Immunobiology of the Head and Neck
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TABLE OF CONTENTS

Contributors .......................................................... ii
Preface and Introduction .............................................. vii

PART I: GENERAL IMMUNOLOGY
  Chapter 1—Cells and tissues of immunity ..................... 1
  Chapter 2—Immunoochemistry .................................. 23
  Chapter 3—Nonspecific immune response ..................... 55
  Chapter 4—Specific immune responses ....................... 83
  Chapter 5—Mucosal immune responses ....................... 103

PART II: IMMUNOBIOLOGY OF THE HEAD AND NECK
  Chapter 6—Tonsillitis and adenoiditis ....................... 129
  Chapter 7—Immunology of otitis media ....................... 137
  Chapter 8—Nasal allergy ..................................... 157
  Chapter 9—Hyperimmune and autoimmune diseases ........... 215
  Chapter 10—Immunodeficiency diseases ..................... 231
  Chapter 11—Cancer ........................................... 257
  Chapter 12—Transplantation in otolaryngology ............. 277
  Chapter 13—Clinical and Experimental Immunobiology of the Ear .......................................................... 323

Author Index .......................................................... 345
Subject Index .......................................................... 363
PREFACE

This work reviews the basic concepts of immunology and introduces the reader to the latest findings on immunological aspects of diseases of the head and neck. In the past two decades, there has been an explosion of new knowledge in immunology. The contributors to this volume, all of whom have been active in clinical and basic research, describe how recent discoveries in immunology play an increasingly vital role in the understanding and care of patients with head and neck diseases.

An important teaching tool for the resident in training and a valuable reference work for physicians in practice, this book will be of special interest to otolaryngologist-head and neck surgeons, surgical oncologists, pediatricians, allergists, rheumatologists and educators desiring an advanced text in the field.

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INTRODUCTION

Immunology has been traced back at least to 1000 AD, when the Chinese discovered that the inhalation of smallpox crusts had some value in prevention of the disease. However, immunology as a science has developed almost entirely within the last 100 years.

Immunity was the primary concept from which this specialty developed, due to clinical preoccupation with host defense against infection. The discovery by Edward Jenner, then a medical student, that inoculation with cowpox crusts protected man from smallpox, assured the future of immunobiology. With the work of Louis Pasteur at the end of the 19th century on fowl cholera organisms and rabies, active rather than passive immunization became the procedure of choice in the prevention of many infectious diseases. Robert Koch, around the same time, discovered delayed hypersensitivity to tuberculosis which unwittingly opened the field of cell-mediated immunity. The last 20 years of the past century were rich in discoveries, primary among them the work of Roux and Yersin on the exotoxin of the diphtheria bacillus. Their work led to that of von Behring on the production of antitoxin and opened the way to immunotherapy. The discovery by Pfeiffer and Border of complement, a substance in the serum distinct from antibody, led to the use of the agglutination reaction in the diagnosis of typhoid fever (Widal test).

At the turn of the 20th century, two different concepts emerged from which modern immunology has developed. Paul Ehrlich proposed the humoral theory of antibody formation, and Elie Metchnikoff developed a competing, cellular theory of immunity. Both were correct and it is now recognized that cellular and humoral aspects of immunity are both interrelated and interdependent. At about the same time, von Pirquet coined the term allergy to mean altered reactivity of the host.
Immunology has since moved toward defining the mechanisms involved in immunity and in subdividing these responses into specific and nonspecific. It became evident that immunologic responses served three functions—defense, homeostasis, and surveillance. Defense is involved in resistance to infection, homeostasis in removal of worn-out self components, and surveillance refers to the detection and destruction of mutant cells. Major discoveries in immunology accumulated slowly over the first half of the 20th century, marked by the work of Landsteiner on the major human blood groups with the ABO system, the work of Prausnitz and Kustner with the PK test, and the description of reagin or IgE. Wiener and Landsteiner in 1940 teamed for the discovery of the Rh antigen system and Witebsky established the criteria which proved the existence of autoimmune diseases. Haurowitz and Burnet are credited with the development of modern theories of antibody formation leading to the concepts of template theory and clonal selection theory.

Since about 1960, a virtual explosion in knowledge about immunobiology has occurred, first in humoral immunity, and more recently in cell-mediated immunity. The knowledge upon which the first section of this volume is based represents the fruits of this period of rapid growth in immunology as a science.

The development of immunobiology has not gone unnoticed by those working in head and neck medicine. Application of the science of immunology to problems in otolaryngology has begun. For example, nasal allergy, asthma, nasal polyps, intolerance to aspirin, and chronic inflammation of the tonsils and adenoids are common clinical conditions facing the otolaryngologist. To some degree, all involve immune responses. Cancer of the head and neck has been shown to have specific epidemiological factors which predispose to its development, a fact which makes it unique when compared to many cancers that develop in other sites of the body. The roles of cell-mediated reactions, soluble immune complexes, and local reactivity need to be defined with regard to these factors and may give rise to more elegant diagnostic procedures and eventually to more precise modalities of treatment.

The mechanical theory of eustachian tube obstruction is probably of prime importance in serous otitis media with effusion. However, the role of inflammation and the intervention of nonspecific and specific immune responses may significantly hinder the restoration of a normally functioning middle ear. Immune mechanisms involving delayed hypersensitivity may also manifest themselves by chronic infection and/or inflammation in the middle ear. The mucosa of the middle ear is now recognized as a target organ in otitis media with microscopic and biochemical factors that reflect immunologic injury. Greater recognition of these factors in the pathogenesis of ear disease demands a better comprehension of immunology from otolaryngologists. Additionally, a growing knowledge of the pathophysiology of chronic otitis media will probably come in part from the study of protease inhibitors, the subpopulations of lymphocytes in middle ear effusions, and the role and classes of immunoglobulins in the secretions. For example, Yust et al., have shown that impaired cellular immunity of patients with malignant external otitis may be a predisposing factor in the development of their illness. Animal experiments on the immune response of the inner ear will most probably open new horizons in the study of the function of the endolymphatic sac and its role in endolymphatic hydrops.
A better understanding of the immunology of transplantation may possibly lead to improved methods of middle ear reconstruction.

The last half of this volume addresses these and other otolaryngologic problems closely related to immunology. A broad background in immunology is now necessary for clinicians who deal with cancer patients, treat allergies, or are interested in transplantation surgery.

DEFINITION OF TERMS

The term immunity was used initially to define the host's resistance to infection. Today, the term refers to the sum of reactions involved in eliminating foreign substances. A broader sense of the term now designates all humoral and cellular factors, specific and nonspecific, protecting the organism against infectious processes or malignant diseases. Sometimes the immune reaction is not favorable to the host and is marked by hypersensitivity reactions (eg, autoimmune diseases, anaphylaxis).

Antigens are customarily defined as any substance that causes the production of antibodies and reacts specifically with those antibodies to produce an immune reaction. By convention, the antigen is schematically represented in this text by a triangle.

In general, there are four characteristics of an antigen: (1) It must be recognized as a foreign substance by the host; (2) It evokes the most vigorous host response when introduced parenterally; (3) It has a high molecular weight; (4) It is proteinic in nature.

Immunogenicity is defined as the capacity to generate an immune reaction, and the degree of immunogenicity is related to the structural and chemical characteristics of the antigenic molecule. There are certain antigenic sites or determinants on the antigen molecule that combine with specific antibodies or sensitized lymphocytes. These may represent only a relatively small portion of the entire molecule. Chapter 2 elaborates on the nature, role, and constituents of antigens.

Haptens are molecules of less than 5,000 molecular weight which alone cannot elicit an antibody response; however, when they are conjugated with larger molecules, they can provide antigenic specificity.

Adjuvants are substances which enhance the immune reaction against an antigen. Adjuvants usually do not modify the specific antigenicity of a substance; however, certain adjuvants may generate different immune responses to the same antigen from the responses generally expected. Adjuvants can be classified as simple (mineral oil) or bacterial (Freund's adjuvant; see chapter 2).

Antibodies are globulins (immunoglobulins, Ig) elaborated by the organism in response to antigenic stimulation. There are five distinct Ig classes which have differing structures and functions (IgA, IgD, IgE, IgG, IgM). These molecules combine with antigens in a "lock and key" fashion and may form an immune complex.

The complement system is a series of serum proteins which serves primarily to amplify the effects of an interaction between a specific antigen and its corresponding antibody.
The complement cascade consists of 9 functional entities or 11 discrete proteins which when activated follow two recognized pathways: (1) the classical pathway and (2) the alternative pathway. These are discussed in chapter 3.

**Humoral and Cellular Immunity**

The immune system may be divided functionally into two main categories, representing two types of effector mechanisms mediating specific immune responses: (1) The humoral immune system mediated by antibody-forming plasma cells (B cells); (2) The cellular immune system mediated by specifically sensitized lymphocytes (T cells).

Various cellular elements and mediators are involved in both the humoral and cellular responses. They are discussed in detail in chapters 1-4.

**Lymphocytes**

The lymphoid cells (lymphocytes, plasma cells, lymphoblasts) of the immune system react specifically with antigen. The lymphocytes and their products are the means by which antigen is recognized, and thus are responsible for the specificity of host defense. There are two major categories of mature lymphocytes, T cells and B cells, which although morphologically similar, are quite distinct in function (see chapters 1 and 3).

**Afferent and efferent limbs.** The immune response is further temporally and functionally divided into afferent and efferent limbs. In the afferent limb, the immunogen is processed by macrophages, presented to lymphocytes through macrophage-lymphocyte interaction, and subsequently results in the activation of lymphocytes. In the efferent limb these specifically activated lymphocytes proliferate and differentiate to become engaged in specific humoral and cell-mediated immune responses.

**Classification of Gell and Coombs.** Gell and Coombs have classified the tissue-damaging allergic hypersensitivity reactions into four reaction types based on animal models. The first three types are antibody mediated and the fourth is cell mediated.

Type I reactions are caused by the secretion of mediators such as histamine and slow-reacting substance of anaphylaxis (SRS-A) from mast cells and/or other cells. Allergic rhinitis is an example of type I mediated reaction.

Type II reactions are mostly cytolytic in nature and usually initiated by antigen-antibody reactions. The mechanisms of cell injury also involve complement-mediated cytolysis. Intravascular hemolytic reactions are the most dramatic expression of the type II.

In the type III reactions, both antigen and antibody are free and react forming complexes which may be soluble and precipitate, or soluble and deposit elsewhere in tissues. Arthus reaction is the best example of type III.

In type IV reactions, various mediators are involved such as chemotactic factors, transfer factor, and migration inhibition factor. Rejection of grafts or tumors best illustrates this last type. This classification is an oversimplification and, in general, the four reactions may be intermingled.
Chapter 1

Cells and Tissues of Immunity

Allen F. Ryan

OUTLINE

INTRODUCTION

LEUKOCYTES
  Hematopoiesis
  Lymphocytes
    T lymphocytes
    B lymphocytes
    Natural killer cells
  The Reticuloendothelial System
    Polymorphonuclear leukocytes
      Neutrophils
      Eosinophils
      Basophils
    Mononuclear phagocytes
  The Mast Cell

LYMPHOID TISSUES
  The Structure of Lymphoid Organs
  Bone Marrow
  Thymus
  Lymph Nodes
  Spleen
  GALT
  Mucosae
  Lymphocyte Circulation
  Response of Lymphoid Tissue to Antigen

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INTRODUCTION

The cells responsible for the many aspects of immune response are leukocytes, which originate in hematopoiesis. The effector cells of immunity are members of the lymphoid, myeloid, and mononuclear systems. The lymphoid system consists of the lymphocytes, the cells most centrally involved in the expression of immunity. The myeloid group contains the polymorphonuclear granulocytes, while the mononuclear system consists of the monocytes and tissue macrophages. The myeloid and mononuclear systems are frequently referred to collectively as the reticuloendothelial system (RES), classically defined as consisting of those cells that exhibit phagocytic behavior. An understanding of the origins and characteristics of the cells of the lymphoid system and RES is essential to understanding immune responses.

The tissues that play a major role in immunity contain large quantities of lymphocytes, macrophages and plasma cells, and are called lymphoid tissues or organs. Lymphoid tissue is normally present in the organs of the central lymphoid system, the bone marrow, thymus, and gastrointestinal-associated lymphoid tissue (GALT), and in the peripheral lymphoid organs, the lymph nodes and spleen. Other tissues can also take part in immune responses, when local inflammation leads to accumulation of lymphoid cells. This is especially true of mucosae, some of which appear to have associated with them discrete populations of lymphocytes which are specific to that mucosa. These local populations can generate a local immune response which is independent of systemic immunity.

LEUKOCYTES

Hematopoiesis

The cells of the immune system are formed in the bone marrow. Here they attain at least partial maturity, and it is from the marrow that they are dispersed. The stem cell for all leukocytes is the reticulum cell, which differentiates into a precursor cell for each cell line. Each of the recognized leukocytic cell types originates from a series of intermediate cells. About 75% of the nucleated cells in bone marrow are dedicated to the production of leukocytes. The proportion of leukocytes to erythrocytes in peripheral blood is small because of the relatively short circulation life of most leukocytes. For example, the lifespan of a circulating polymorphonuclear neutrophil is only about ten hours, compared to 120 days for the erythrocyte (Bainton, 1980). After release from the bone marrow some leukocytes, most notably the lymphocytes, undergo further differentiation and maturation. The processes of leukocytic origin, differentiation, and maturation are represented schematically in Fig 1-1.
FIG 1-1. Schematic representation of the processes of hematopoiesis and lymphocyte differentiation. These processes give rise to the mature population of leukocytes which are the effector cells of immunity.

**Lymphocytes**

The cell which is central to all forms of immune response is the lymphocyte. This small (7 to 8 μm), round leukocyte is found in peripheral blood, lymph nodes, spleen, thymus, tonsils, the appendix, and scattered throughout many other tissues. The typical lymphocyte has relatively little cytoplasm, being composed almost entirely of a circular nucleus with prominent nuclear chromatin, as illustrated in Figs 1-2 and 1-7. The surrounding rim of cytoplasm is almost devoid of cytoplasmic organelles. Lymphocytes in their many recognized forms are the effector cells responsible for recognition of antigen, production of antibodies, cell-mediated immune cytotoxicity, and immunologic memory.
They are often long lived, with their tenure in blood and tissue lasting for months or even years. The secretion products of lymphocytes, both antibodies and lymphokines, regulate a number of other cells and biochemical pathways involved in inflammation.

Lymphocytes also originate in the hematopoietic system, from stem cells in the bone marrow. They differentiate into lymphoblasts at this site. These maturing lymphocytes are then released into the circulation as null cells; that is, they bear none of the cell surface markers which are normally used to identify the two major classes of mature lymphocytes, T cells and B cells. These cellular characteristics are acquired after the lymphocytes leave the bone marrow. The most important events in the terminal maturation of lymphocytes occur in the thymus, and at sites which have not been positively identified in mammals. Recent research has established that there are other classes of mature lymphocytes within the null cell population, such as the natural killer cell.
**T lymphocytes**

The term T cell is applied to lymphocytes which are derived from the thymus. They enter the circulation from their origin in the bone marrow as precursor lymphoblasts (pre-T cells), and subsequently enter the thymus where they are transformed into T lymphocytes. It is not possible to distinguish T cells from other small lymphocytes on morphological grounds (Dantchev & Belpomme, 1977). However, the surface membranes of T cells are quite distinct from those of B cells (Dwyer, 1976). Several techniques which take advantage of these differences in membrane markers have been used to differentiate between lymphocyte populations. For example, T cells adhere to sheep erythrocytes, while B cells do not. If T cells and sheep erythrocytes are incubated in the proper proportions, they will form rosettes with a T cell in the center of a surrounding layer of erythrocytes. There are also surface markers on T cells to which an antibody can be formed. An antibody to this T\textit{antigen} will not react to B cells. These markers have been used to demonstrate that about 80% of lymphocytes in peripheral blood are T cells.

The process of initial T-cell sensitization is not completely understood. However, when a T cell which has been sensitized to antigen encounters that antigen again, it undergoes a period of growth and cell division known as lymphocyte transformation or blast transformation. The lymphocyte transforms into a blast cell, which then divides to form a large population of T cells which are all sensitized to the original antigen.

Several functional subpopulations of T lymphocytes have been identified. Helper T cells assist B cells in the production of antibodies to what are called T-cell–dependent antigens. These antigens are more complex than those to which B cells can respond directly. Suppressor T cells retard or even completely suppress the production of antibody by B cells. Killer T cells act directly to eliminate tumors or transplanted tissues. Other T cells are responsible for the development and expression of delayed hypersensitivity.

Many of the functions of T cells appear to be mediated by soluble factors which are distinct from the immunoglobulins. This diverse family of lymphocyte mediators are known as lymphokines. Via the lymphokines, T lymphocytes can regulate the antibody production of B cells, inhibit the spread of viruses, and kill foreign or neoplastic cells. The lymphocyte mediators are discussed in detail in chapter 3.

**B lymphocytes**

The term B cell is used to describe those small lymphocytes which are the precursors of antibody-producing cells. In birds, B-cell maturation occurs in an organ known as the bursa of Fabricus, and B lymphocyte is shorthand for bursal lymphocyte. Mammals lack this organ, and their bursal equivalent has not been identified with any certainty. While the GALT has been the leading candidate, recent evidence suggests that fetal liver, spleen or even the bone marrow itself may be more likely sites of B-cell determination.

B lymphocytes are similar to T cells in their morphological appearance. A number of differences in surface membrane characteristics exist, as discussed above. However, the most important surface marker by which B lymphocytes can be distinguished from T cells is the presence of large quantities of immunoglobulin on the B cell membrane.
In the case of the B lymphocyte, it is this surface antibody which serves as the cell receptor for antigen.

When a B lymphocyte encounters an antigen to which it is sensitized, it undergoes blast transformation similar to that of the T cell. The blast cell then produces a large number of progeny which are all of the same clone; that is, they all produce antibodies directed against the same antigen. The plasma cell, which is specialized for the production of large quantities of specific antibody, is the terminal stage of this replication.

There are at least five recognized classes of B lymphocytes, which correspond to the five classes of immunoglobulin: IgM, IgG, IgA, IgD, and IgE. At any one time, each B cell or antibody-produced cell manufactures only one class of antibody, directed toward one antigenic determinant. However, B cells may switch from one antibody class to another. It has recently been demonstrated that virtually all B cells synthesize IgM in the very early stages of their development, and most then switch to another antibody class during their development into active antibody-forming cells (Hammerling, 1981).

While lymphokine production is usually associated with T cells, it has recently been demonstrated that B cells can, under certain circumstances, also produce lymphocyte mediators (Rocklin, Bendtzen, & Greinieder, 1980).

**Plasma cells** are the final stage of B-cell blast transformation. The plasma cell is a small oval or round cell characterized by an eccentric nucleus, and abundant cytoplasm which consists primarily of laminated rough endoplasmic reticulum, is illustrated in Fig 1-3. The nucleus of the plasma cell often has a "cartwheel" appearance due to the condensation of chromatin along the nuclear membrane with filaments extending toward the nuclear center. Plasma cells are a prominent feature of lymph nodes, the spleen, and sites of chronic inflammation. They increase in numbers in draining lymphoid organs approximately 1 week following an antigenic challenge.

**Natural killer cells**

A new nonclassical subpopulation of lymphocytes, designated natural killer cells, has recently been described (Herberman, Nunn, & Lavrin, 1975; Kiessling, Klein, & Wigzell, 1975). While these cells have not yet been fully characterized, it is clear that they are an important surveillance mechanism against certain tumors and allografts, which operates independently of the T-cell cytotoxic system. While the cytotoxicity of killer T cells is dependent upon antibody, that of the natural killer cells occurs in unimmunized hosts, and appears to be completely independent of antibody or sensitization to the target cell. The recognition of the target cell by the natural killer cell is under genetic control, and surface glycoproteins on the target cell membrane are important for recognition (Roder, Karre, & Kiessling, 1981). The recognition receptor has not been identified. It has recently been reported that natural killer cells bear a unique glycolipid marker, asialo-GMI (Kasai et al., 1980), which should aid greatly in the investigation of this lymphocyte type. Natural killer cells represent about 1% to 2% of the total circulating lymphocyte pool (Roder & Kiessling, 1978). The independence of natural killer cell cytotoxicity from sensitization suggests that this system may be the initial defense against neoplasms.
FIG 1-3. Human plasma cell. The most characteristic feature of the plasma cell at the electron microscopic level is the laminated rough endoplasmic reticulum which occupies virtually all of the extranuclear space. The chromatin of the plasma cell nucleus occurs in large clumps along the nuclear membrane, with occasional bridges into the center of the nucleus. The electron-dense bodies in the cytoplasm of this cell (arrows) may be lysosomes or Russell bodies, suggesting an early stage of cell degeneration (20,000×).

The Reticuloendothelial System

*Polymorphonuclear leukocytes*

Polymorphonuclear leukocytes are phagocytic cells characterized by their relatively small size (9 to 12 μm) compared to other phagocytic cells, by a multilobate nucleus, and by prominent cytoplasmic granules. This system is usually subdivided into three cell types, based upon the staining characteristics of their granules: neutrophils, basophils, and eosinophils.
FIG 1-4. Human polymorphonuclear neutrophil. The nucleus of the neutrophil is lobed, with the divisions connected by chromatin bridges. The larger azurophilic granules (ag) are rich in lysosomal enzymes and peroxidase, and thus are well equipped for a role of killing and digesting bacteria. The smaller neutrophilic granules (ng) contain lysozyme, collagenase, and lactoferrin. Their function is not known (20,000 ×).

**Neutrophils.** Neutrophils are those polymorphonuclear leukocytes which do not take on strong acidophilic (red) or basophilic (blue) staining with the dyes normally used for staining blood smears. As illustrated in Figs 1-4 and 1-7, the abundant cytoplasmic granules which characterize the neutrophil are small and their contents are amorphous in appearance. There are two morphologically distinct types of granules. Azurophilic granules contain microbicidal elements such as peroxidase and lysozyme as well as a variety of digestive enzymes. The smaller neutrophilic granules have not been as well characterized, but while they contain lysozyme and collagenase, they have neither peroxidase nor acid hydrolases, and thus cannot be considered true lysosomes (Baggiolini, 1981). The multilobed nucleus is surrounded by a prominent perinuclear space. Neutrophils are the most common leukocyte in peripheral blood, making up from 50% to 70% of the total.
FIG 1-5. Human eosinophil. The large cytoplasmic granules of the eosinophil are relatively uniform in size. Each contains a dense crystalline core of one or more cationic proteins. The configuration of the core crystals is characteristic for a given species, apparently determined by the types of proportions of cationic proteins which make up the core. The remaining, amorphous portion of the granule is rich in peroxidase and other lytic enzymes (20,000 ×).

white blood cell population. They are rapidly migrating, highly phagocytic, cells which are frequently the first cells to appear in areas of inflammation.

_Eosinophils._ The large cytoplasmic granules of eosinophils stain a bright red with standard stains. This cell type constitutes only 1% to 3% of the leukocytes in peripheral blood. As can be seen in Figs 1-5 and 1-7, under electron microscopy the granules of the eosinophil consist of a crystalline core, composed of cationic protein of unknown function, and a noncrystalline component rich in peroxidase, lysosomal enzymes, and histaminase (Smith & Goetzl, 1981). Eosinophils respond to specific chemotactic factors which are released during the activation of the complement pathways, during mast cell degranulation, and during arachidonic acid metabolism. They thus are drawn to the sites of several types of immune reaction. They can be the predominant leukocyte in certain allergic responses, such as allergic rhinitis. The function of eosinophils is poorly
FIG 1-6. Human basophil. Only a small portion of the nucleus (n) of the cell is visible in this section. The granules of the basophil are approximately the same size as those of the eosinophil, but they are uniformly amorphous. Basophil granules are similar in some respects to mast cell granules, although with lower levels of histamine (43,000 ×).

understood, but they appear to subserve several distinct roles. While eosinophils exhibit typical polymorphonuclear traits such as phagocytosis and are at least weakly microbicidal, they also mediate antibody-dependent destruction of nonphagocytosable parasites. They also appear to modulate mast cell reactions via the inactivation of mast-cell–derived mediators (Wasserman, 1976). The eosinophil may thus be both an effector cell and a regulator cell.

Basophils. Basophil cytoplasmic granules, like those of the eosinophil, are large. However, they stain blue with standard blood smear stains and, as shown in Figs 1-6 and 1-7, they appear uniformly amorphous in electron micrographs. Basophils constitute only 0.5% of the leukocytes in peripheral blood, and depend upon chemotaxis to be drawn into tissues. While basophils originate from a different cell line, they are in many ways analogous to mast cells, with somewhat similar granule contents and physiological responses. The granules of basophils contain histamine, although in much smaller
FIG 1-7. Leukocytic infiltration of the guinea pig middle ear mucosa during a secondary immune response. Three days after antigenic challenge of the middle ear cavity of an immunized guinea pig, both the epithelium and submucosa are heavily populated by neutrophils (PMN), eosinophils (Eo), basophils (Ba), and lymphocytes (Ly) (2,500 ×). From Ryan and Catanzaro, 1983.

quantities than found in mast cell granules, and they degranulate in response to IgE interaction with antigen (Lagunoff & Chi, 1980). The normal function of basophils is unknown. However, their participation in certain types of inflammatory responses, such as delayed cutaneous hypersensitivity, is well documented.

**Mononuclear phagocytes**

The other major cell group in the reticuloendothelial system is the mononuclear phagocytes, consisting of the monocyte and the tissue macrophage. The structure of a typical macrophage is illustrated in Fig 1-8. The monocyte or blood macrophage, at 12 to 15 µm, is the largest cell in peripheral blood. The tissue macrophage or histocyte differs