Basic immunology and its medical application

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Preface

The emphasis on immunology in medical, dental, and other health science curricula is not surprising. Immunology has been the scene of many significant discoveries in the past few decades. Those discoveries of medical importance have quite naturally been incorporated into the clinical practice of pediatrics, medicine, obstetrics, surgery, and others. However, this period of expansion in immunology has not been restricted to its human and medical applications; the entire subject of immunology has grown dramatically. This has required more extensive discussions of immunochemistry, immunopharmacology, immunopathology, and immunity in such fields as biochemistry, anatomy, pathology, pharmacology, and microbiology. For the most part, these changes have been all to the good, but it is clear that instruction in immunology has fallen into the classic pattern in which the fundamental features of the subject are presented in the first and second years of an educational program, followed by a consideration of its applications at some later time.

It is obvious that there are many applied aspects of immunology that can be presented successfully to students in the preclinical years. A student need not have training in obstetrics and gynecology to understand the practical aspects of hemolytic disease of the newborn and Rh problems any more than he is required to study pediatrics and medicine to appreciate the importance of prophylactic immunizations in the control of infectious disease. In fact, the description of these professional applications of immunologic knowledge whets the appetite for further understanding of immunology in both its basic and applied form. The advice "Teach by example" can be interpreted appropriately either to present or be the example.

This book was written with two goals in mind: to present the basic subject matter of immunology to the reader in a condensed form and to illustrate by case histories and clinical correlations how this information is applied to the solution of medical problems. The title of the text was chosen to indicate this emphasis. Since it was expected that the primary users of this text would be preclinical students, the case histories have not included the entire clinical laboratory "printout" of all the data often assembled by these laboratories. Much of this data would be superfluous to the case histories presented and, by forcing the student to refer constantly to a table of normal values, would detract from the primary immunologic message. Examples of exotic conditions are few in number and, when included, are designed to emphasize some basic immunologic tenet rather than to represent a regular encounter in medical practice. Instead, a genuine effort has been made to include and discuss everyday immunologic problems—penicillin and ragweed allergy, myeloma, serologic tests for syphilis, immunization schedules, and the like, since these are the problems the student is most likely to face later in the "real world."

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chapter 1

Scope of medical immunology

HISTORICAL BACKGROUND

There is no disputing the fact that immunology originated from the study of immunity. The study of immunity itself had little scientific basis until the investigations of Louis Pasteur in the second half of the 19th century. It was at approximately this time that techniques were being developed to recognize, cultivate, and attenuate the microbes that caused certain infectious diseases. Pasteur's genius allowed him to capitalize on these developments, to add to them his own knowledge from his background in chemistry and biology, and to emerge as the father of immunology.

The groundwork of immunity as a science probably originated in ancient China, where the inhalation of dried smallpox crusts was practiced as a preventive of this disease. Presumably the viral agent of this disfiguring and lethal disease lost some of its infectivity in drying, so that it was a mixture of inactivated and active viral particles that was actually inhaled. Because of the long incubation period for smallpox, some immunity could be developed during the period in which the few active viral particles generated a sufficient number of its kind to produce disease. Consequently, the disease was milder than "wild" smallpox, and this form of immunization was perpetuated.

In Turkey a different form of variolation (smallpox was then known as variola) was observed by Lady Montagu, wife of the British Ambassador. There, pustular material was taken from the lesions of a person with a mild case of smallpox and transferred by a common needle into a vein or tissue of the person desiring the immunization. Hopefully, a mild form of smallpox would develop and apparently did with sufficient regularity for Lady Montagu to have her own children vaccinated in this manner. In 1718 she introduced this procedure in England, and she is credited with introducing the method to the western world.

Obviously these earlier methods of immunization had inescapable risks—there was no assurance that variolation would result in only a mild case of smallpox, and there was also a possibility of transferring syphilis, leprosy, hepatitis, or most any other disease of the donor. Jenner's system of smallpox vaccination, advanced by him in 1798 as a result of his study of cowpox and smallpox in English milkmaids, avoided these problems and began to place immunity on a firm scientific footing. Jenner observed simply that milkmaids who contracted cowpox were thereafter immune to smallpox. Cowpox is a mild pox of cattle that causes pustule formation on the teats of the cow. Milkers are inescapably exposed to the disease and develop cowpox lesions on their hands. These heal and disappear with little outward noticeable change in the individual. However, Edward Jenner, an English countryside physician, noted that such persons never contracted smallpox, and he set up an experiment to test this more critically. Jenner took pustular material from a cowpox lesion on the thumb of a milkmaid named Sarah Nelmes and used it to inoculate a

farm boy named James Phipps. Surely enough young Phipps developed cowpox. Then Jenner performed the critical part of the experiment. After Phipps had recovered from cowpox, Jenner inoculated him with smallpox and demonstrated his immunity to this disease as well. Like so many remarkable advances, this lifesaving discovery was mocked and not widely adopted until well into the 19th century. Admittedly, Jenner had capitalized on a rare occurrence—the creation of a permanent immunity to one disease on recovery from another. This phenomenon is known as cross-immunity, and Jenner had witnessed it in its most perfect form. We now recognize that the cowpox and smallpox viruses are nearly identical twins, and because of their close relationship, immunity to one is immunity to the other. There is, in fact, only one other example of good cross protective immunity of this sort practiced in human medicine and that is the use of the bovine strain of the tubercle bacillus to immunize against the human form of tuberculosis.

Pasteur's fame and status as the father of immunology also stems in part from an unusual circumstance. Of course, Pasteur made many famous discoveries, including the relationship of crystal structure to optical isomerism, the process of pasteurization, the attenuation of virulence of infectious agents, and his rabies vaccine (Fig. 1-1). Prior to his study of rabies but eventually to be closely linked to it was Pasteur's recognition that the virulence of the anthrax bacillus and that of the bacterium

Fig. 1-1. French five franc notes illustrate many of Pasteur's scientific accomplishments in a true art form. Upper left and upper right arrows point to sheep and chickens that commemorate development of attenuated vaccines for anthrax and chicken cholera. Lower arrow indicates rabid rabbit spinal cord in a drying jar first used to treat Joseph Meister, the young boy shown battling a rabid dog. Rabbits in lower left corner possibly portray Pasteur's entry into bacterial warfare and his deliberate infection of rabbits who were burrowing into a friend's wine cellar and dislodging the masonry with disastrous results. Crystals at left and right center illustrate relationships of crystal structure to optical rotation, grape clusters refer to Pasteur's study of diseases of wine and discovery of pasteurization, and swan-necked flask near Pasteur's portrait is a reminder of his disputation of the theory of spontaneous generation. Flagellated bacilli surrounding number 5 in each upper corner of note refer to his discovery of anaerobic life. The reverse side of the bill is also beautiful and illustrates fungi, mulberry, and grapes with the portrait of Pasteur.

that causes chicken cholera could be reduced by manipulation of the age or growth temperature of cultures of these bacteria. Both of these discoveries were serendipitous—the first from an effort to use cultures that had been placed in a faulty incubator and the second from a similar use of cultures that had set for several days on a laboratory bench. When Pasteur observed that dried spinal cords of rabbits dead from experimental rabies could not transmit the disease although fresh spinal cord material from these rabbits would, he correctly reasoned that, as in the experiments with chicken cholera and anthrax, the noninfective material might make a good vaccine. Laboratory studies confirmed this, and eventually he was prevailed on to try his Pasteur treatment on a young boy, Joseph Meister, who had been bitten many times by a rabid dog. The Pasteur treatment consisted of a series of inoculations beginning with aged and ending with fresh spinal cord from a rabid rabbit. This method protected Joseph Meister and thousands like him from rabies and led to the great popular fame of Pasteur and the construction of Pasteur Institutes throughout the world dedicated to him and his discovery.

In the case of rabies a second unique situation exists—an exceptionally long incubation time of the disease. As a consequence of this, immunization with rabies vaccine after exposure to the virus has time to generate sufficient immunity to resist the disease. For practically all other diseases except smallpox, which also has a long incubation time, vaccination must be performed prior to exposure. The word "vaccination" (from the Latin *vacca*, meaning cow) was used by Pasteur to honor Jenner's contribution and the use of microorganisms to prevent the very diseases they cause.

Another successful form of immunization, and one in which the use of the term "vaccination" is generally considered less appropriate, is the use of bacterial toxoids. It is surprising that toxoids were not used for prophylactic immunization against human diseases until 1923, since Behring and Kitasato had recognized as early as 1890 that certain bacteria, of which diphtheria and tetanus are examples, cause disease almost entirely by virtue of the potent exotoxins they excrete. Moreover, complete immunity against these diseases is based on the presence of special toxin-neutralizing antibodies, or antitoxins, present in the blood of individuals who have recovered from these diseases. Such antibodies can be formed by a person who is injected with tiny doses of these toxins, but this is obviously a dangerous undertaking. Nontoxic, neutral mixtures of toxin and antitoxin (taken from an immune laboratory animal) were used for immunization instead, that is, until 1923 when Ramon found that treatment of these exotoxins with formaldehyde would convert them to harmless molecules called toxoids. These toxoids would generate the same degree of immunity as the toxins without their obvious drawback, and toxoids have been used for immunizations ever since. Unfortunately there are few diseases caused by exotoxins, but diphtheria and tetanus are such widespread and serious diseases that toxoid-induced immunity is still considered an important development in preventive medicine.

Emil von Behring received a Nobel Prize in 1901, the first ever offered in medicine and physiology, for his studies with antitoxins. However, immunity is not entirely founded on the ability of an animal to respond to vaccines or toxoids of pathogenic organisms by the formation of antibodies. Metchnikoff, the volatile Russian, was one of the first to recognize this when he noticed that the cell-eating behavior of certain cells, the circulatory and tissue phagocytes, resulted in the death of the foreign cells they ate. Presently there is a resurgence of interest in phagocytic cells

as the key to tumor immunity. Other recent studies of human patients with functionally inept phagocytes, who consequently suffer from a continuous stream of bacterial infections, are beginning to unravel the means these cells use to destroy their phagocytic victims. For his discovery of phagocytic cells, Metchnikoff received a Nobel Prize in 1908.

In the three quarters of a century that have passed since these early awards to immunologists for their contributions in the realm of immunity, immunology has taken new directions in chemistry, genetics, medicine, and surgery. Immunologists are concerned with the chemistry of blood proteins, of histocompatibility antigens, of the red blood cell membrane, of mast cell degranulation, and of other biochemical problems. Problems of tissue transplantation, hemolytic disease of the newborn, the inheritance of allergies, the functions of lymphocytes, and other topics outside the realm of immunity as such dominate much of modern-day immunology. At the same time diseases, not necessarily infectious in nature, such as tumor immunity and the autoimmune diseases are under investigation by immunologists. The expanding interest in and information about the subdivisions of immunology have been so great that special methods and a special jargon for each has emerged. Old terms are being used in new ways and new terms are being originated. Unfortunately this has resulted in duplicate definitions and vague or imprecise descriptions. Normally a vocabulary for a science develops gradually as knowledge of the science itself grows, but wherever uncertainty exists, reference to a dictionary or glossary becomes inevitable. Such a glossary is presented at the end of this book. Although it might be possible to memorize a brief glossary, a better appreciation of the manner in which immunologic terms are used may be conceived from the following condensed introductory sketch of medical immunology.

IMMUNOLOGIC REAGENTS

The science of immunology is dynamic in the sense that it analyzes the response of the body to substances that are foreign to the body. Often the first foreign substances that come to mind are bacteria, viruses, or other infectious agents that the immunologist calls *antigens*. Actually, cells are composed of many complex macromolecules that are antigenic, and this includes such molecules in red blood cells, grafted tissues, and other noninfectious as well as infectious cells. The body can also respond to many nonantigenic substances, *haptens*, when these are linked into hapten-antigen conjugates, but not to the hapten alone. Haptens are customarily of lower molecular weight or simpler structure than antigens, so it can be seen that the animal body has evolved a method of reacting to simple as well as complex molecules. This response can be magnified if the antigen or *neoantigen* is presented to the animal with an *adjuvant*.

Adjuvants improve the immune response (immune response is the term used even though the antigen or hapten has no connection with an infectious agent) by influencing the behavior of host cells. Tissue *macrophages*, a type of *phagocyte*, engulf and partially degrade the antigen, passing on *antigenic determinants* to *B* and *T lymphocytes*. The B lymphocytes in birds are easily recognized because they pass through and are altered by a cloacal gland called the *bursa of Fabricius*. This alteration allows them to respond to antigenic determinants with a reproductive burst that terminates in the *plasma cell* as the product of *lymphocyte transformation*. The plasma cell excretes *antibodies (immunoglobulins)* that are found in the gamma globulin fraction of the blood. These antibodies are synthesized in such a way that they can combine with that specific antigen (and certain *cross-reactive* antigens) that stimulated its formation. Several different molecular classes of these immunoglobulins are

formed. This includes IgG, IgM, IgA, IgD, and IgE plus several subclasses, or *allotypes*. Oncogenesis of plasma cells results in an excessive synthesis of the immunoglobulins or their structural parts as seen in *multiple myeloma, Waldenström's macroglobulinemia*, or other *immunoproliferative diseases*. Since this may create an imbalance in the defensive armory, plasma cell proliferation, just as a genetic absence of plasma cells, may produce an *immunodeficiency disease*. Immunodeficiency due to *hypogammaglobulinemia* may be either genetic or acquired.

Simultaneous with these events, the antigen-exposed T lymphocyte has emitted a message that results in the appearance of a more actively phagocytic and a more powerfully digestive macrophage known as the *activated macrophage*, which is consequently more active in modifying the antigen. The T lymphocyte progresses through a proliferative phase and becomes concentrated with macrophages in cell packets termed *germinal centers*. Proliferating B cells also create germinal centers. The T lymphocyte, so named because it is modified by the thymus, may stimulate the B cell in its immunoglobulin response *(helper T cell)*, or restrict B cell activities *(suppressor T cell)*. Perhaps more important is the T cell production of *lymphokines* that alter host cells to make them refractory to intracellular parasites *(interferon)*, attract macrophages *(chemotaxin)*, arrest macrophage migration *(macrophage migration inhibitor factor)*, or attack foreign cells directly *(lymphotoxin)*. Other lymphokines may function in *cell-mediated immune* reactions or *cell-mediated (delayed) hypersensitivity*. *Humoral immunity* and the *immediate hypersensitivities* are dependent on antibodies.

To these adaptive responses or reactants must be added those of the *complement* system that participate in antigen-antibody reactions to stimulate phagocytosis by generating *opsonins* and *chemotaxins* and encouraging *immune adherence*. Other undesirable complement-related activities include those associated with *anaphylatoxin* and *kinin* formation. Complement activation can also be initiated by the antibody-independent *properdin* pathway.

IMMUNOLOGIC REACTIONS

The union of an antigen with its antibody with or without the participation of complement or other accessory factors is the subject matter for serology. When the antigen is soluble, the reaction is described as a *precipitation* reaction. Serologic precipitates can also form when the reagents diffuse through gels and combine with each other. There are many variations to such *immunodiffusion* tests—*radial (Mancini) immunodiffusion*, double diffusion of the *Ouchterlony type*, *immunoelectrophoresis*, *crossed immunoelectrophoresis*, *counterimmunoelectrophoresis*, etc. When the antigen is cellular or particulate, the serologic reaction is an *agglutination* reaction or, as in the case of erythrocyte antigens, *hemagglutination*. Fluid antigens can be absorbed to cells to convert precipitation tests to *passive agglutination* tests. When complement is present, it is fixed in the serologic reaction *(complement fixation)*, and this may be measured as a cytolytic reaction *(bacteriolysis* or *hemolysis)*. When phagocytic cells are present, the serologic reaction may be seen to favor phagocytosis of the antigen. Occasionally no outward sign of an antigen- or hapten-antibody reaction may be noted. This may demand the use of *fluorescent antibody* procedures, *radioimmunoassay*, or *antiglobulin* (double antibody) techniques.

The result of immunologic reactions in vivo that destroy or resist foreign cells or their products is usually classified as immunity. This explains the origin of the terms "transplantation immunity" and "tumor immunity," since tumors usually have a new set of antigens that makes them foreign. When the immune response is di-

rected against self-antigens, an *autoimmune disease* is often the result. This may take the form of an *autoimmune hemolytic disease* or *immune complex disease* involving antigens of thrombocytes, kidney, or other cells. Autoimmune diseases associated with misdirected T cell activities as in postinfectious encephalomyelitis are also known. When disease results from immune responses to external antigens, these diseases are usually labeled *allergies*. The *immediate* or *immunoglobulin-dependent allergies* rely on the attachment of *reagin (cytotropic IgE)* to the surface of *mast cells*. Combination of this IgE with antigen initiates *mast cell degranulation* with the liberation of *vasoactive amines* such as *histamine* and *serotonin*. The antigen-antibody reaction may trigger the *Hageman pathway* and the eventual release of *bradykinin* and other *kinins*. White blood cells may also release pharmacologically active substances. *Antihistamines* and *β-adrenergic drugs* such as adrenaline modify these toxic reactions. In their milder forms these reactions are associated with the *atopic illnesses*, hay fever or other *respiratory allergies*, and *food allergies*. In their more severe form these are seen as life-threatening *anaphylactic reactions*.

T cell activities may also be expressed as allergies and *contact dermatitis*, including reactions to cosmetics, dyes, animal products, and *poison ivy*, and other sources of haptenic compounds have much in common with *tuberculin reactions* and other *allergies of infection*.

From this compact overview of immunology it is apparent that the behavior of the involved cells is complex, and this will be treated in the following chapter on immunocytology. The chemicals these cells respond to and the cell products they respond with are considered in the chapter on immunobiochemistry. Serologic reactions and immunity are discussed in separate chapters, as is immunohematology. Thereafter separate chapters will fill in the details of B and T cell–mediated allergies, autoimmunity, transplantation, and tissue immunity. It can be seen that the first chapters are devoted to basic immunology, whereas the latter are devoted to its medical applications.

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chapter 2

Immunocytology

The cells of the body that respond to antigens are variously categorized as belonging to the hematopoietic system, the reticuloendothelial system, or lymphoid system. The organs and tissues comprising these systems are not as well defined as those of the nervous system, endocrine system, etc., which tend to exist as distinct structural organs and have a clear, often singular, physiologic role. The cells of the immune system originate from hematopoietic tissue, and after leaving this they acquire or express functions that place them in the reticuloendothelial or lymphoid system (Fig. 2-1).

HEMATOPOIETIC SYSTEM

The cells of the reticuloendothelial and lymphoid systems and those of the recently delineated mononuclear phagocytic system arise from the bone marrow. The average adult has about 3 kg of bone marrow, making it the largest organ of the body. In addition to the vascular and adipose tissue of marrow that represent about one half of the tissue, about one half of the tissue in bone marrow is dedicated to hematopoiesis or blood cell formation. The development of blood cells arises from a primitive, undifferentiated stem cell, the reticulum cell, and diverges into several distinct lines. Of these, only the cells of the granulocytic, lymphocytic, and monocytic series are of fundamental importance in the immunologic response, although cells of the erythroid and megakaryocytic series are often important as targets of the immune response.

RETICULOENDOTHELIAL SYSTEM

The so-called reticuloendothelial system (RES) is a collection of cells of diverse morphology and tissue residence united by the sole property of an ambitious phagocytic behavior. Classically the RES has been divided into tissue and blood phagocytes of large size, macrophages, and those of lesser size, microphages. The macrophages have now been united and elevated to the status of a system by a WHO expert committee and called the mononuclear phagocytic system. The characteristics of the cells in the new system include a pronounced phagocytic ability, a cell diameter of 10 to 25 μ, a nucleus-cytoplasm ratio of about 1:1 or somewhat less, a relatively large oval or kidney-shaped nucleus, a granular texture in their cytoplasm due to its content of lysosomal granules, and numerous cytoplasmic vacuoles. These cells arise from the monocytic series of the hematopoietic system and are represented in blood by circulating monocytes. The peripheral blood monocytes serve as the source of the free and fixed tissue macrophages. Tissue macrophages have specific names according to their anatomic location; thus histiocytes are found in connective tissue, Kupffer's cells in liver, alveolar macrophages in lung, microglial cells in the neural system, and free and fixed macrophages in spleen, lymph nodes, and other organs (Fig. 2-2).

The mononuclear phagocytes have surface receptors for immunoglobulins and complement that may assist in the attachment of antigens to these cells. Other blood

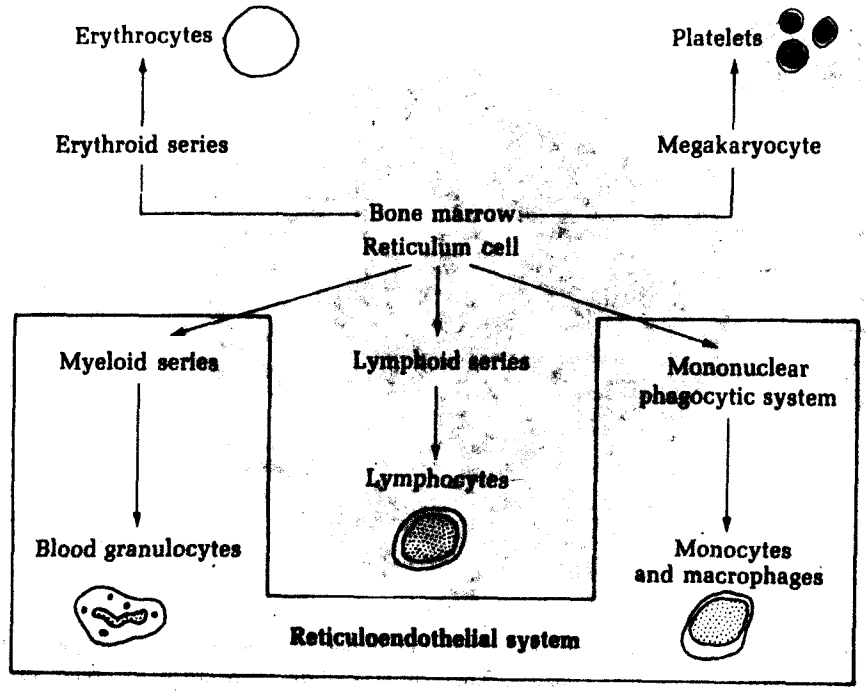

Fig. 2-1. Origin of immunologically vital cells from bone marrow. Granulocytes and monocytes have traditionally been considered as the two halves of the reticuloendothelial system, but the latter are now being treated as a separate unit. The lymphoid system represents the third important cell line. Cells of the erythroid series and megakaryocytes are important as antigens.

proteins (opsonins—to prepare for eating) may assist in phagocytosis. Once the engulfed particle is taken internally, it eventually contacts a lysosomal granule. When this occurs, the lysosome disgorges an array of hydrolytic enzymes into the phagocytic vacuole. This now becomes the phagolysosome, a structure in which a combination of forces seeks to reduce bacteria, viruses, other pathogens, or antigens into their smaller constituents. These forces include an acid pH resulting from the intracellular accumulation of lactic acid arising from glycolysis. Antibody and complement, which may also utilize the enzyme lysozyme, are lytic for certain cells. Oxidative halogenation and hydrolytic degradation also destroy antigens. Among the lysosomal hydrolases known to be released during phagocytosis are phosphatases, ribonucleases, deoxyribonucleases, proteases, lipases, glycosidases, and esterases. Certain lysosomal proteins may contribute to the destruction of engulfed cells by nonenzymatic processes, for example, phagocytin.

The polymorphonuclear neutrophilic (PMN) leukocytes, the neutrophilic granulocytes of blood, represent about 60% of all blood leukocytes. The eosinophils and basophils, the other granulocytes, represent only 1% each. These two latter cell types are important in allergic reactions but have feeble phagocytic powers compared to the PMNs. The granulocytes are about 12 μ in diameter (Fig. 2-3) and have a granulated cytoplasm that has an affinity for either basic dyes (basophils), acid dyes such as eosin (eosinophils), or both (neutrophils). The neutrophils are easily recognized by their neutrophilic granula-

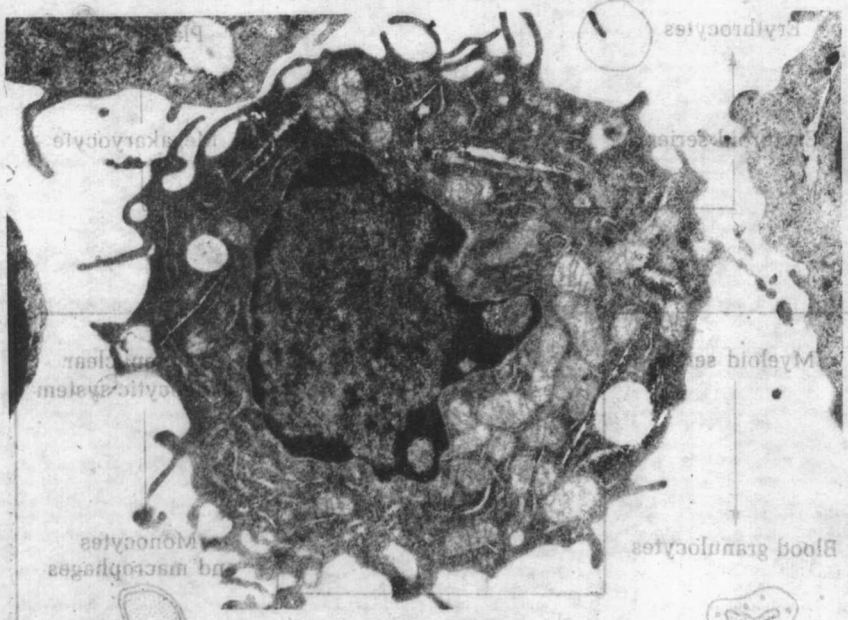

Fig. 2-2. This macrophage, seen as it appears under the electron microscope, is not necessarily typical of all macrophages. They differ slightly from organ to organ, except for their large cytoplasmic volume and numerous inclusions and granules. The numerous extensions from its cytoplasmic membranes are an indication of its extensive membrane activity, which is helpful for both motility and phagocytosis. (Courtesy Dr. E. Adelstein.)

tion and their tri- or multilobed nucleus. Their granules apparently do not differ from the lysosomal granules of tissue macrophages, but the granules of eosinophils and basophils are not lysosomal. Thus the result of phagocytosis by PMNs and macrophages is essentially the same, the enclosure of the engulfed object into a phagocytic vacuole, coalescence of the phagocytic vacuole and lysosome to form a phagolysosome, and the death and digestion of the cell.

Although enzymes derived from lysosomes are undoubtedly important in the degradation of ingested pathogenic bacteria or other cells, it is no longer believed that these enzymes are directly responsible for the death of such bacterial cells. Examination of leukocytes with impaired bactericidal activity from patients with chronic granulomatous disease and similar disorders reveals that inept phagocytes lack the ability to form singlet oxygen ($^1O_2$). Singlet oxygen is believed to be the ultimate bactericidal weapon of the phagocyte. Singlet oxygen might be provided by the decomposition of the superoxide radical (O_2^-) formed during oxidation of reduced pyridine nucleotides. The feasibility of this hypothesis is strengthened by the knowledge that phagocytic cells exhibit a respiratory burst during phagocytosis and have the possibility to involve nicotinamide adenine dinucleotide (NAD or NADP) extensively in oxidation-reduction reactions. Alternatively an excited singlet oxygen could arise from the interaction of the myeloperoxidase–hydrogen peroxide–halide system in which hypochlorite or other halides could interact with myeloperoxidase and H_2O_2 as indicated in Fig. 2-4. Absolute proof that granulocytes form singlet oxygen is not available; however, they can form the superoxide ion, and since they lack the enzyme superoxide dismutase that decomposes the superoxide ion, singlet oxygen

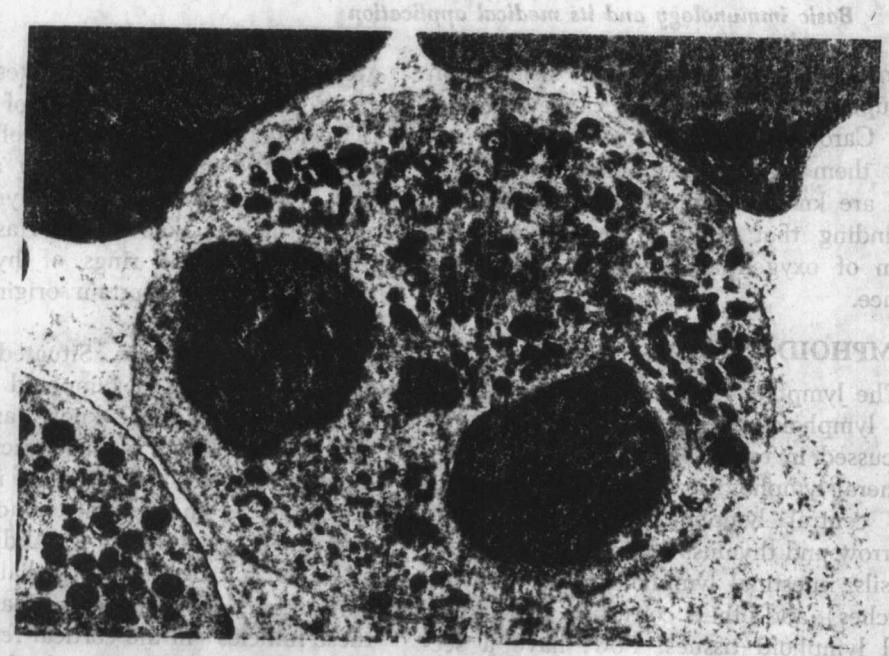

Fig. 2-3. Electron microscopic appearance of polymorphonuclear leukocyte (PMN or neutrophil). Section through the cell gives the illusion that its trilobed nucleus exists as three separate nuclei. Many of the dark granules in the upper portion of the cell are lysosomes. Phagolysosomes are not in evidence. (Courtesy Dr. E. Adelstein.)

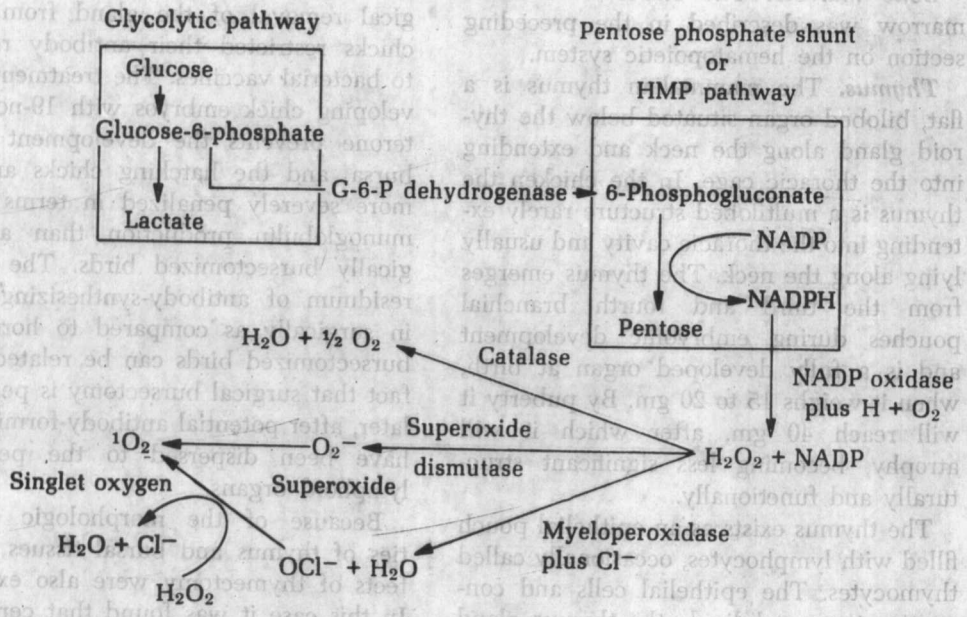

Fig. 2-4. Metabolism by normal phagocytes in glycolytic and pentose phosphate shunt leads to formation of H_2O_2. Then the microbicidal singlet oxygen is formed by alternate pathways, two of which are shown. Phagocytic defects at the level of G-6-P dehydrogenase, NADP oxidase, myeloperoxidase, and superoxide dismutase would obviously impair intracellular killing by the phagocyte.