ADVANCES IN
Immunology

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PREFACE

The fourth volume of *Advances in Immunology*, like its predecessors, contains reviews which range over the whole field of immunology, from a study of the biological origins of specific immunologic responses, through various aspects of their protective and pathogenic effects, to the present knowledge of the chemical structure of antibodies. We think that by including contributions of so wide a range, we not only recognize the very broad approach of immunologists to their subject but also acknowledge its fundamental unity. For example, the problems of the complexity of the immunoglobulins, on which chemical and genetic analyses are now beginning to shed light, are intimately bound with those of their evolutionary and cellular origins and their biological functions. This is one of the main reasons why immunology fascinates those who study it.

The first chapter by Robert A. Good and Ben W. Papermaster provides a comprehensive review and comparison of the ontogeny and phylogeny of adaptive immunity. It deals with the acquisition of passive and active immunity by the developing fetus in relation to the phylogenetic development of active immunologic responses and relates immunologic capacity to the function of the thymus and of the bursa of Fabricus—a study which is ripe for review and in which the group at Minnesota has played a notable part. The second chapter by E. Suter and H. Ramseier concerns the killing of parasites by phagocytic cells and discusses the evidence for the existence and importance of mononuclear phagocytes which have an enhanced capacity to destroy intracellular parasites, apart from recognizable assistance by specific antibodies. The possible connection between such cellular immunity and delayed-type hypersensitivity is a matter of great practical interest. Current knowledge of the chemistry of cell wall antigens of gram-positive bacteria is reviewed in the fourth chapter by M. McCarty and S. I. Morse. In contrast to the soluble capsular antigens, especially those of pneumococci, the true cell wall antigens have only relatively recently been available in undegraded form suitable for chemical and immunochemical analysis; and even now it is mainly the carbohydrate and teichoic acid rather than the protein components which have been studied. Since the cell walls appear likely to provide the best source of immunizing antigens, a review of their structure should be timely as well as interesting. The fact that bacteria and their products can affect immune responses other than by acting as a source of antigenic materials has been recognized for many years. In the last chapter J. J. Munoz has

drawn together much relevant information concerning the adjuvant effects of mycobacteria, the action of endotoxins of gram-negative bacteria on antibody responses, and the peculiar activity of *Bordatella pertussis* in enhancing anaphylactic sensitivity in rodents. Although none of these actions has a satisfactory explanation, the reader will find a full account of the attempts to provide one.

The third chapter by J. D. Feldman, Ultrastructure of Immunologic Processes, shows how electron microscopic studies have verified visually some immunologic processes whose nature was already surmised and have deepened our understanding of others, notably of the pathologic consequences of antigen–antibody interaction in the renal glomerulus. H. G. Kunkel and E. M. Tan, in their review on Autoantibodies and Disease, provide both an up-to-date account of the autoantibodies which have been discovered in autoimmune diseases and a comparison of the reactivity against the Gm groups on human γ-globulin of rheumatoid factors on the one hand with the "serum normal agglutinators" on the other. The latter are thought to often arise as a result of isoimmunization of the fetus by maternal γ-globulin. This chapter includes a discussion of the possible beneficial as well as pathologic effects of certain autoantibodies.

Finally, S. Cohen and R. R. Porter have contributed a clear and full review of the Structure and Biological Activity of Immunoglobulins which discusses not only the evidence supporting the current views of the structure and linkages of the four recognized chains of immunoglobulins, the positions of their various genetic markers, and the nature of the antibody-combining sites, but also considers the mounting indirect evidence for the existence of two separate chains within the A or heavy chain.

We are deeply grateful to the authors for the effort which they have put forth into making their chapters both informative and stimulating and to the publishers and printers for maintaining their high standards of presentation; we are confident that this volume will prove to be at least as useful as its predecessors.

September, 1964

F. J. Dixon, Jr.
J. H. Humphrey

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Ontogeny and Phylogeny of Adaptive Immunity[1]

ROBERT A. GOOD[2] AND BEN W. PAPERMASTER[3]

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I. General Introduction

Although we recognize as hazardous an attempt at a critical review of the broad field we have chosen and appreciate the special treachery of writing a review of the subject during the period of its most rapid change, our own pressing concern with developmental immunobiology permits us to address this task. It seems to us that understanding of the origin of immunity in both ontogenetic and phylogenetic terms could well be a basis of operational answers to some of the most basic questions of immunology, as well as approaches to manipulation and control of immunologic processes. Already observations are at hand which

[1] Original studies included were aided by grants from the U.S. Public Health Service, The National Foundation, the American Heart Association, Minnesota Heart Association, and the Minnesota Division of the American Cancer Society.

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sketch out a sequence of events in the ontogeny of immunologic responsiveness and which suggest that true adaptive immunity is a characteristic only of vertebrates. These findings suggest further that the thymus plays a key role in both the ontogenesis and phylogenesis of the specific adaptive process which we recognize as immunity.

In spite of the popularity of theorizing about the nature of the immunologic process (Mudd, 1932; Pauling, 1940; Haurowitz, 1952; Jerne, 1955; Talmage, 1957, 1959; Burnet, 1959; Lederberg, 1959; Karush, 1962), neither instructive nor selective theories have yet led to experiments that establish the nature of antigenic stimulation. Further the concept that specific immunologic negativity is based on a single mechanism (Mariani *et al.*, 1959; Martinez *et al.*, 1959; Medawar, 1961; Michie and Howard, 1962), rather than taking many forms, demands even more that these phenomena be fully explained in operational terms. Both of these central problems in immunobiology, the nature of specific positive immunologic adaptation and the nature of specific negative immunologic adaptation, seem approachable in a most direct manner through an analysis of the development of immunologic reactivity. Considerations of ontogeny and phylogeny raise basic questions concerning the process of cell adaptation and the essential role of the immune response in the body economy.

Certainly, to consider these problems effectively in this review, it is necessary that we define our conception of the immune response. The group of defenses historically considered to be in the category of acquired, specific, immune responses are those that were distinguished from innate protective mechanisms at the end of the 19th century by such workers as Pasteur (1881), Metchnikoff (1905), Behring and Kitasato (1890), Nuttall (1888), and Ehrlich (1892). The classical acquired, immune response is antitoxin formation (Behring and Kitasato, 1890). During subsequent investigations allergic reactions were defined (von Pirquet, 1906) and grouped into immediate and delayed types (reviewed by Chase, 1958; Lawrence, 1956). Both forms of hypersensitivity are clearly representative of acquired immune responses. Finally, homotransplantation immunity has been shown to be a manifestation of acquired immunity (Medawar, 1943, 1944, 1945; reviewed by Lawrence, 1959). In the mammal, all these responses (antibody formation, immediate allergy, delayed allergy, and homograft immunity) are well developed. All encompass specific recognition of antigenic structural patterns; some—and perhaps all—are based on active secretion of specific globulin molecules; and each is activated with the development of a pattern of specific memory or anamnesis.

The cellular basis for acquired immunity is the lymphoid family of

cells, as first postulated by Pfeiffer and Marx (1898) and L. Deutsch (1899). From the studies of Nossal and Mäkelä (1962) and Mäkelä and Nossal (1962), reviewed by Nossal (1962), and those of Urso and Makinodan (1961), and Vazquez (1961, 1964), it is clear that adaptive immunity is essentially a proliferative process, also involving cellular differentiation. Pathologic (reviewed by Good, 1957a), cytologic (Kolouch, 1938; Bjørneboe and Gormsen, 1943; Fagraeus, 1948), histochemical (Ehrich *et al.*, 1949; T. N. and S. Harris, 1949), immunohistochemical (Coons *et al.*, 1955; Leduc *et al.*, 1955), and tissue culture studies (Nossal, 1958, 1959a,b, 1960) inextricably link the proliferative process of immunity to the lymphoid system of cells. The consideration of ontogeny in mammals, as well as consideration of the phylogeny of immunity, of necessity becomes, at least in part, a study of the ontogeny and phylogeny of the development, distribution, morphology, and adaptive potentialities of the lymphoid cells. The lymphoid system of cells is a system that develops and differentiates relatively late in the ontogenetic and phylogenetic sequences. Thus, it will be shown in this review that *adaptive immunity*, which we are here considering, although perhaps having roots in more primitive processes, is primarily a function achieving full expression late in phylogeny and ontogeny.

Recently, Burnet (1959) has referred to this system of cells as "immunologically competent cells," and still more recently, Dameshek (1964) used the term "immunocyte" to describe the elements of this line. Whatever terminology ultimately holds sway, it is important to recognize that this system of cells represents an advanced stage of evolutionary adaptation for specific reactivity. The most prominent functional characteristic of these cells is their highly developed capacity to react to antigens, to proliferate in the presence of antigenic stimulation and, as a line of cells, to remember prior experiences with antigens.

In this review, we shall be concerned primarily with the origins of immunity as a biologic phenomenon embodying primary and secondary responses, with antibody synthesis and release, reactions of immediate and delayed allergy, and homograft immunity. We shall not concern ourselves with a whole host of other complex mechanisms of defense such as natural antimicrobial factors, enzymes in body fluids, polyelectrolytes capable of electrostatic interaction, complement, and phagocytosis. Some of these defense mechanisms have been reviewed in recent years (Suter, 1956; Skarnes and Watson, 1957), and the comparative aspects of some of these have been considered (Huff, 1940; Bisset, 1947; Cushing and Campbell, 1957; Sirotinin, 1960).

By using this relatively narrow definition of immunity, which we

prefer to call adaptive immunity, we may, of course, be avoiding a central issue, namely, the basic origin of this process or these processes in other bodily activities such as those involving protein synthesis, protein-protein interactions, transport mechanisms, and functional complementarity of macromolecules. This question concerning the basis of adaptive immunity in pre-existing physiologic processes is, we believe, a separate question, which at this moment has been too little studied and is far too speculative for review.

We shall attempt to consider the ontogenesis of immunity in terms of the following relationships and processes: interrelationship of fetus and mother, particularly serum immunoglobulin and antibody transfer; the beginning production of immunoglobulins during fetal and neonatal life; the origins of antibody-producing capacity and ability to initiate and express delayed allergic responses; the development of capacity for homograft rejection and the decrease of susceptibility to production of tolerance in the fetal and neonatal period; and the key role of the thymus and other central lymphoid tissue in the ontogeny of the lymphoid system and adaptive immunity. Further, we shall summarize present knowledge of the phylogeny of immunity and attempt to show that, here too, the development of the lymphoid system, particularly the thymus, plays a key role in development of the potential for adaptive immune response.

II. Ontogeny of Immunity

A. Relationship of Fetus to Mother

The developing fetus in mammals is essentially in the position of a well-tolerated homograft. Abundant evidence is at hand (reviewed by Greene, 1955; Nace, 1955, 1957; Woerdeman, 1955; Goldstein and Baxter, 1958) that the embryo and fetus develop characteristic individual specificity at an early stage of development and, thus, should be rejected by the mother were normal transplantation immunity to operate. Such a reaction does not regularly occur. Although the well-known lack of immunologic reactivity during early fetal life and the effective separation of the fetus from the cells of the maternal circulation preclude reactivity in the direction of fetus toward maternal antigens, the mechanisms by which rejection of the fetus by the mother is avoided are far from clear. The fetal membranes appear in some species to be lacking certain transplantation antigens (Hašková, 1961); however, studies by Dancis *et al.* (1962) suggest that both transplantation immunity and immunologic tolerance can be induced by injection of placental cells. It seems possible from available data that the placental membranes in this situation

function as does the membrane of the hamster's cheek pouch in the studies of Billingham *et al.* (1960). Their experiments have shown that skin homografts to which the hamster was completely reactive at a skin site were well tolerated when the cheek pouch membrane was interposed between the graft and connective tissue bed. If this is, indeed, the basis for toleration of the fetal transplant by the maternal host, it would be essential that the fetal membranes themselves lack effective transplantation antigenicity; then the source of the antigenicity demonstrated in the studies of Dancis *et al.* (1962) would have to be blood cells or cells on the fetal side of the membrane. Whatever its mechanism, it remains that the fetus is a homotransplant usually well tolerated without evidence of rejection. There can be no question that in spite of the effective separation of maternal and infant serums, cells with antigenic characteristics foreign to the mother occasionally gain access to the maternal circulation, giving rise to an immune response, transmission of the antibody to the fetus, and a destructive attack on fetal cells. Red cells (Pickles, 1949), platelets (Shulman *et al.*, 1962; Vandenbroucke and Verstraete, 1955; Schoen *et al.*, 1956), and white cells (Stefanini *et al.*, 1959; Hitzig, 1959), are known to accept the brunt of such immunologic attack in man. That maternal cells may gain access to the fetal circulation has also been demonstrated (Lee and Vazquez, 1962), and it has been postulated that such transfers account for the more favorable treatment of maternal skin grafts by offspring (Peer, 1958), and might, under unusual circumstances, provide a basis for cellular chimerism and graft–versus–host reactions as a basis for human disease. Studies by Lengerová (1957), Nathan *et al.* (1960), and Najarian and Dixon (1963) have shown that manipulations designed to alter the permeability of the placenta result in a high incidence of tolerance to reciprocal skin transplants of mother and offspring.

B. The Immunoglobulins

Electrophoretic analysis, coupled with immunologic studies, established that, of the proteins of the serum, those with the lowest charge density at neutral or slightly alkaline pH are those that contain the bulk of the circulating antibodies (Tiselius and Kabat, 1939). These antibody-containing globulins, the γ_2- and the γ_1- or β_2-globulins, can be further divided into a low molecular weight component(s), 7S, and a high molecular weight component, 19S, on ultracentrifugal analysis (H. F. Deutsch *et al.*, 1946). With the introduction of immunoelectrophoretic techniques by Grabar and Williams (1953), it became clear that four immunochemically distinct fractions comprise the γ_2 and β_2 components.

These include the classical γ_2-globulins, which are a single, immunochemically identifiable family of protein molecules with electrophoretic mobility extending from the slowest migrating serum protein constituents as far as the α range on electrophoresis (Grabar, 1956); the β_{2M} (γ_{1M}) component, which has been shown to be the same as the 19S or γ_1-macroglobulin fraction (Burtin *et al.*, 1957); and the β_{2A} (γ_{1A}) fraction which is said to have a sedimentation constant of 7S and to be characterized by a high carbohydrate concentration (Heremans *et al.*, 1959). The β_{2M}- and γ_2-globulins are known to contain antibodies, and some evidence is at hand that the β_{2A} component also contains antibodies (Fireman *et al.*, 1963).

The 7S or γ_2-globulin possesses the bulk of the circulating antibodies, among them virus-neutralizing antibodies, precipitating antibodies, complement-fixing antibodies, antidiphtheria and antitetanus antibodies, incomplete hemolysins, hemagglutinins, and such agglutinating antibodies as antiflagellar antibodies (Enders, 1944; H. F. Deutsch *et al.*, 1946; reviewed by Fahey, 1962). The β_{2M} (γ_{1M}) or 19S globulin contains such antibodies as Wassermann reagins (B. D. Davis *et al.*, 1945), heterophile antibodies (Kunkel, 1960), rheumatoid factor (Franklin *et al.*, 1957), cold agglutinins (Gordon, 1953), isohemagglutinins (Pedersen, 1945), and other agglutinins such as antityphoid O (H. F. Deutsch *et al.*, 1946). The β_{2A} fraction is less well understood; but evidence is beginning to accumulate that this is the protein containing the heat-labile skin-sensitizing allergens (Rockey and Kunkel, 1962; Fireman *et al.*, 1963; Heremans and Vaerman, 1962).

A fourth constituent which appears in the immunoglobulin area on immunoelectrophoresis, but is less clearly classifiable as an immunoglobulin, is the γ_X of Heremans (1960), subsequently defined as C-reactive protein. The behavior of this protein in specific protein-protein interactions may justify its classification as an immunoglobulin; however, since this protein, unlike the other immunoglobulins, behaves as an acute phase reactant, it will not be considered in any detail in this review. Because of clear differences in the developmental biology of these separate protein fractions, it has been necessary, in considering the development of immunologic potential, to bear in mind the three separate components of this family of immunoglobulins.

C. Passive Transfer of Immunoglobulins to Developing Embryo

Although proteins, produced for the most part by the liver (L. L. Miller and Bale, 1954), appear in the serum at an early stage, no species thus far studied produces demonstrable amounts of immunoglobulins

during normal fetal life. Instead, an elaborate complex has evolved by which antibody-containing proteins are transmitted to the fetus and to the newly hatched or newly born animal. In the chicken, the antibody-containing β-globulins are transmitted from the hen to the ova 4–5 days before ovulation via the follicular epithelium (Patterson *et al.*, 1962) and then to the blood of the embryo late in incubation via the yolk sac (Weller and Schechtman, 1957, 1962). In the porcine and bovine species, probably because of the highly developed placental membrane structure (Mason *et al.*, 1930), no immunoglobulins whatever are transmitted to the fetus during gestation, and, since none are produced by the fetus, these animals are entirely lacking in antibodies and γ-globulin at birth. However, antibody-containing lactoglobulins are delivered in high concentration into the colostrum and thence gain access to the circulation of the neonate which remains highly permeable to protein for several days after birth (Mason *et al.*, 1930; Hansen and Phillips, 1949; McCarthy and McDougall, 1953). The permeability of the gut for protein in newborn calves is not entirely selective (Bangham *et al.*, 1958b), and proteins other than the immune lactoglobulins are also absorbed during this period. Studies by Pierce (1959, 1961) have shown that the low molecular weight proteins, absorbed as whole molecules by the newborn calf, are eliminated by a proteinuria which parallels the period of whole protein absorption by the gut. A similar proteinuria was observed earlier in calves by T. Smith and Little (1924) and in lambs by McCarthy and McDougall (1953). Apparently the proteinuria is a necessary corollary of the nonselective uptake of so large a protein load over so short a period.

In 1953, Moog had observed that alkaline phosphatase appears in the intestinal mucosa of suckling mice at about 14 days of age under normal conditions, but occurs 2–4 days earlier if the animals are given cortisone or ACTH. Halliday (1956, 1957, 1959), using rats and mice, found that corticosteroids, given orally or parenterally, induced premature appearance of alkaline phosphatase in these species, and that this was correlated with premature cessation of transmission of immunoglobulins and antibodies across the gut wall. Thus, in calves, lambs, mice, and rats, antibodies are transferred from maternal serum to offspring via the colostrum. In ruminants the intestinal absorption of the newborn is relatively nonselective; in rats and mice this absorption is more selective (reviewed by Brambell, 1961, 1962) and may be under endocrinologic control. It is apparent that both in the chicken and in these mammals, the means of providing passive immunologic protection to the young during the period of transition from immunologic inactivity to full reac-

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