an antigen

on the glomerular basement membrane with specific antibody, followed by accumulation of complement and polymorphonuclear leukocytes and damage to the membrane.

In contrast to glomerulonephritis, the following pertinent facts are presented with reference to rheumatic fever.

Rheumatic fever may be brought on by successive attacks of pharyngitis by any of the known 55 serotypes of Group A streptococci. Prior sensitization of the individual is essential. Serum complement is normal. Prophylaxis is mandatory to prevent recurrent attacks. Attempts to immunize either human subjects or rabbits with various nonliving products of Group A streptococci have not produced rheumatic fever. However, the authors were unwilling to commit themselves to any explicit hypothesis regarding the pathogenesis of rheumatic fever.

I venture to carry this discussion a step further. Kaplan and associates and Zabriskie, Freimer, and Seegal have demonstrated cross reactive antigens between Group A streptococcal cells and human heart tissue. Chase and Rapaport (Chase, R. M., and F. T. Rapaport. 1965. The bacterial induction of homograft sensitivity. I. Effects of sensitization with Group A streptococci. J. Exper. Med. *122:*721–732) have sensitized guinea pigs to Group A streptococci of various serotypes and shown that such sensitized animals reject skin homographs in a manner which is indistinguishable from that which results from sensitization with homologous tissues. Sensitization with streptococci of Lancefield groups B, C, D, E, G, H, L, and O or pneumococcus types II, III, and XIV was ineffective in inducing such graft rejection (Rapaport, F. T., and R. M. Chase. 1965. The bacterial induction of homograft sensitivity. II. Effects of sensitization with staphylococci and other microorganisms. J. Exper. Med. *122:* 733–744).

Taking all these observations together, I venture to propose the hypothesis that rheumatic fever is mediated by a phenomenon essentially resembling graft rejection. The prior attacks of streptococcus pharyngitis sensitize the subject to one or more antigens of the streptococcus which cross react with heart tissue, and the precipitating streptococcal pharyngitis induces both immune reaction to the streptococcus and a reaction of rejection against heart tissue, which has an antigenic determinant in common with streptococci of Group A (cf. Rapaport, F. T. 1967. Heterologous cross-reactions in mammalian transplantation, and discussion following. *In:* Trentin, J. (Ed.): Cross-Reacting Antigens and Neoantigens. Williams & Wilkins Co., Baltimore).

Viewed in this way, the nonsuppurative complications of streptococcal infection would seem to fall essentially into two categories: (1) classic antigen-antibody-complement reactions in acute glomerulonephritis, and (2) reactions of rejection essentially cell-mediated (see Chapter 2) in rheumatic fever.

Circulating antibodies are enormously useful in the diagnosis of infection by viruses. Moreover the efficacy of immunization procedures against viruses is often evaluated in terms of antibody titers (Chapter 5). However, viruses are obligate intracellular parasites. What of delayed hypersensitivity, and the ability of cells of the lymphoid-macrophage system to inactivate intracellular disease agents? Practical measures in immunizing against viral infections got off to quite a dramatic start with reference to hypersensitivity:

"It is remarkable that variolous matter, when the system is disposed to reject it, should excite inflammation on the part to which it is applied more speedily than when it produces the Small Pox. Indeed it becomes almost a criterion by which we can determine whether the infection will be received or not. It seems as if a change, which endures through life, had been produced in the action, or disposition to action, in the vessels of the skin; and it is remarkable too, that whether this change has been effected by the Small Pox, or the Cow Pox, that the disposition to sudden cuticular inflammation is the same on the application of variolous matter." (Jenner, E. 1798. An Inquiry into the Causes and Effects of the Variolae Vaccinae. London, p. 13.)

Is something of vital importance being underemphasized in modern virological lore? Dr. Allan Downie in Chapter 21 indicates that the pox viruses of animals and smallpox virus in man multiply during the incubation period in the reticuloendothelial cells of lymph glands, spleen, liver, and bone marrow. In the opening chapters of this book it is emphasized that the efficacy of the reticuloendothelial defense can be significantly augmented by first inducing a state of delayed hypersensitivity and then activating with homologous antigen. The macrophages thus activated are nonspecifically effective in the destruction of intracellular disease agents. Can this nonspecific mechanism be exploited against viruses which have a multiplication period in the reticuloendothelial system?

We have obtained a positive answer in one trial system. Mice rendered hypersensitive to tuberculosis by H37Ra and further stimulated by O. T. injections are being shown to be significantly more resistant to vaccinia virus than control mice. (Mudd, S., P. Zappasodi, and J. H. Taubler. 1969. Bact. Proc. M16.)

As Editor I express my profound appreciation and gratitude to the authors who have contributed so richly to this volume, and I think it is not too much to believe that a generation of teachers, investigators, and students will share this gratitude for these records of experience and insight into the interaction of parasite and host.

STUART MUDD, M.D.

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Chapter 1

THE NEWER IMMUNOLOGY: AN EVOLUTIONARY APPROACH

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THE CHANGING ACCENT IN IMMUNOLOGY

My first published investigation was on the H and O agglutinins present in the serum of typhoid fever patients (Burnet, 1924) and ever since then I have been deeply interested in immunology. Immunological memory fascinated me from the beginning and I remember in 1923 covering sheets of paper in an attempt to apply Semon's mnemic theroy of memory to immune phenomena. So I can claim to have had an open and enquiring mind on the subject as well as a ringside seat from which to watch the development of immunology over 45 years. Changes in outlook have been as deep seated as in any other field of medical science over the wonderful years since 1920.

In retrospect there have been striking changes during that period in the topics which on the one hand guided the practical applications of immunology to medicine and, on the other, held the center of the stage for scholarly investigation. At the practical level, immunization against diphtheria dominated the picture from 1922 to 1930, with serum treatment of pneumonia probably coming next in importance in that decade. In the 1930's the use of serological methods to elucidate the epidemiology of yellow fever and the development of a live virus vaccine probably held most attention. Other virus infections, notably influenza, also became susceptible to immunological study in the late 30's and 40's and the concept of immunological drift as a factor emerged. In 1940, Landsteiner and Wiener discovered the Rh antigen and the rapid elucidation of hemolytic disease of the newborn followed. Blood transfusion became a standard type of treatment and a vast collection of immunological

anomalies and catastrophes became known. With the development of tissue culture techniques a whole new world of possibilities in preventing viral disease arose in the early 1950's with the Salk vaccine against poliomyelitis and tissue culture titration of poliomyelitis antibody as the first fruits. Since 1960 the growing edge of practical application has turned to renal transplantation and the immunosuppressive drugs, and on the other side of the same coin, as it were, to the study and chemotherapeutic treatment of autoimmune disease.

Laboratory investigations have gone in parallel with the practical topics but have had many other interests, some of which at one time or another tended to dominate activity. One may mention the great increase in the study of transplantation that followed the discovery of experimental immunological tolerance by Medawar's group in 1953 (Billingham, Brent, and Medawar, 1953). Similarly, the thymus suddenly became the center of immunological interest with Miller's work on neonatal thymectomy in 1961.

One can almost sum up the situation in half a dozen sentences. Immunology was born from the demand for protection against infectious disease. Effectively what was needed has been provided. Today, immunology is concerned essentially with the way the normal body maintains its structural and biochemical integrity, how that integrity can be broken down by autoimmune disease and the various forms of malignancy, and how methods to counter these calamities may be devised. At a more active level the challenge of organ transplantation has now been accepted. Here the problem is how to circumvent the normal processes of immune homeostasis and compel the body to accept an alien tissue.

My objective in this essay is to attempt to present to readers interested in the way immunology has developed over the last 30 or 40 years, a tentative picture of the place of immunology in relation to living function in general, in other words, to express the nature and development of adaptive immunity in evolutionary terms. I believe that in the last few years it has become possible for the first time to approach such a discussion with the feeling that there are at least *some* facts on which it can be based. There is also the progressive acceptance as a theoretical basis of the genetic origin of immune pattern in antibody. Throughout this chapter I am adopting the approach which emerged as the predominant one at the Cold Spring Harbor Symposium on Antibodies in June, 1967. It was expressed both in my opening remarks and in Jerne's final summary at that meeting. I still prefer to think of that approach as clonal selection theory but others would prefer it to be called simply the modern genetic approach to antibody pattern. A full account of my own elaboration of the approach can be found in *Cellular Immunology* (Burnet, 1969).

THE PHYLOGENETIC APPROACH

Limitations of Adaptive Immunity to Vertebrates

The most important finding of comparative immunology is that adaptive immunity is confined to the vertebrates. No invertebrate produces antibody

and when tested by a suitable technique any invertebrate will accept tissue from another individual of the same species as readily as autologous tissue.

Invertebrates must exist in the same world as vertebrates, amidst a myriad of pathogenic and potentially pathogenic microorganisms. In general they survive like vertebrates without overt evidence of infection.

It seems logical, then, to look at the evolutionary origin of the apparatus of immunity as being initiated by some other need than protection against infection by microorganisms. Judging, as we must, by the reactions of modern forms, the appearance of immune apparatus came early in vertebrate history. Of the two existent groups of agnathous vertebrates, hagfishes and lampreys, the first show no evidence of any antibody production. The lamprey has produced agglutinins to *Brucella* and rejected homografts. In crude form it shows, according to Good and Papermaster (1964), all the essentials that go with adaptive immunity—immunoglobulin, circulating lymphocytes, and a thymus-like structure in the pharyngeal region. All cartilaginous and bony fishes conform much more closely to the standard vertebrate pattern. Elasmobranchs have immunoglobulins of 19S and 7S types although these are antigenically similar and probably correspond essentially to mammalian IgM (Marchalonis and Edelman, 1965). Lymphocytes are readily recognizable and there is a thymus. Antibody production is poor by mammalian standards in all cold-blooded animals but homograft rejection is very well marked in those bony fishes in which it has been tested. There is a hint here, to be developed in later pages, that the capacity to produce antibody is a later development arising from a basic mechanism that is expressed experimentally in the phenomena of homograft rejection, and is mediated wholly by cells.

Immunoglobulin production has been well established in the fishes and there is already some evidence of a progressive complexity and effectiveness of the antibody mechanism as we come up to the higher mammals. When laboratory methods of determining amino acid sequences in antibody chains have developed a little further, they should provide almost a precise picture of the evolution of the immunoglobulins. In principle the plasma proteins of all the forms from hagfish to man are available for study. A full series of mammalian K and L light chains and their evolutionary precursors could provide data of unique evolutionary interest. It is already evident that the type L light chains of mice have an amino acid structure quite strikingly similar to that of L light chains of man (Kabat, 1967).

It is very clear that the evolution of the adaptive immune system—the thymus, lymphocyte, immunoglobulin, antibody, plasma cell system—did not mean the disappearance of the invertebrate system of defense against microorganisms. Polymorphs and macrophages are still vital for mammalian defense and those subtle and complex functions of blood and blood vessels that deal with hemorrhage and minimize infection after superficial trauma are at the same time essential and virtually unrelated to adaptive immunity.

The art of the theoretical immunologist—if we can use such a phrase—is to unravel the evolutionary story of how and why adaptive immunity appeared and to interpret the progressive mutual coordination and interaction of the primitive and the new systems. It is a program of pure biological research which might cause eyebrows to be lifted today. But if we allow our-

selves a little unfashionable optimism it may yet prove to be a typical major topic for academic study in the affluent years ahead when scholarly work need no longer be judged by its apparent relevance to human needs.

The Origins of Adaptive Immunity

In the absence of a great corpus of scholarly work on comparative immunology we are reduced to speculation, and what logic is possible, in dealing with the sparse experimental material we have. If, when primitive vertebrates began to develop to the stage represented by the modern lamprey, there was no new need for defense against microbial infection, we have to look for some other basic function that the immune mechanism was "invented" by nature to fulfill.

The first answer to that question was suggested by Thomas in 1959. In the laboratory, immunological research is concerned with models of natural infection by microorganisms, and with a great variety of manipulation which has no direct bearing on any aspect of mammalian life that could have had evolutionary significance—such things as the injection of alien blood and of artificial antigens and adjuvants, and transplantation of tissues or organs from other races or species. In looking for immunologically significant phenomena which might have an evolutionary relevance, Thomas seized on two, the relation of fetus to mother in placental mammals and the very widespread vertebrate character of susceptibility to spontaneous malignant disease.

Placental reproduction evolved late in vertebrate history long after the appearance of immunoglobulins and the rest. Adaptive immunity clearly did not evolve as an answer to the problems of placentation and we are left with the possibility that malignant disease or its equivalent was in some way concerned. Strictly speaking we should be seeking evidence for such a hypothesis in lampreys and sharks rather than in laboratory mammals but we know vastly more about mice than about dogfish. Both mice and goldfish reject a transplant of foreign skin or scales and show accelerated rejection on a retest with tissue from the same donor. Such homograft immunity has two necessary aspects. On the one hand, each individual of a species has its characteristic pattern of histocompatibility antigens which is in general distinct from that of any other individual. When two individuals are derived from the same zygote, as in human identical twins, the antigens will be the same, but in any other natural circumstances the chances of all antigens being the same is vanishingly small. Animals artificially bred as pure line strains are of immense importance as laboratory tools but they are outside the order of nature. The second complementary aspect is that each individual can recognize at least one antigen in any other individual as foreign and produce specifically patterned immunocytes or antibodies against it. Since transplantation of normal tissues is something unknown in vertebrate evolution we have to seek some logic for this two-sided capacity to assert individuality. In a slight elaboration of Thomas's point of view I have looked for the source of the evolutionary initiative in changes that were bound to develop in the genetic situation of somatic cells when animals became larger, lived longer, and developed more elaborate and labile mechanisms for differentiation

(Burnet, 1962). Under such circumstances, somatic mutation in the broad sense introduces both new dangers and the potentiality of dealing with these dangers.

Somatic mutation, used in a broad sense to include both point mutation and any other chromosomal anomalies that are inheritable and randomly occurring, must be frequent in any large long-lived animal species. By far the most likely explanation of most malignant conditions in man is that they arise by a process of sequential somatic mutation (see Burnet, 1957b). For the present it is reasonable to take malignant disease as the natural danger which adaptive immunity evolved to counteract. There were two basic requirements needed to minimize the biological significance of malignant disease. The first was a lability, in the germ cell line, of the genes concerned with the detailed structures of the lipoprotein surface of somatic cells —the molecular structures which we now speak of as histocompatibility antigens. A high degree of neutral polymorphism in the genetic sense could so develop. The second requirement was that the capacity of the wandering mesenchymal cells to recognize gross foreignness be sharpened so that mutant cells within the body could be recognized and effectively dealt with. One can dramatize the situation by saying that without these two characteristics all superficially located malignant disease would be contagious, particularly to the young.

On this view the initial capacity to arise would be an ability of wandering cells, lymphocyte progenitors, to react with any surface component of another cell that could be recognized as foreign. The beginning of adaptive immunity, on this view, was initially an adaptation of cell surface to recognize anomaly in another cell surface. This may be a general statement of considerable importance for the understanding of a number of immunological fields. It is underlined by recent work in which it has been shown that if cells as disparate as HeLa cells and mouse lymphocytes can be induced by Sendai virus to abrogate surface activity and become heterokaryons, the nuclei flourish in the composite cytoplasm and may even fuse to form a hybrid nucleus (Harris, 1966). Cellular incompatibility is wholly a surface matter.

HOMOGRAFT REJECTION AND DELAYED HYPERSENSITIVITY

Most immunologists are willing to recognize the close similarities or analogies of homograft immunity and delayed hypersensitivity. Both are associated with cells and there is little or no evidence that antibody plays a significant part in either.

If ideas of cell to cell contact can provide an evolutionary basis for adaptive immunity they are obviously relevant to the phenomena of delayed hypersensitivity. I have developed this approach extensively in another context (Burnet, 1969) and believe that it can cover in an interesting fashion the phenomena as observed by conventional techniques in man and the common laboratory animals.