IMMUNOLOGY

Understanding the Immune System

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IMMUNOLOGY

PREFACE

The past three decades have seen extraordinarily productive investigations of the body's immune mechanism, particularly the development of molecular biochemical techniques to identify and characterize the "gene stuff," DNA. Because knowledge of the immune system accumulates so rapidly, it is impossible for even the most dedicated researcher/instructor, let alone a student, to be familiar with all the advances in this field. The next few years will probably witness an even quicker pace, partly because of the need to halt the AIDS epidemic. The consequence is that a one-semester immunology course taught at the advanced undergraduate level (consisting of accelerated juniors, seniors, and some graduate students) is becoming a staple curricular offering at virtually every college and university. The extraordinary growth of immunology as an academic discipline is unrivaled by any other field. *Immunology: Understanding the Immune System* is an introductory text that grew out of the shared interests of former students and the author in examining ways to answer four frustrating complaints: (1) "I don't know the direction the chapter is taking me"; (2) "What am I expected to learn from the reading?"; (3) "This new information is overwhelming me; I need *mental breathers* within the chapter to reassess the material just covered"; (4) "I need to know if I comprehend the material and be able to test my knowledge of the material *before* an exam!" This text remedies these problems. *Immunology: Understanding the Immune System* assumes that the reader or student has a working knowledge of organic chemistry and microbiology, and so at times concentrates on the presentation of experimental data/foundations and on discussions of the concepts that led to these experiments, particularly for topics that explain the basic principles of how the immune system works. It should be useful both to students with only a passing interest and to those planning further study.

The first chapter (especially the later part) is a mini-version of the book. Once students finish this chapter, they will have an overall view of immunology as each new topic is introduced. The remaining 18 chapters are organized into the following sequence: Chapters 2 through 6 discuss the immune system's cells and organs, and antigens and antibodies—where and how the participants of the immune system work, the substances that induce an immune response, the immune substances that are induced, the interactions between the two (serology: methods used to test for the immune substances that are induced), and the genes that encode antibodies. Chapters 7 through 14 discuss immunobiology—the location of genes that control the immune response, how these genes allow immune cells to communicate with each other, how T cells recognize antigen, what molecules immune cells release once they are activated by antigen, what events are involved in an immune response at the intact animal level and the cellular interactions required for the response, how the immune response is downregulated, how the immune response tolerates self-constituents, and how antigen-antibody interactions start the complement system that leads to enhanced protective events and destruction of antigen. Chapters 15 through 19 discuss immunopathology (the immune system is not infallible)—problems encountered due to antibodies, T cells, reactions against innocuous substances or intracellular organisms, reactions against self, and reactions against helpful nonself tissues and organs. Also discussed is the failure of the immune system to respond to harmful self; lastly, how the immune response can be modulated, both from within and by clinical methods.

In particular chapters, such as those dealing with genetics, cellular interactions, and tumor immunology, but also generally throughout the text, emphasis is placed on the experimental basis for our acceptance of important concepts. Describing a moderate amount of experimental evidence greatly deepens our appreciation of the concepts presented.

The reference value of the book is further enhanced by a selected list of further readings presented at the end of each chapter. Rather than simply listing the readings, a few words about why each was chosen are included. This book's value as a reference also is heightened by the material at the end: a glossary, an abbreviations and acronyms section, appendixes, and particularly the lengthy index.

Any endeavor of this magnitude is never done alone, and this book is no exception. The exception will be my inability to articulate my indebtedness to all who contributed. Beyond simply a sincere thank you, here goes the rest. Throughout the preparation of this book, I have become deeply indebted to many friends and colleagues for discussing the book with me and for their invaluable constructive criticisms and information. First, to Dr. Carol J. Burger, who graciously undertook the task, not once but several times, of reviewing the entire manuscript and individual chapters. Then to Dr. Kevin M. Connolly, who had the misfortune of my knowing that he had graduated from Johns Hopkins University with a double major, English and biology, and that he had received his masters and doctorate in immunology with an eminent immunologist. Thus, I was able to persuade him to suffer through several reviews of the entire text. His conceptual contributions were excellent. Dr. Thomas M. Walker, whom I have dubbed the "surgeon," was able to cut out the fat from the original manuscript, while expertly leaving all the vital organs intact. I am happy to say that these individuals, who devoted many hours to the book in order to provide extensive technical advice, are still my friends. For advice on specific points, I thank Dr. Noel R. Krieg, Alumni Distinguished Professor, American Society for Microbiology Carski Awardee, and fellow author, who demonstrated his long experience of teaching and book authorship by showing me how to remove some of the book's faults and how to draw using a computer. A gold medal and hard-earned payment go to Ms. Mary C. Holliman for developmental editing. I also thank Ms. Geriann P. Park, a former undergraduate student of mine, who volunteered (can you believe it?) to proofread the original manuscript. To say the least, I received valuable help from many sources, the too-many-to-count reviewers, who shared their expertise with me by critically reviewing chapters of the book; the staff of John Wiley & Sons, Inc., who kept it a pleasurable experience; and particularly Dr. Susan King (not only an editor but also, what luck, an immunologist), the responsible editor through most of the writing of the book also, Ms. Colette E. Bean, and Ms. Shirley Thomas, who expertly took it to the finish line and kept the devil out of the details. To Virginia Polytechnic Institute and State University, appropriately called *Virginia Tech*, its computer facilities (You want 200 plus pages printed per minute, you got it!), and the many individuals who directly or indirectly furthered this project, thanks. Appreciation is extended to the students who have passed through 20 years of my classes, not realizing that I would take to heart their complaints about the difficulty of learning immunology. This book was inspired by them and was created in an attempt to make learning this field more palatable for beginners. My hope is that the book will provide a solid foundation and, in turn, inspire students to continue their studies of immunology. To the graduate students in my laboratory at the time of this writing, particularly David W. Mullins, whose critical eye imprinted a student's view on many of the figures, special thanks for tolerating this interruption of my usual compulsive laboratory involvement. A big thanks to the *G*enerator *O*f *D*iversity for bringing me through this project. Let me end with a tribute to my wife, Kathleen, to whom this work is dedicated as a small expression of my gratitude for her love and acute criticism, which were always encouraging, and to my two girls, Heather and Colleen, whose favorite four words, "Are you *still* writing?", would always get me to stop and pay attention to them.

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NOTE TO READER

Immunology is not an easy discipline. It is as complex as the natural system it scrutinizes. However, just a brief dose of the basics of immunology will prepare you for the many upcoming, seemingly formidable concepts that you will be required to understand. The way to this "dose" is through the (highly recommended) reading of the first chapter and especially the ***Overview*** starting on page 13, which represents an expanded outline that emphasizes the basics, or the big picture. The *Overview* is a mini-version of the book and is written in less technical language. The prudent reader will find that *the time invested early avoids the need to invest a disproportionately large amount of time later.* One chapter cannot describe *all* the interrelationships of immunology that influence a topic. If the reader, however, first views immunology on the *Overview* big screen, how the "star" (the topic under discussion) fits into the surrounding act becomes apparent.

Reading an immunology text for the first time, you might be overwhelmed by the bewildering array of unknown terms and complex abbreviations. This book will help you move yourself into the land of immunology. By learning to speak the language, you begin to think in immunologic terms, and once you have managed the jargon, the learning comes easily. When first introduced, important terms are presented in **boldface** type and fully defined. Words that are to be focused on and remembered are presented in *italics*.

The book's brief *CONTENTS* expands as each chapter begins with a detailed ***Chapter Outline*** that serves as both a road map and a survey of things to come. The Chapter Outline is followed by a list of ***Objectives*** or "take-home" lessons that the reader should comprehend.

Other support systems are used within each chapter. *Footnotes* provide descriptive comments about specific passages in the text. **Fast Focus** comments are interspersed in boxes throughout the chapters and give the book a more interactive quality. These boxes may provide slanted extensions or present informed speculation on certain topics. Throughout every chapter at major breaks, ***Mini Summaries*** are offered that allow the reader to concisely reinforce the material and mentally "switch gears" to a new topic. Each chapter concludes with a ***Summary*** that contains highlighted terms. The summaries should help you recall and reinforce the information just covered; it should not be used as *the* tool to learn the material. If you read only certain parts of the chapter, the result may be reminiscent of the oft-told Hindu fable of the six blind men who examined an elephant from different parts, rather than examining the whole animal, and came up with six different descriptions.

To better prepare for an exam or comprehend the material just read, review questions are provided in the ***Self-Evaluation*** section at the end of each chapter. The Self-Evaluation section includes recalling key terms, multiple-choice questions, and short-answer essay questions. In lieu of answer keys, the page numbers for answers to the multiple-choice questions are provided. These page numbers will direct you to the correct section of the chapter when the answer to the question is not readily apparent.

Although immunology is still a young science, it has become vast and complex. To obtain greater clarification through additional study or to satisfy a desire to learn more about the chapter's topic, a section called ***Further Readings*** appears at the end of each chapter to point you in the right direction. Most of the

entries contain brief commentaries to further assist you in selection. The *Appendixes* (which include a Molecular Biology Refresher), an extensive *Glossary,* and an *Abbreviations and Acronyms* section are located at the back of the book.

As you progress from one chapter to the next, remember to be like the mythical Phoenix, *rising renewed and ready to begin again.*

CONTENTS

1

INTRODUCTION TO THE IMMUNE SYSTEM

CHAPTER OUTLINE

1. **Immunology as a science has a short history.**
2. **Innate immunity in vertebrates is nonspecific; it protects through two mechanisms.**
   a. External innate immunity, natural barriers to infection, prevents the penetration of pathogens into tissues.
   b. Internal innate immunity offers many forms of protection after pathogens enter the body.
3. **Acquired immunity in vertebrates is that achieved through experience because of either recovery from disease or medical intervention.**
   a. Acquired immunity is humoral, cell-mediated, or both.
   b. Acquired immunity can be active or passive.
4. **Clonal selection of lymphocytes explains diversity, specificity, and memory.**
5. **The immune system has two levels of development.**
6. **The architecture and mechanisms of the immune system are varied and complex. An Overview.**

OBJECTIVES

The reader should be able to:

1. Appreciate the two functions of the immune system.
2. Gain perspective on immunology's historical foundations.
3. Distinguish between innate immunity and acquired immunity.
4. Discuss how the selective theory explains the immune system's ability to recognize millions of antigens.
5. Follow the development of the immune system in a species and within an individual member of a species.
6. Understand the basic structural and functional components of the immune system.

The body is a citadel under relentless siege from disease-causing agents (such as bacteria or viruses) and cancer cells.[1] Vertebrate animals acquire immunity against these challengers because of the cells and molecules that make up the body's defense system—*the immune system*. Successful immunity depends on the successful collaboration of these cells, which leads to many new cells and molecules that match up with and counteract each challenger. This activity constitutes the *immune response*. In an anthropomorphic sense, the immune system identifies invaders as either friends or enemies and subsequently directs its various components either "to pass in peace" or "to seek and destroy." Our health depends on the accuracy of such decisions. Furthermore, the immune system can "remember" invaders (a characteristic that we exploit when we are vaccinated). Because of the protection it provides, the immune system is vital to an organism's livelihood. Vertebrate animals lacking functional immune systems are without defense and consequently perish.

However, a dark side to the immune system's behavior exists. In some instances, the efficiency of the immune system can actually be harmful to the organism it is designed to protect. Sometimes the immune system responds negatively to an innocuous substance or a life-saving organ transplant (Fast Focus 1). The immune system also may cause destruction of what is thought to be nonself tissue but is really normal self tissue. This aberration can lead to autoimmune diseases. Fortunately, as our knowledge of immunology increases, we are learning how to safely modify or prevent undesirable immune responses.

FAST FOCUS 1

Whether an immune response leads to protection or disease, the mechanisms of recognition and response are the same. The single-mindedness of the immune system does not allow it to distinguish between good and bad foreign substances, or foreign substances it is better off leaving alone.

The immune system has two primary functions: (1) recognition of, and defense against, foreign substances and (2) establishment of immunosurveillance. The recognition of a foreign substance protects against disease, but immunity is not restricted to pathogens (disease-causing organisms). We develop immunity against many harmless substances. In some cases, immunity also can be harmful to the host. Allergies are the classical examples of detrimental immune responses. The second major function of the immune system is surveillance.[2] Surveillance consists of the recognition and destruction of mutant cells that can become cancerous. The incidence of malignant diseases is much lower than predicted by the frequency of abnormal cell generation. A depressed immune surveillance system (caused by immunodeficiency diseases or by chemotherapy-induced immunosuppression) may lead to the appearance of some types of cancer.

The increase in basic immunologic information has been explosive during the past century and particularly during the past four decades. In addition to organ transplantation and allergy therapy, the rise in knowledge has allowed the development of vaccines to prevent infectious disease and of new methods to detect and treat cancer. The prospect of being able to bolster failing immune defenses in different clinical situations is truly epochal. Also, scientists have used immunologic discoveries in the laboratory to identify pathogens, hormones (such as in the home pregnancy test), drugs (such as tests for anabolic steroids), and food contamination (such as tests that detect horse meat in hamburgers).

This chapter introduces the complex and sensitive system of checks and balances that permit (when provoked) the development of an immune response.

IMMUNOLOGY AS A SCIENCE HAS A SHORT HISTORY

Immunology, *or the science that studies the structure and functioning of the immune system,* began long before anyone knew about disease-causing microbes or even that individuals had an immune system that protected the body against disease (Fast Focus 2). The Greek historian of the Peloponnesian War, Thucydides (430 B.C.), recorded that during the plague of Athens only those persons who recovered from the disease could nurse the sick because they did not catch the disease a second time. During the fifteenth century the Arabs and the Chinese translated this knowledge into a crude form of clinical practice by infecting individuals with material from the pustules of smallpox patients. The intentional infection usually gave the infected person a mild form of the

FAST FOCUS 2

Immunology began through efforts to understand, and to intervene in, states of disease.

[1]The term **immunity** (L. *immunis,* free of burden) originally denoted freedom from some kind of service to the Roman state; now, in medical terms, it denotes freedom from disease.

[2]There are supporting and nonsupporting data for immune surveillance; thus, whether it is fact or still theory is widely debated.

disease and induced immunity. This practice became established in Western Europe in 1718 when Lady Mary Wortley Montagu (the wife of the English ambassador in Constantinople) performed this technique, called **variolation** (L. *variola,* smallpox), on her children. Variolation was improved by Edward Jenner, an English physician, in 1796—the birth of immunology. Although he knew nothing about the immune system, Jenner observed that milkmaids who contracted cowpox from cows rarely contracted smallpox. Jenner reasoned that the mild cowpox disease protected an individual against the killer smallpox. He tested this hypothesis by inoculating an 8-year-old boy with fluid from a milkmaid's cowpox pustule and later inoculated the boy with smallpox. The experiment proved successful because the boy was protected from smallpox. Thus, Jenner is credited with the technique of **vaccination**[3] (L. *vacca,* cow), which replaced variolation (Fast Focus 3). Because cowpox and smallpox viruses were structurally similar, the immune system could not differentiate between the look-alikes. The flip side would be that the immune system *does* distinguish between the two. The similar structures allowed for cross-reactive protection to smallpox with cowpox vaccine.

FAST FOCUS 3

Effective vaccination programs eradicated the smallpox virus in 1979 from the face of the earth.

A century later, Louis Pasteur formulated the germ theory of disease. This theory suggested that disease is caused by microorganisms rather than by an imbalance of body humors or the position of the moon. Although Pasteur was the founder of bacteriology, he was much more interested in preventing the diseases caused by microorganisms than in studying the microorganisms themselves. To induce immunity to microbes, Pasteur used **vaccines.** These substances contain components from infectious organisms that stimulate immunity (but not disease), which protects against reinfection by those organisms. The **attenuation of virulence** *(elimination or reduction of disease-causing potential)* was achieved in two ways: aging of cultures and variation of culture temperature. Pasteur showed (accidentally at first) that the causative agents of chicken cholera and rabies lost their virulence when maintained in culture for long periods of time but still could induce immunity (Fast Focus 4). Pasteur also showed that temperature attenuated *Bacillus anthracis* (the causative agent of anthrax). The vaccines against chicken cholera, rabies, and anthrax are called **attenuated vaccines.** Later, two other types of immunizing agent vaccines were introduced: **killed vaccines** *(suspensions of killed bacteria or viruses)* and **toxoids** *(attenuated bacterial toxins).*[4] Pasteur's many contributions to the discipline, in particular his development of the rabies and chicken cholera vaccines, marked the beginning of modern scientific immunology.

FAST FOCUS 4

Before leaving on vacation, Pasteur accidentally left a culture of chicken cholera bacteria out on a shelf. When he returned after 2 weeks, he inoculated the culture into some experimental animals. The animals developed immunity to the disease rather than the disease itself. Pasteur did not discard the results—an accident led to insight. He recognized that attenuation of the chicken cholera bacteria had occurred. "Chance favors a prepared mind" is Pasteur's brief and elegant statement on the investigator's importance in ensuring gains from serendipity.

At the time of Pasteur, the underlying mechanisms of acquired immunity were unknown. Building on Pasteur's achievements, the new field of immunology began developing in two directions. Efforts continued to extend the range of diseases treated by vaccination and to find new ways of preparing these vaccines; simultaneously, bacteriologists began trying to explain the mechanisms responsible for immunity. The evolution of immunology from the nineteenth century to the 1930s can be summarized as follows: (1) identification of the principal mediators of immunity, (2) recognition of the detrimental side of immunity, (3) description of the main human blood groups, and (4) observation that a host normally cannot induce immunity to its body constituents.

The first three principal mediators described were (1) the phagocytic cells, (2) antibodies, and (3) complement. At the same time that these mediators were identified, the hallmark of immunity, *specificity,* was described. Immunologically, specificity means that the antibody or immune cell that protects you from mea-

[3]Vaccination is the process of using substances to do harmlessly what the body does after recovering from a disease—establishes resistance.

[4]The Sabin polio vaccine, the Salk polio vaccine, and the vaccines against diphtheria and tetanus toxins are contemporary examples of attenuated, killed, and toxoid vaccines, respectively. There are new categories of vaccines: *subunit, glycoconjugate,* and *nucleic acid vaccines.* Subunit vaccines are made using pieces of an infectious agent. Subunit vaccines are available for hepatitis B, meningitis, and pneumonia. To protect against bacteria, through their carbohydrates, carbohydrates are conjugated to proteins. Glycoconjugate vaccines are available for *Hemophilus influenzae* type B. Naked-antigen DNA, when injected into muscle, induces sustained expression of the antigen and generation of an immune response. This has been used to immunize mice against malaria and influenza.

sles will not protect you from mumps. However, antibody that protects one person from a specific disease can be transferred to another and protect that person from the same disease. These early results showed that the body is capable of producing specific antibodies when invaded by infectious agents. In the 1920s, the dangers of immunity were recognized by Arthus, Dale, and others, who found that such diseases as hay fever and poison ivy are immunologically based. For example, when certain people are exposed to pollen, their bodies make a specific antibody that overreacts and produces the hay fever. In the 1940s, scientists finally realized that an injured or absent immune system eliminates protection against disease-causing agents or malignancy.

The discovery by Karl Landsteiner in 1900 of the three main human blood groups (A, B, and O) showed that immunologic reactions can affect tissues. Red blood cells may differ from person to person; if a wrong blood type is transfused, an immune response called a *transfusion reaction* occurs. A naturally occurring equivalent arises during childbirth when an Rh incompatibility occurs between the fetus and the mother (Fast Focus 5). If the mother becomes immunized to the fetus's red blood cells, the resulting antibodies can destroy the fetus's red cells. This disease is called *hemolytic disease of the newborn*.[5]

FAST FOCUS 5

Rh red blood cell markers were also discovered by Landsteiner. Because of these diverse contributions to the field of immunology over roughly 40 years, Landsteiner can probably be placed at the top of the list as "premier immunologist of the century."

Another important characteristic of the immune system was observed by Paul Ehrlich early in this century. He noted that our bodies do not normally produce antibodies against our own tissues; he called this phenomenon *horror autotoxicus* (fear of self-poisoning). Currently, it is called *immunologic tolerance*. The maintenance of this peaceable coexistence of immune cells and other body cells, or self-tolerance, is the balancing feature of the immune system, preventing the continual initiation of autoimmune diseases.

During World War II, urgent medical problems shifted emphasis from immunochemistry to immunobiology and helped to develop immunology into a major discipline of basic science that delved into problems of infectious disease, allergy, maternal–fetal interactions, immunologic tolerance, immunologic deficiency diseases, autoimmunity, transplantation, and cancer. This shift in interest is illustrated by the research on immunologic tolerance. The experimental basis for an understanding of tolerance was provided in 1946 by Ray Owen, who observed that some nonidentical twin cattle were incapable of an immune response against their nonidentical sibling. These cattle had shared a common blood supply during fetal development because of a birth defect. Because they were of differing types, the expectation had been that the components of each other's blood would elicit immune responses (Fast Focus 6). From these observations, Peter Medawar (1953) designed an experiment in which he exposed fetal animals to foreign skin cells and thus deliberately induced tolerance to foreign skin grafts. He also showed that tolerance was specific because these animals as adults still rejected unrelated skin grafts. Others helped to show that cells of the immune system are responsible for the rejection of grafts. The work of Snell and others in the 1930s on the genetics of graft rejection showed that the problem of transplantation was partly genetic and that inherited tissue markers recognized by the immune system that distinguish self from nonself frequently lead to graft rejection. A self-arising transplant, or cancer, also was shown to have unique markers that can be recognized as foreign. This discovery of tumor-specific immune responses produced an entirely new area of medicine, immunotherapy, and opened a major subdiscipline of immunology called *tumor immunology*.

FAST FOCUS 6

What is recognized as self and nonself depends partly on when it is encountered by the immune system. If a host is exposed to nonself material before the development of the host's immune system, the host recognizes the nonself material as self and tolerates it.

One of the most significant findings during the late 1940s involved the recognition of the importance of certain white blood cells (*lymphocytes*), which can be activated to perform many biologic functions. Most of contemporary immunology is devoted to studies dealing with the activation, proliferation, and differentiation of lymphocytes and the functions that these lymphocytes are then able to perform. This knowledge of immune cells and the previous knowledge of antibodies formed the basis for the separation of immunology into its classical and current divisions—*humoral (antibodies) and cellular (immune cells) immunology*. This distinction, however, can be traced back to Ehrlich at the turn of the century. The recognition that two types of lymphocytes were responsible for this division led to an explanation of how lymphocytes recognize foreign substances.

[5]Landsteiner also pioneered studies on the specificity of antibody reactions and founded the sciences of immunochemistry and serology.

INNATE IMMUNITY IN VERTEBRATES IS NONSPECIFIC; IT PROTECTS THROUGH TWO MECHANISMS

Initially, the term *immunity* only implied resistance to disease because infectious diseases were the main cause of death in humans. Early immunologists focused primarily on the development of immunity to infectious agents. Contemporary immunologists investigate all aspects of the immune response, and, as a result, immunity has acquired a much broader meaning.

Spore-forming bacteria may be considered capable of immune responses because they produce spores when confronted with hostile conditions. However, immunologists evaluate the specialized responses of vertebrate hosts. *When foreign substances such as bacteria, viruses, fungi, or parasites are introduced into a vertebrate host, the host either (1) nonspecifically clears the infectious agent using preformed components or (2) produces specific cells and molecules directed against the foreign invader. The latter response is traditionally called an* **immune response.** The foreign invader that induces and reacts with immune cells and the molecules it induced (such as antibodies) is called an *antigen*. These two responses, or two kinds of immunity—innate and acquired—are the subject of the pages that follow.

Innate immunity *(also called natural resistance) operates nonspecifically during the early phases of an immune response.* Specific recognition of pathogens initially activates nonspecific cells and molecules. Innate immunity serves as the first line of defense and includes both external and internal nonspecific responses. External defenses occur in those areas of the body exposed to the outside environment (the contact areas for pathogens). Internal defenses come into play when the pathogen has penetrated the external defenses. *Taken together, the components of innate immunity are preformed* (the components are present before challenge), *standardized* (the response magnitude is consistent), *without memory* (the host does not realize it has been reexposed to the same invader), and *nonspecific* (innate immunity does not distinguish between invaders).

An organism's innate immunity depends on its species, race or strain, and sex. Humans demonstrate innate immunity to hog cholera and canine distemper. Dogs are resistant to anthrax, whereas humans, cattle, and sheep are not. Humans get mumps, but cats and dogs do not. The genetic endowment of the host determines this immunity. In humans, different levels of resistance are also attributable to race. African Americans and Native Americans are more susceptible to tuberculosis, while Caucasians are more susceptible to diphtheria and influenza. The sexes do not have equal resistance to pathogens; for example, certain strains of female mice are more resistant than males to *Listeria monocytogenes* infections.

External Innate Immunity, Natural Barriers to Infection, Prevents the Penetration of Pathogens Into Tissues

External, innate immunity (skin, body secretions, and mucous membranes) prevents the penetration of pathogens into host tissues. Intact skin prevents penetration of most pathogens; exceptions include *Treponema pallidum* and *Schistosoma mansoni* (the causative agents of syphilis and schistosomiasis, respectively). *T. pallidum* is acquired through sexual contact, attaches to host cells by coating itself with fibronectin, and invades intact mucous membranes or abraded skin by boring through them. *S. mansoni* can be acquired by contact with water containing the infective forms, which penetrate the skin by means of enzymes that break down the skin. Skin also secrets lactic acid and fatty acids that act as bacteriostatic agents by lowering skin pH. Tears protect the eye by providing a washing action. Tears also contain a hydrolytic enzyme against gram-positive bacteria called *lysozyme*. If pathogens are inhaled, mucus and the ciliated epithelium of the respiratory tract act as filters. If pathogens are swallowed, mucus in the digestive tract prevents adsorption and penetration of pathogens into cells. The low pH in the stomach kills organisms, and the normal flora of the lower intestine inhibits the attachment of pathogens.

Internal Innate Immunity Offers Many Forms of Protection After Pathogens Enter the Body

If a pathogen breeches the external innate defenses and invades the tissues, internal defense mechanisms provide protection. Internal, innate immunity includes three general mechanisms: (1) *physiologic barriers,* (2) *phagocytosis,* and (3) *inflammation*. Physiologic barriers offer inhospitable environments to pathogens. These barriers include body temperature and oxygen tension. For example, chickens are resistant to anthrax because of their high body temperature. If their temperature is lowered, they become susceptible. Anaerobic organisms (such as *Clostridium perfringens,* the causative agent of gangrene) cannot grow in tissues

where oxygen concentrations are high. Microorganisms themselves also can activate physiologic barriers called *complement proteins* that mediate cell lysis. Virally infected cells release *interferons,* which interfere with the infection of neighboring cells by the viruses.

A more effective innate internal defense is phagocytosis. **Phagocytosis** *involves the engulfment and destruction of pathogens and particulate matter by cells of the* **mononuclear phagocyte system.** The cells that make up this network are the *mononuclear phagocytic cells* (monocytes and macrophages). These cells also provide help during acquired immunity. Monocytes and macrophages are called *professional* phagocytes—professional in the sense that their primary role is phagocytosis. Phagocytic cells, the first line of internal defense, respond immediately and without specificity (Figure 1-1). Macrophages ingest and digest whole bacteria and even injured and dead host cells. Macrophages constitutively express receptors for polysaccharides found on bacteria; these receptors facilitate phagocytosis. Also, during phagocytosis, macrophages release powerful chemical molecules, called *monokines,* such as interleukin-1, interleukin-6, and tumor necrosis factor-α that activate many nonspecific protective effects through the inflammatory response. However, phagocytosis against soluble antigens (such as toxins) is poor.

Another important group of phagocytic cells, filled with granules containing potent digestive chemicals, not included in the mononuclear phagocyte system are the *polymorphonuclear neutrophilic leukocytes,* or *neutrophils* for short (so named because they exhibit large, lobed nuclei). These cells are arbitrarily excluded from the mononuclear phagocyte system because they are not participants in normal specific immune induction reactions; they only internalize microorganisms for digestion, not for subsequent presentation to other immune cells. Along with their phagocytic activity, neutrophils are the main source for small peptides called *defensins*. Defensins have a broad antimicrobial spectrum and exert nonspecific cytotoxic activity against a wide range of normal and malignant targets. Another group of granule-filled cells called *natural killer (NK) cells* are not phagocytic but contribute to nonspecific defense against infected body cells and tumor cells.

The other component of the internal innate defenses is a complex group of reactions leading to **inflammation.** The inflammatory response is initiated by chemical mediators whenever phagocytosis alone fails to prevent infection or when tissues are injured. Inflammation (literally, "setting on fire") of a particular body region is indicated by the suffix *-itis;* for example, inflammation of the tonsils is called *tonsillitis,* and

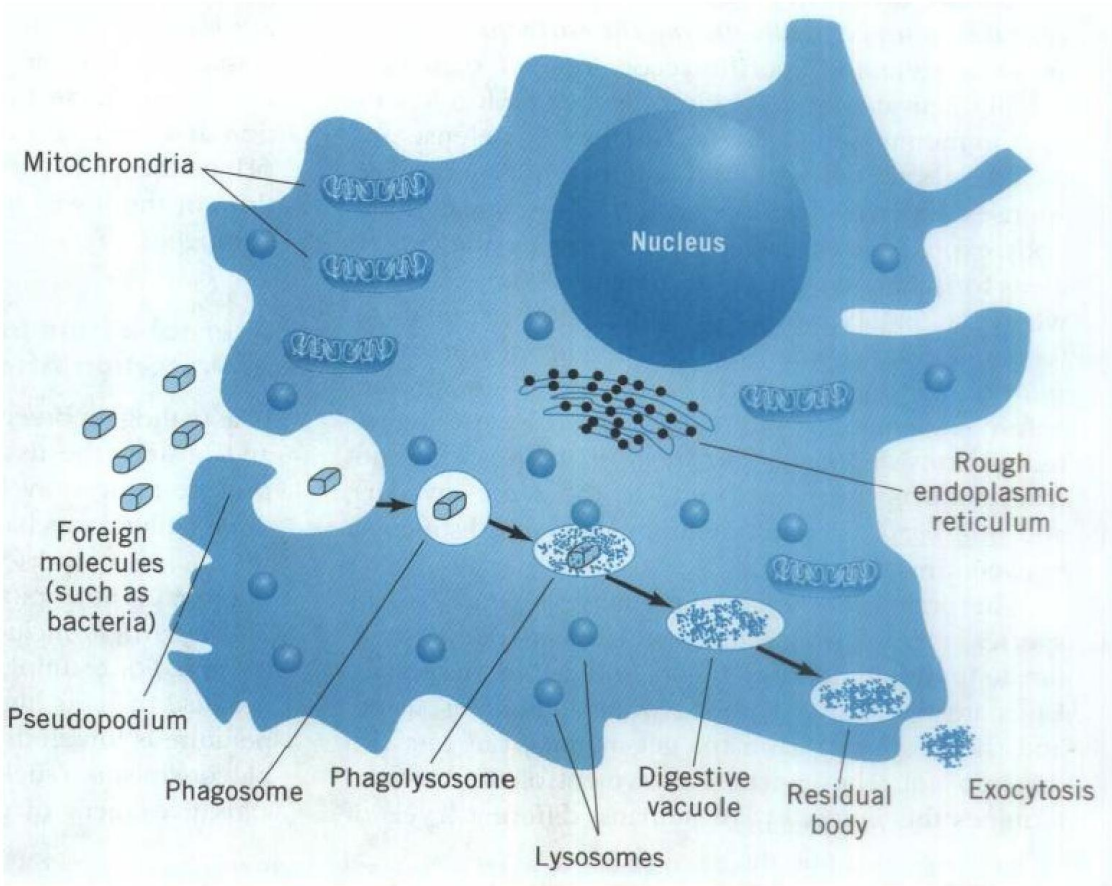


FIGURE 1-1 Phagocytosis. Cells of the mononuclear phagocyte system are attracted to the site of infection by factors released by pathogens, damaged host cells, and other blood components. The phagocytes engulf the pathogens, using pseudopodia, and internalize them as membrane-bound organelles (*phagosomes*) within the phagocyte. The phagosomes fuse with other organelles (*lysosomes*) containing hydrolytic enzymes. These organelles are then called *phagolysosomes.* Inside the phagolysosome, azurophile and specific granules discharge two groups of toxic substances into the organelle: (1) oxygen-dependent products formed by reactive oxygen metabolites and (2) oxygen-independent reactants, such as proteases, lactoferrin, and phospholipase A_2. Organisms are killed by the action of superoxide ions, hypochlorite, and hydrogen peroxide. The phagocyte's activity is enhanced by other parts of the immune system.

inflammation of the appendix is called *appendicitis*. The four cardinal signs of inflammation were described by the Roman physician Celsus roughly 2000 years ago. The four distinct symptoms that always accompany short-term, or acute, inflammation are redness, swelling, heat, and pain. Two hundred years after Celsus's description, another physician, Galen, added a fifth sign: loss of function. *Inflammation collectively involves a series of vascular events that serve as a defense mechanism. Inflammation includes (1) clotting mechanism activation, (2) increased blood flow, (3) increased capillary permeability, and (4) enhanced influx of phagocytic cells.* At the site of infection, the clotting mechanism in the blood is activated. As pathogens are trapped in the clots, the infection becomes localized. At the same time, immune cells (mostly phagocytic cells) move to the site in response to chemicals. The first cells, neutrophils, accumulate within 30–60 min. If the cause of the inflammatory response persists beyond this time, within 5–6 hr macrophages and lymphocytes will infiltrate the area. If the inflammation continues, it will be augmented by elements of acquired immunity including antibodies and molecules from activated lymphocytes. These cells attach to the newly expressed adhesion molecules on the surrounding blood vessel walls. Vasodilating substances such as histamine and bradykinin increase blood flow to the site of infection and help direct more phagocytic cells to the area. Because these substances also cause increased capillary permeability, the blood vessel walls near the infection site become more permeable to the passage of phagocytic cells into the tissue spaces. Once in the tissue spaces, phagocytic cells can engulf the pathogens, mediate repair, and produce molecules that control further cellular interactions.

Multiple mediator systems, including soluble blood plasma proteins of the clotting system, the kinin system, and the complement system help regulate inflammation. The molecules that induce these systems are derived from invading microorganisms, injured tissues, and products from participating white blood cells. One of the better-characterized groups of molecules produced during tissue-damaging infections are the serum *acute-phase proteins*. One specific acute-phase protein, *C-reactive protein,* is produced by the liver in response to macrophage-derived interleukin-6 (IL-6). C-reactive protein binds to the C-polysaccharide cell-wall component of many bacteria and fungi and activates the complement system. Surface-associated complement increases phagocytosis and promotes complement-mediated lysis of the organism.

Because microorganisms evolve rapidly, they can devise ways to evade the standardized innate immune responses of slower-evolving hosts. Vertebrates use an additional immune recognition strategy called *acquired*, or *adaptive* or *specific, immunity*. Acquired immunity permits the host to recognize and respond to a specific invader, even without prior exposure, and is marked by an enhanced response on repeated exposures to the invader. Nonetheless, both innate and acquired immune defenses work together to enhance each other's effects. Innate mechanisms reduce the workload and set the stage for acquired defenses, and acquired mechanisms amplify and focus innate defenses. For example, the early interplay between NK cell-produced IL-4 and macrophage-produced IL-12 by the innate immune system determines the helper T lymphocyte type of the acquired immune response.

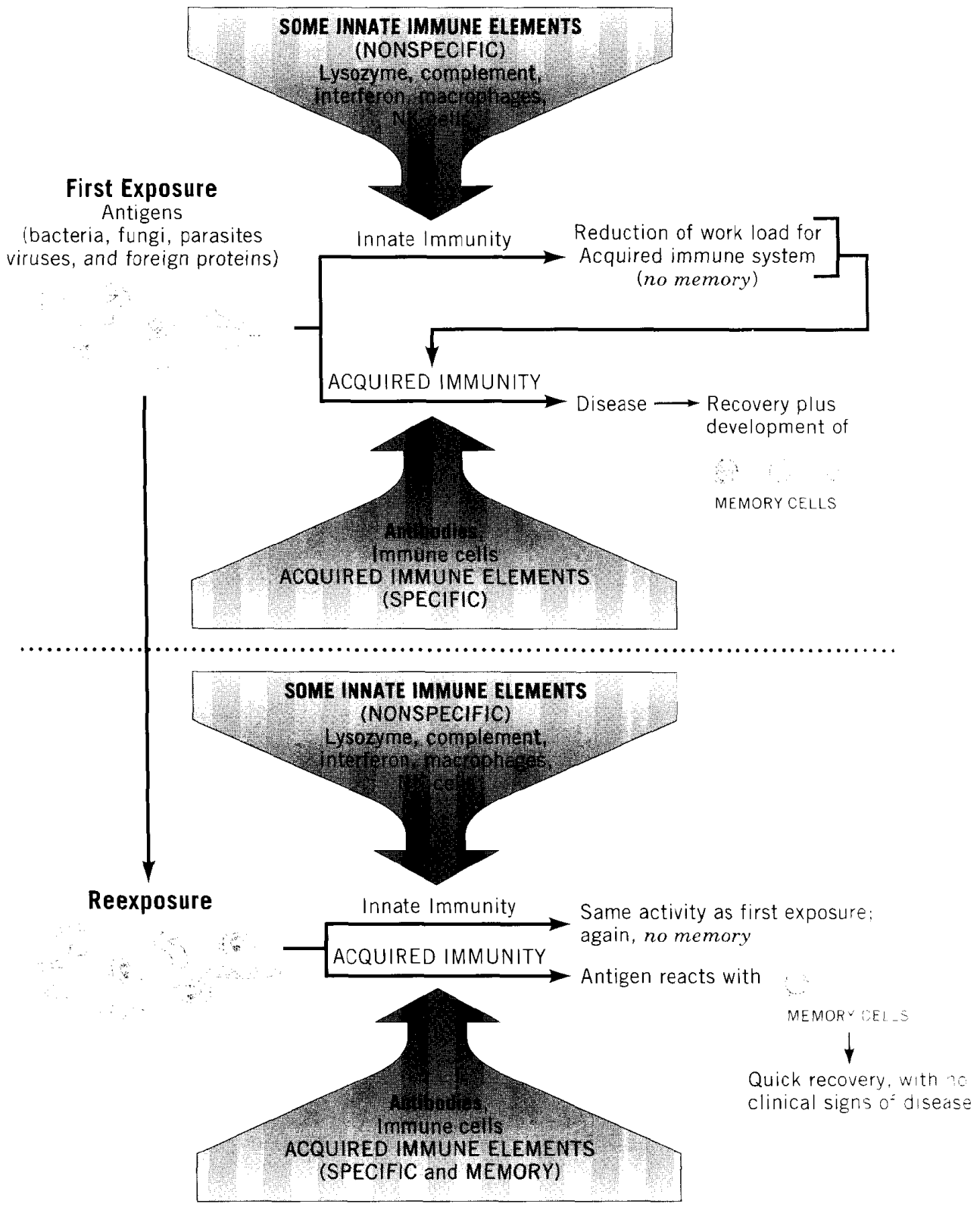
MINI SUMMARY

The immune system has two primary functions: (1) recognition of and defense against foreign substances and (2) immunosurveillance. The components of external and internal innate immunity are preformed, standardized, without memory, and nonspecific. When external defenses such as skin, secretions, and mucous membranes fail to prevent invasion by pathogens, internal innate defenses such as temperature, oxygen tension, phagocytosis, and inflammation control infections. Collectively, innate immunity reduces the workload for the immune system's specific defenses.

ACQUIRED IMMUNITY IN V[illegible]
THAT ACHIEVED THROUGH [illegible]
BECAUSE OF EITHER RECOVE[illegible]
DISEASE OR MEDICAL INTER[illegible]

Acquired immunity *develops during a host's lifetime and is based partly on the host's experiences* (Figure 1-2). This exposure process is called **immunization.** Acquired immunity is the surveillance mechanism of vertebrates that *specifically* recognizes foreign *antigens* and *selectively* eliminates them, and on reencountering the antigens has an enhanced response. Once a host has been exposed to a specific disease, the host will develop specific immunity and will probably not catch the disease again. This section briefly describes the six major characteristics of acquired immunity: *(1) specificity, (2) inducibility, (3) diversity, (4) memory, (5) distinguishing self from nonself,* and *(6) self-limiting.*

The persistence of a foreign antigen in a host initiates, or induces, acquired immunity. The recognition



This develops during the lifetime of a person. During the first exposure to antigen, the antigen-specific acquired immune system is activated and its antibodies and immune cells eliminate the antigen, while some of the immune cells become memory cells. The next time the individual encounters the same antigen, the immune system is primed (has memory cells) to destroy the antigen more quickly. Innate immune elements also help eliminate the antigen but lack specificity and memory cell development.

of and response to the antigen are highly specific, although immune specificity is not absolute. **Cross-reactions** *happen when acquired immunity to one substance gives immunity to another substance.* The earlier example of cowpox exposure causing immunity to smallpox illustrates cross-reactive protection (Fast Focus 7). This cross-reactivity is due to the physical similarity of the agents. If there was no immunity to a foreign substance before exposure, immunity to that substance can be induced by that substance. In fact, there is an opulence, or diversity, to the immune system's resources once the system is induced. It can recognize and mount a unique response to a seemingly endless variety (10^9) of antigens. This diversity is the result of a matching number of antigen receptors. Once immunity has been acquired, reexposure to the same antigen leads to a rapid and more effective immune response called a *secondary immune response. The ability of the immune system to remember antigenic intrusion is called* **immunologic memory** (in contrast, innate immunity lacks specificity and memory). Although the immune system can respond to at least 10^9 different foreign antigens, it is unresponsive to, or tolerant of, self antigens present in that individual. A breakdown in the maintenance of self-tolerance can lead to autoimmune disease. When the antigen has been brought under control, the immune response is downregulated through antigen removal, limited immune cell activity, and feedback regulation of the induced response.

FAST FOCUS 7

Cross-reactivity occurs when immunity to one substance gives immunity to some other substance. Ignorance of *limited* cross-reactivity among infectious agents delayed the use of vaccination for other diseases.

Acquired Immunity Is Humoral, Cell-Mediated, or Both

Vertebrates possess two types of acquired immunity based on the components the immune system uses to mediate immunity (Figure 1-3). **Humoral immunity**[6] *is mediated by antigen-specific blood proteins called antibodies* (see Chapter 4). Antibodies are secreted only by plasma cells (the daughter cells of *bone marrow- or bursa-derived, or B, lymphocytes*). This immunity protects against circulating extracellular antigens such as bacteria, microbial exotoxins, and viruses in their extracellular phase; that is, antibodies normally interact with circulating antigens but are unable to penetrate living cells. Humoral immunity's concomitant counterpart during an immune response is **cell-mediated immunity.** *This immunity is mediated by antigen-specific cells called thymus-derived, or T, lymphocytes; there are two subpopulations of T cells: T helper (T_H) cells and T cytotoxic (T_C) cells* (see Chapter 2). Cell-mediated immunity protects against intracellular parasites, such as viruses, and is important in the rejection of organ transplants and tumor cells. Because activated, antigen-specific B and T lymphocytes eliminate antigen, they are called *effector cells*. B cells act as effector cells by releasing antibodies, while T_H cells release communication molecules (*cytokines*) and T_C cells lyse target cells. Both humoral and cellular immune responses are evoked during antigen insult, although one of these two responses predominate based on the type of challenge.

[6]The word *humoral* is used because plasma cells secrete antibodies into the body's fluids, or humors.

Acquired Immunity Can Be Active or Passive

Humoral and cell-mediated acquired immunity can each be divided into **active** and **passive immunity.** Active immunity is acquired gradually (5 to 14 days after antigen exposure), lasts for years, and is highly protective. Passive immunity is immediate, lasts for days to months, has low to moderate protective effectiveness, and does not develop memory in the recipient (Fast Focus 8). Both active and passive immunity can be further subdivided into *natural* and *artificial* forms. In active immunity, an individual has acquired immunity mediated by antibodies or sensitized T lymphocytes (T cells) *formed by that individual.* If an individual is exposed to foreign substances naturally through the environment, rather than by immunization with a vaccine, that individual acquires the *natural* rather than the *artificial* form of active immunity. In passive immunity, an individual has acquired immunity mediated by antibodies (or sensitized T cells) *formed in another individual.* Antibodies are transferred from one host to another to confer immunity. The passage of antibodies between individuals is called *passive transfer. Adoptive transfer* is the passage of T cells (or any immune cells) between inbred animals of the same strain to grant immunity. The passage of antibodies from the mother to the fetus across the placenta or to the infant through the colostrum is a form of natural, passive acquired immunity. Artificial, passive acquired immunity occurs when preformed antibodies or immune cells are given to a nonimmune individual (such as gamma globulin injections for hepatitis).

FAST FOCUS 8

Some diseases, such as tetanus, often kill a person before immunity can be established. To avoid such a drastic result, the person can be given immediate protection by the infusion of antibodies, but the effect is short-lived.