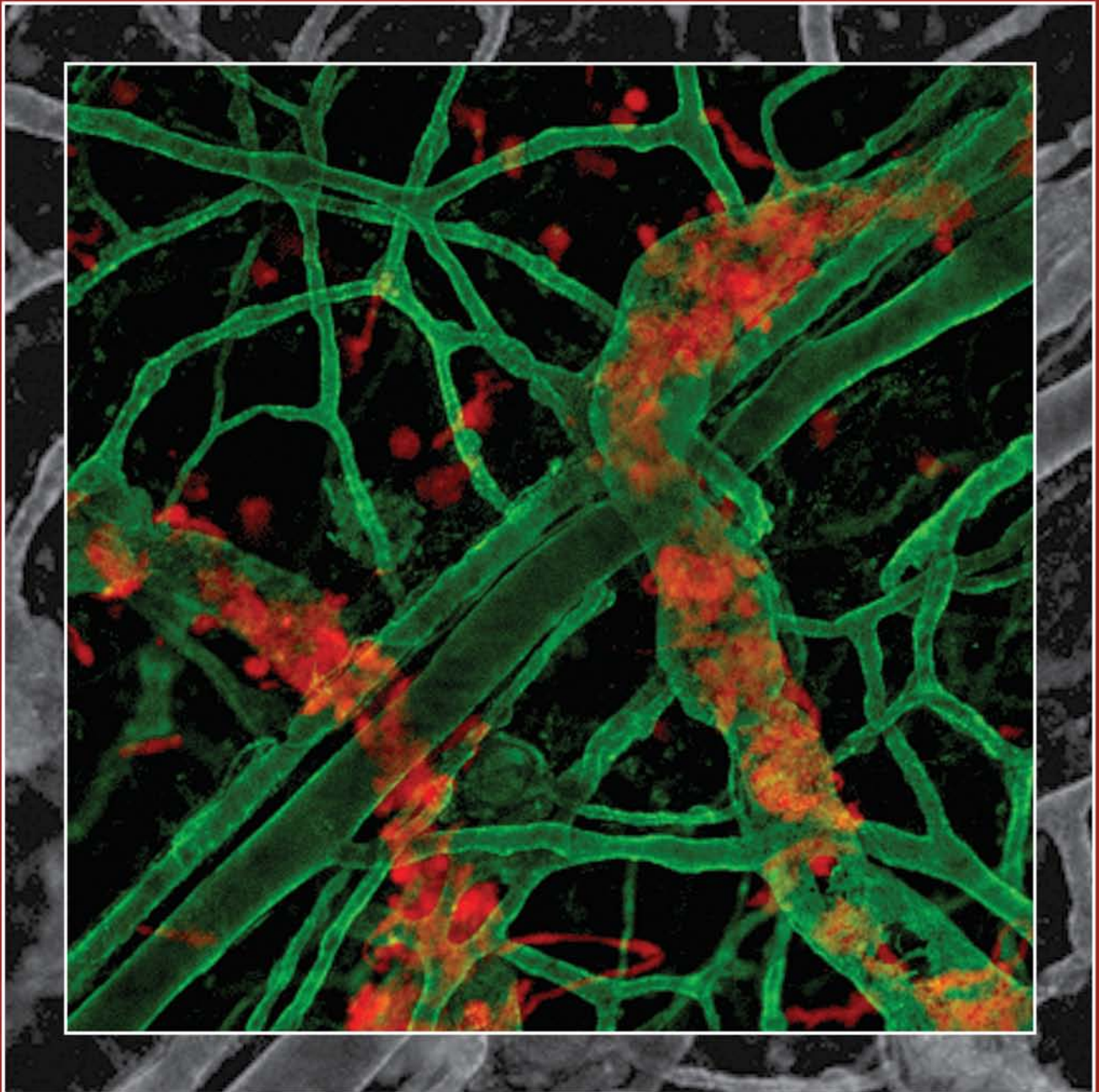# Kuby
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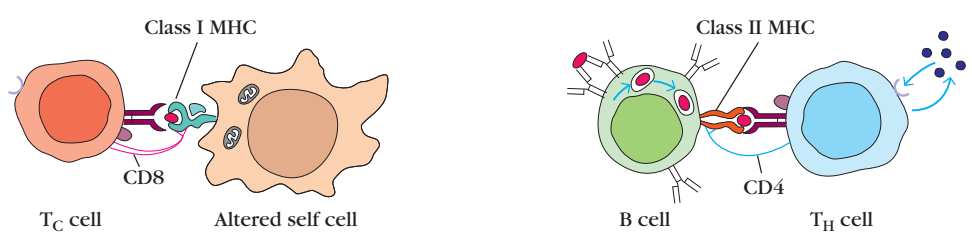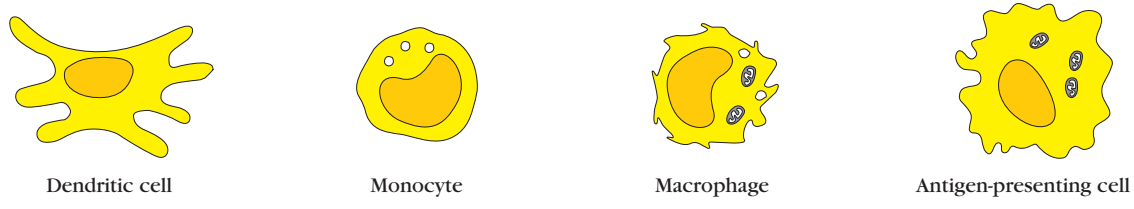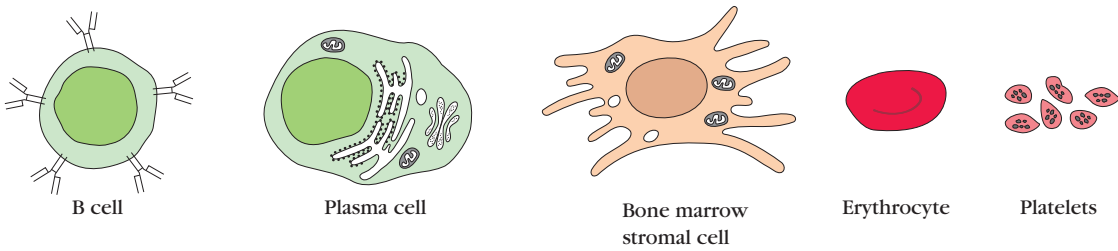

OWEN | PUNT | STRANFORD

KUBY

Immunology

Icons Used in This Book

Antigenic peptide

T cell receptor

CD4

Class I MHC

Cytokine

Antibody

CD3

CD8

Class II MHC

Cytokine receptor

Immature thymocyte

T_H cell

T_C cell

Cytotoxic T cell

Natural killer cell

B cell

Plasma cell

Bone marrow stromal cell

Erythrocyte

Platelets

Neutrophil

Basophil

Eosinophil

Mast cell

Dendritic cell

Monocyte

Macrophage

Antigen-presenting cell

Class I MHC

CD8

T_C cell

Altered self cell

Class II MHC

CD4

B cell

T_H cell

KUBY
Immunology

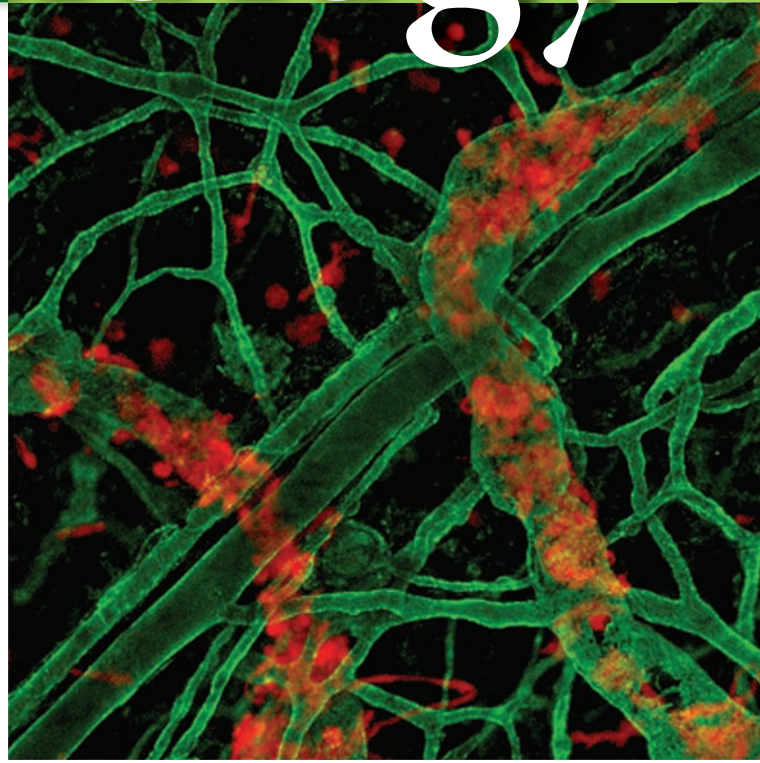**Judith A. Owen**
Haverford College

Jenni Punt
Haverford College

Sharon A. Stranford
Mount Holyoke College

with contributions by
Patricia P. Jones
Stanford University

Seventh Edition

To all our students, fellows, and colleagues who have made our careers in immunology a source of joy and excitement, and to our families who made these careers possible. We hope that future generations of immunology students will find this subject as fascinating and rewarding as we have.

About the Authors

All four authors are active scholars and teachers who have been/are recipients of research grants from the NIH and the NSF. We have all served in various capacities as grant proposal reviewers for NSF, NIH, HHMI, and other funding bodies as well as evaluating manuscripts submitted for publication in immunological journals. In addition, we are all active members of the American Association of Immunologists and have served our national organization in a variety of ways.

Judy Owen holds B.A. and M.A. (Hons) degrees from Cambridge University. She pursued her Ph.D. at the University of Pennsylvania with the late Dr. Norman Klinman and her postdoctoral fellowship with Dr. Peter Doherty in viral immunology. She was appointed to the faculty of Haverford College, one of the first undergraduate colleges to offer a course in immunology, in 1981. She teaches numerous laboratory and lecture courses in biochemistry and immunology and has received several teaching and mentorship awards. She is a participant in the First Year Writing Program and has been involved in curriculum development across the College.

Jenni Punt received her A.B. from Bryn Mawr College (*magna cum laude*) majoring in Biology at Haverford College, She received her VMD (*summa cum laude*) and Ph.D. in immunology from the University of Pennsylvania and was a Damon Runyon-Walter Winchell Physician-Scientist fellow with Dr. Alfred Singer at the National Institutes of Health. She was appointed to the faculty of Haverford College in 1996 where she teaches cell biology and immunology and performs research in T cell development and hematopoiesis. She has received several teaching awards and has contributed to the development of college-wide curricular initiatives.

Together, Jenni Punt and Judy Owen developed and ran the first AAI Introductory Immunology course, which is now offered on an annual basis.

Sharon Stranford obtained her B.A. with Honors in Biology from Arcadia University and her Ph.D. in Microbiology and Immunology from Hahnemann (now Drexel) University, where she studied autoimmunity with funding from the Multiple Sclerosis Foundation. She pursued postdoctoral studies in transplantation immunology at Oxford University in England, followed by a fellowship at the University of California, San Francisco, working on HIV/AIDS with Dr. Jay Levy. From 1999 to 2001, Sharon was a Visiting Assistant Professor of Biology at Amherst College, and in 2001 joined the faculty of Mount Holyoke College as a Clare Boothe Luce Assistant Professor. She teaches courses in introductory biology, cell biology, immunology, and infectious disease, as well as a new interdisciplinary course called Controversies in Public Health.

Pat Jones graduated from Oberlin College in Ohio with Highest Honors in Biology and obtained her Ph.D. in Biology with Distinction from the Johns Hopkins University. She was a postdoctoral fellow of the Arthritis Foundation for two years in the Department of Biochemistry and Biophysics at the University of California, San Francisco, Medical School, followed by two years as an NSF postdoctoral fellow in the Departments of Genetics and Medicine/Immunology at Stanford University School of Medicine. In 1978 she was appointed Assistant Professor of Biology at Stanford and is now a full professor. Pat has received several undergraduate teaching awards, was the founding Director of the Ph.D. Program in Immunology, and in July, 2011, she assumed the position of Director of Stanford Immunology, a position that coordinates activities in immunology across the university.

Contents

Chapter 3

Receptors and Signaling: B and T-Cell Receptors 65

Chapter 6

The Complement System   187

Chapter 7

The Organization and Expression of Lymphocyte Receptor Genes   225

Chapter 8

The Major Histocompatibility Complex and Antigen Presentation   261

Chapter 9

T-Cell Development   299

Chapter 10

B-Cell Development   329

Chapter 11

T-Cell Activation, Differentiation, and Memory 357

Chapter 12

B-Cell Activation, Differentiation, and Memory Generation 385

Chapter 13

Effector Responses: Cell-and Antibody-Mediated Immunity   415

Chapter 14

The Immune Response in Space and Time   451

Chapter 15

Allergy, Hypersensitivities, and Chronic Inflammation   485

Chapter 16

Tolerance, Autoimmunity, and Transplantation 517

Chapter 17

Infectious Diseases and Vaccines 553

Chapter 18

Immunodeficiency Disorders   593

Chapter 19

Cancer and the Immune System   627

Chapter 20

Experimental Systems and Methods   653

Feature Boxes in Kuby 7e

Preface

Like all of the previous authors of this book, we are dedicated to the concept that immunology is best taught and learned in an experimentally-based manner, and we have retained that emphasis with this edition. It is our goal that students should complete an immunology course not only with a firm grasp of content, but also with a clear sense of *how* key discoveries were made, what interesting questions remain, and how they might best be answered. We believe that this approach ensures that students both master fundamental immunological concepts and internalize a vision of immunology as an active and ongoing process. Guided by this vision, the new edition has been extensively updated to reflect the recent advances in all aspects of our discipline.

New Authorship

As a brand-new team of authors, we bring experience in both research and undergraduate teaching to the development of this new edition, which continues to reflect a dedication to pedagogical excellence originally modeled by Janis Kuby. We remain deeply respectful of Kuby's unique contribution to the teaching of immunology and hope and trust that this new manifestation of her creation will simply add to her considerable legacy.

Understanding Immunology As a Whole

We recognize that the immune system is an integrated network of cells, molecules, and organs, and that each component relies on the rest to function properly. This presents a pedagogical challenge because to understand the whole, we must attain working knowledge of many related pieces of information, and these do not always build upon each other in simple linear fashion. In acknowledgment of this challenge, this edition presents the "big picture" twice; first as an introductory overview to immunity, then, thirteen chapters later, as an integration of the details students have learned in the intervening text.

Specifically, Chapter 1 has been revised to make it more approachable for students who are new to immunology. The chapter provides a short historical background to the field and an introduction to some of the key players and their roles in the immune response, keeping an eye on fundamental concepts (Overview Figure 1-9). A new section directly addresses some of the biggest conceptual hurdles, but leaves the cellular and molecular details for later chapters.
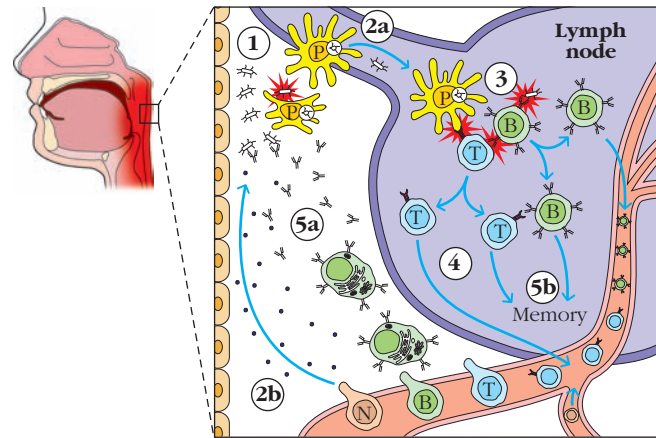
OVERVIEW FIGURE 1-9 Collaboration between innate and adaptive immunity in resolving an infection.

A new capstone chapter (Chapter 14) integrates the events of an immune response into a complete story, with particular reference to the advanced imaging techniques that have become available since the writing of the previous edition. In this way, the molecular and cellular details presented in Chapters 2-13 are portrayed in context, a moving landscape of immune response events in time and space (Figure 14-5).
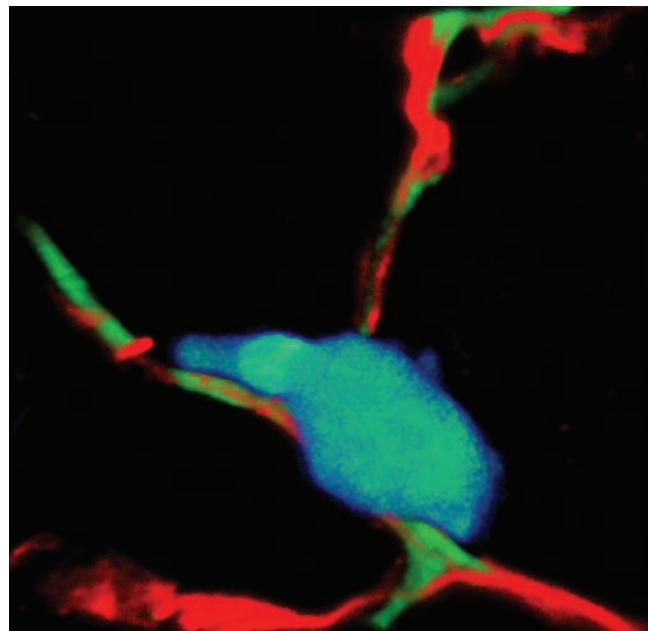
FIGURE 14-5 A T cell (blue) on a fibroblastic reticular network (red and green) in the lymph node.

Focus on the Fundamentals

The order of chapters in the seventh edition has been revised to better reflect the sequence of events that occurs naturally during an immune response in vivo. This offers instructors the opportunity to lead their students through the steps of an immune response in a logical sequence, once they have learned the essential features of the tissues, cells, molecular structures, ligand-receptor binding interactions, and signaling pathways necessary for the functioning of the immune system. The placement of innate immunity at the forefront of the immune response enables it to take its rightful place as the first, and often the only, aspect of immunity that an organism needs to counter an immune insult. Similarly, the chapter on complement is located within the sequence in a place that highlights its function as a bridge between innate and adaptive immune processes. However, we recognize that a course in immunology is approached differently by each instructor. Therefore, as much as possible, we have designed each of the chapters so that it can stand alone and be offered in an alternative order.

Challenging All Levels

While this book is written as a text for students new to immunology, it is also our intent to challenge students to reach deeply into the field and to appreciate the connections with other aspects of biology. Instead of reducing difficult topics to vague and simplistic forms, we instead present them with the level of detail and clarity necessary to allow the beginning student to find and understand information they may need in the future. This offers the upper level student a foundation from which they can progress to the investigation of advances and controversies within the current immunological literature. Supplementary focus boxes have been used to add nuance or detail to discussions of particular experiments or ideas without detracting from the flow of information. These boxes, which address experimental approaches, evolutionary connections, clinical aspects, or advanced material, also allow instructors to tailor their use appropriately for individual courses. They provide excellent launching points for more intensive in class discussions relevant to the material.

Some of the most visible changes and improvements include:

- A rewritten chapter on the cells and organs of the immune system (Chapter 2) that includes up to date images reflecting our new understanding of the microenvironments where the host immune system develops and responds.

- The consolidation of signaling pathways into two chapters: Chapter 3 includes a basic introduction to ligand:receptor interactions and principles of receptor

signaling, as well as to specific molecules and pathways involved in signaling through antigen receptors. Chapter 4 includes a more thorough introduction to the roles of cytokines and chemokines in the immune response.

- An expanded and updated treatment of innate immunity (Chapter 5), which now includes comprehensive coverage of the many physical, chemical, and cellular defenses that constitute the innate immune system, as well as the ways in which it activates and regulates adaptive immunity.

- Substantial rewriting of chapters concerned with complement (Chapter 6) and antigen receptor gene rearrangement (Chapter 7). These chapters have been extensively revised for clarity in both text and figures. The description of the complement system has been updated to include the involvement of complement proteins in both innate and adaptive aspects of immunity.

- A restructured presentation of the MHC, with the addition of new information relevant to cross-presentation pathways (Chapter 8) (Figure 8-22b).
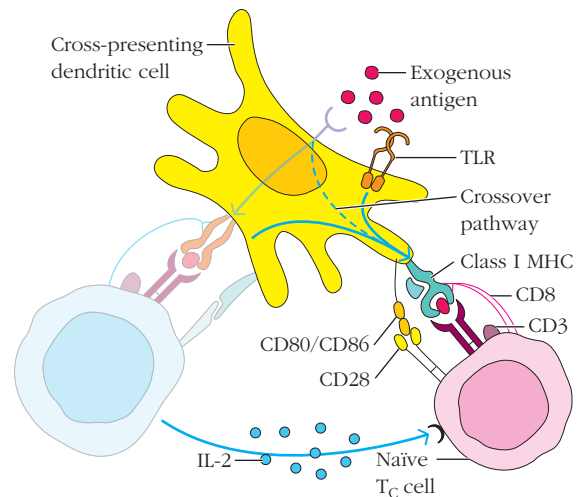
FIGURE 8-22b Exogenous antigen activation of naïve T_c cells requires DC licensing and cross-presentation

- The dedication of specialized chapters concerned with T cell development and T cell activation (Chapters 9 and Chapter 11, respectively). Chapter 11 now includes current descriptions of the multiple helper T cell subsets that regulate the adaptive immune response.

- Substantially rewritten chapters on B cell development and B cell activation (Chapters 10 and 12, respectively) that address the physiological locations as well as the nature of the interacting cells implicated in these processes.

- An updated discussion of the role of effector cells and molecules in clearing infection (Chapter 13), including a more thorough treatment of NK and NKT cells.

- A new chapter that describes advances in understanding and visualizing the dynamic behavior and activities of immune cells in secondary and tertiary tissue (Chapter 14).
- Substantial revision and updating of the clinical chapters (Chapters 15-19) including the addition of several new clinically relevant focus boxes.
- Revised and updated versions of the final methods chapter (Chapter 20), and the appendices of CD antigens, chemokines, and cytokines and their receptors.

Throughout the book, we attempt to provide a "big picture" context for necessary details in a way that facilitates greater student understanding.

Recent Advances and Other Additions

Immunology is a rapidly growing field, with new discoveries, advances in techniques, and previously unappreciated connections coming to light every day. The 7th edition has been thoroughly updated throughout, and now integrates the following new material and concepts:

- New immune cell types and subtypes, as well as the phenotypic plasticity that is possible between certain subtypes of immune cells.
- A greater appreciation for the wide range of mechanisms responsible for innate immunity and the nature and roles of innate responses in sensing danger, inducing inflammation, and shaping the adaptive response (Figure 5-18).
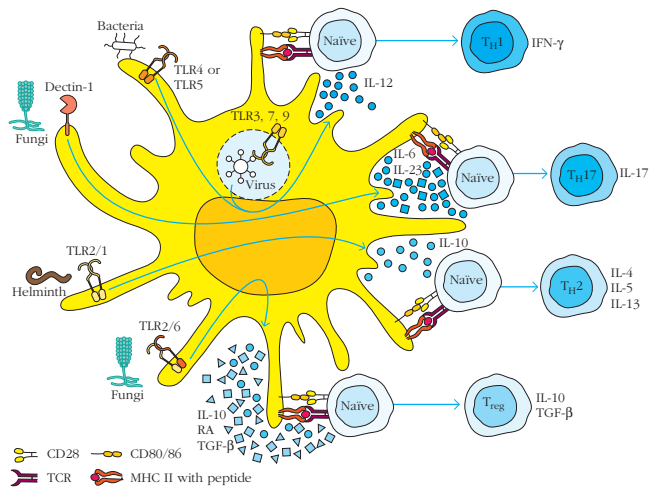
FIGURE 5-18 Differential signaling through dendritic cell PRRs influences helper T cell functions.

- Regulation of immunity, including new regulatory cell types, immunosuppressive chemical messengers and the roles these play, for example, in tolerance and in the nature of responses to different types of antigens (Figure 9-10).
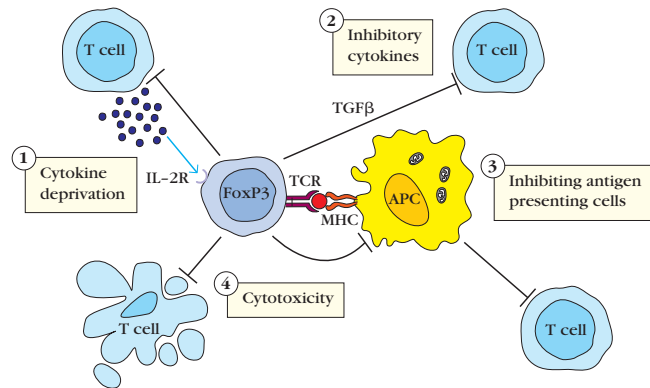
FIGURE 9-10 How regulatory T cells inactivate traditional T cells.

- The roles of the microbiome and commensal organisms in the development and function of immunity, as well as the connections between these and many chronic diseases.
- A new appreciation for the micro environmental substructures that guide immune cell interactions with antigen and with one another (Figure 14-11a).
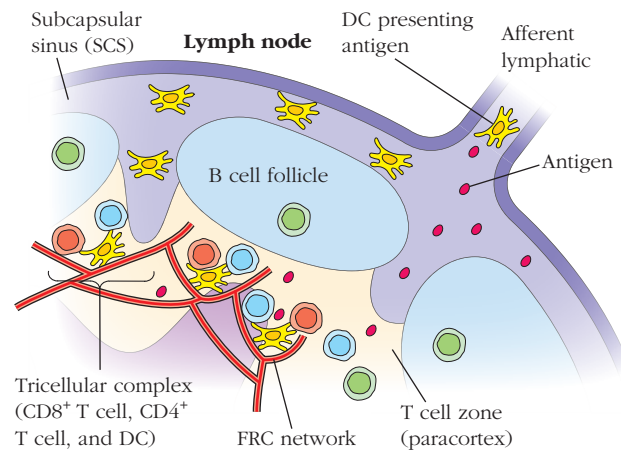
FIGURE 14-11a How antigen travels into a lymph node.

- Many technical advances, especially in the areas of imaging and sequencing, which have collectively enhanced our understanding of immune function and cellular interactions, allowing us to view the immune response in its natural anatomical context, and in real time (see Figure 14-5).

Connections to the Bench, the Clinic, and Beyond

We have made a concerted effort in the 7th edition to integrate experimental and clinical aspects of immunology into the text. In Chapter 2, illustrations of immune cells and tissues are shown alongside histological sections or, where possible, electron

micrographs, so students can see what they actually look like. Throughout the text, experimental data are used to demonstrate the bases for our knowledge (Figure 3-4b), and the clinical chapters at the end of the book (Chapters 15 through 19) describe new advances, new challenges, and newly appreciated connections between the immune system and disease.
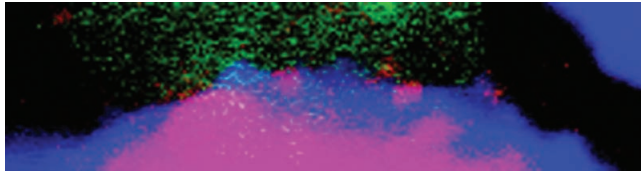
FIGURE 3-4b Targeted delivery of cytokines (pink).

Featured Boxes

Associated with each chapter are additional boxed materials that provide specialized information on historically-important studies (Classic Experiments) that changed the way immunologists viewed the field, noteworthy new breakthroughs (Advances) that have occurred since the last edition, the clinical relevance of particular topics (Clinical Focus) and the evolution of aspects of immune functioning (Evolution). Examples of such boxes are "The Prime and Pull Vaccine strategy," "Genetic defects in components of innate and inflammatory responses associated with disease," "The role of miRNAs in the control of B cell development" and an updated "Stem cells: Clinical uses and potential." We have involved our own undergraduate students in the creation of some of these boxes, which we believe have greatly benefitted from their perspective on how to present interesting material effectively to their fellow students.

Critical Thinking and Data Analysis

Integration of experimental evidence throughout the book keeps students focused on the how and why. Detailed and clear descriptions of the current state of the field provide students with the knowledge, skills, and vocabulary to read critically in the primary literature. Updated and revised study questions at the end of the chapter range from simple recall of information to analyzing original data or proposing hypotheses to explain remaining questions in the field. Classic Experiment boxes throughout the text help students to appreciate the seminal experiments in immunology and how they were conducted, providing a bridge to the primary research articles and emphasizing data analysis at every step.

Media and Supplements

NEW! ImmunoPortal (courses.bfwpub.com/immunology7e)

This comprehensive and robust online teaching and learning tool combines a wealth of media resources, vigorous assessment, and helpful course management features into one convenient, fully customizable space.

ImmunoPortal Features:

NEW! Kuby Immunology Seventh Edition e-Book—also available as a standalone resource (ebooks.bfwpub.com/immunology7e)

This online version of the textbook combines the contents of the printed book, electronic study tools, and a full complement of student media, including animations and videos. Students can personalize their e-Book with highlighting, bookmarking, and note-taking features. Instructors can customize the e-Book to focus on specific sections, and add their own notes and files to share with their class.

NEW! LearningCurve—A Formative Quizzing Engine

With powerful adaptive quizzing, a game-like format, and the promise of significantly better grades, *LearningCurve* gives instructors a quickly implemented, highly effective new way to get students more deeply involved in the classroom. Developed by experienced teachers and experts in educational technology, *LearningCurve* offers a series of brief, engaging activities specific to your course. These activities put the concept of "testing to learn" into action with adaptive quizzing that treats each student as an individual with specific needs:

- Students work through *LearningCurve* activities one question at a time.
- With each question, students get immediate feedback. Responses to incorrect answers include links to book sections and other resources to help students focus on what they need to learn.
- As they proceed toward completion of the activity, the level of questioning adapts to the level of performance. The questions become easier, harder, or the same depending on how the student is doing.
- And with a more confident understanding of assigned material, students will be more actively engaged during classtime.

Resources

The Resources center provides quick access to all instructor and student resources for Kuby Immunology.

For Instructors—

All instructor media are available in the ImmunoPortal and on the Instructor Resource DVD.

NEW! test bank—over 500 dynamic questions in PDF and editable Word formats include multiple-choice and short-answer problems, rated by level of difficulty and Bloom's Taxonomy level.

Fully optimized JPEG files of every figure, photo, and table in the text, featuring enhanced color, higher resolution, and enlarged fonts. Images are also offered in PowerPoint® format for each chapter.

Animations of complex text concepts and figures help students better understand key immunological processes.

Videos specially chosen by the authors to complement and supplement text concepts.

For Students—

All of these resources are also available in the ImmunoPortal.

- Student versions of the Animations and Videos, to help students understand key mechanisms and techniques at their own pace.

- Flashcards test student mastery of vocabulary and allow students to tag the terms they've already learned.
- Immunology on the Web weblinks introduce students to a world of online immunology resources and references.

Assignments

In this convenient space, ImmunoPortal provides instructors with the ability to assign any resource, as well as e-Book readings, discussion board posts, and their own materials. A gradebook tracks all student scores and can be easily exported to Excel or a campus Course Management System.

Acknowledgements

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Overview of the Immune System

The immune system evolved to protect multicellular organisms from pathogens. Highly adaptable, it defends the body against invaders as diverse as the tiny (~30 nm), intracellular virus that causes polio and as large as the giant parasitic kidney worm *Dioctophyme renale*, which can grow to over 100 cm in length and 10 mm in width. This diversity of potential pathogens requires a range of recognition and destruction mechanisms to match the multitude of invaders. To accomplish this feat, vertebrates have evolved a complicated and dynamic network of cells, molecules, and pathways. Although elements of these networks can be found throughout the plant and animal kingdoms, the focus of this book will be on the highly evolved mammalian immune system.

The fully functional immune system involves so many organs, molecules, cells, and pathways in such an interconnected and sometimes circular process that it is often difficult to know where to start! Recent advances in cell imaging, genetics, bioinformatics, as well as cell and molecular biology, have helped us to understand many of the individual players in great molecular detail. However, a focus on the details (and there are many) can make taking a step back to see the bigger picture challenging, and it is often the bigger picture that motivates us to study immunology. Indeed, the field of immunology can be credited with the vaccine that eradicated smallpox, the ability to transplant organs between humans, and the drugs used today to treat asthma. Our goal in this chapter is therefore to present the background and concepts in immunology that will help bridge the gap between the cellular and molecular detail presented in subsequent chapters and the complete picture of an immune response. A clear understanding of each of the many players involved will help one appreciate the intricate coordination of an immune system that makes all of this possible.

The study of immunology has produced amazing and fascinating stories (some of which you will see in this book), where host and microbe engage in battles waged over both minutes and millennia. But the immune system is also much more than an isolated component of the body, merely responsible for search-and-destroy missions. In fact, it interleaves with many of the other body systems,
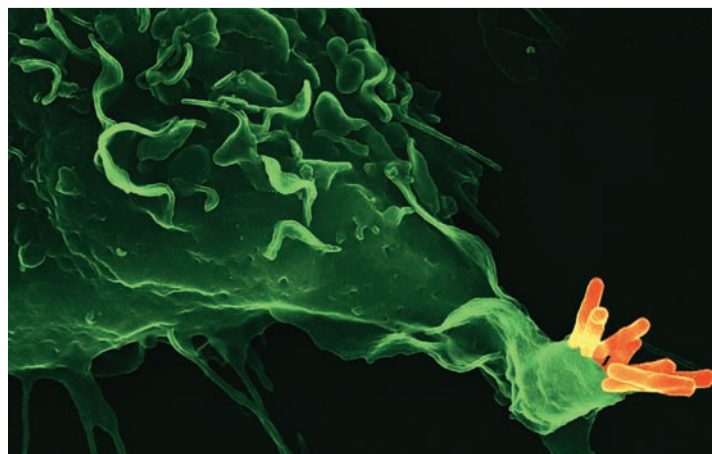
A phagocytic cell (macrophage, green) engulfing the bacteria that cause tuberculosis (orange). Max Planck Institute for Infection Biology/Dr. Volker Brinkmann

- A Historical Perspective of Immunology
- Important Concepts for Understanding the Mammalian Immune Response
- The Good, Bad, and Ugly of the Immune System

including the endocrine, nervous, and metabolic systems, with more connections undoubtedly to be discovered in time. Finally, it has become increasingly clear that elements of immunity play key roles in regulating homeostasis in the body for a healthy balance. Information gleaned from the study of the immune system, as well as its connections with other systems, will likely have resounding repercussions across many basic science and biomedical fields, not to mention in the future of clinical medicine.

This chapter begins with a historical perspective, charting the beginnings of the study of immunology, largely driven by the human desire to survive major outbreaks of infectious disease. This is followed by presentation of a few key concepts that are important hallmarks of the mammalian immune response, many of which may not have been encountered elsewhere in basic biology. This is not meant as a comprehensive overview of the mammalian immune system but rather as a means for jumping the large conceptual hurdles frequently encountered as one begins to describe the complexity and interconnected nature of the immune response. We hope this will whet the appetite and prepare the reader for a more thorough discussion of the specific components of immunity presented in the

following chapters. We conclude with a few challenging clinical situations, such as instances in which the immune system fails to act or becomes the aggressor, turning its awesome powers against the host. More in-depth coverage of these and other medical aspects of immunology can be found in the final chapters of this book.

A Historical Perspective of Immunology

The discipline of immunology grew out of the observation that individuals who had recovered from certain infectious diseases were thereafter protected from the disease. The Latin term *immunis,* meaning "exempt," is the source of the English word **immunity**, a state of protection from infectious disease. Perhaps the earliest written reference to the phenomenon of immunity can be traced back to Thucydides, the great historian of the Peloponnesian War. In describing a plague in Athens, he wrote in 430 BC that only those who had recovered from the plague could nurse the sick because they would not contract the disease a second time. Although early societies recognized the phenomenon of immunity, almost 2000 years passed before the concept was successfully converted into medically effective practice.

Early Vaccination Studies Led the Way to Immunology

The first recorded attempts to deliberately induce immunity were performed by the Chinese and Turks in the fifteenth century. They were attempting to prevent smallpox, a disease that is fatal in about 30% of cases and that leaves survivors disfigured for life (Figure 1-1). Reports suggest that the dried crusts derived from smallpox pustules were either inhaled or inserted into small cuts in the skin (a technique called *variolation*) in order to prevent this dreaded disease. In 1718, Lady Mary Wortley Montagu, the wife of the British ambassador in Constantinople, observed the positive effects of variolation on the native Turkish population and had the technique performed on her own children.

The English physician Edward Jenner later made a giant advance in the deliberate development of immunity, again targeting smallpox. In 1798, intrigued by the fact that milkmaids who had contracted the mild disease cowpox were subsequently immune to the much more severe smallpox, Jenner reasoned that introducing fluid from a cowpox pustule into people (i.e., inoculating them) might protect them from smallpox. To test this idea, he inoculated an eight-year-old boy with fluid from a cowpox pustule and later intentionally infected the child with smallpox. As predicted, the child did not develop smallpox. Although this represented a major breakthrough, as one might imagine, these sorts of human studies could not be conducted under current standards of medical ethics.

Jenner's technique of inoculating with cowpox to protect against smallpox spread quickly through Europe. However, it

FIGURE 1-1 African child with rash typical of smallpox on face, chest, and arms. Smallpox, caused by the virus *Variola major,* has a 30% mortality rate. Survivors are often left with disfiguring scars. *[Centers for Disease Control.]*

was nearly a hundred years before this technique was applied to other diseases. As so often happens in science, serendipity combined with astute observation led to the next major advance in immunology: the induction of immunity to cholera. Louis Pasteur had succeeded in growing the bacterium that causes fowl cholera in culture, and confirmed this by injecting it into chickens that then developed fatal cholera. After returning from a summer vacation, he and colleagues resumed their experiments, injecting some chickens with an old bacterial culture. The chickens became ill, but to Pasteur's surprise, they recovered. Interested, Pasteur then grew a fresh culture of the bacterium with the intention of injecting this lethal brew into some fresh, unexposed chickens. But as the story is told, his supply of fresh chickens was limited, and therefore he used a mixture of previously injected chickens and unexposed birds. Unexpectedly, only the fresh chickens died, while the chickens previously exposed to the older bacterial culture were completely protected from the disease. Pasteur hypothesized and later showed that aging had weakened the virulence of the pathogen and that such a weakened or **attenuated** strain could be administered to provide immunity against the disease. He called this attenuated strain a

vaccine (from the Latin *vacca*, meaning "cow"), in honor of Jenner's work with cowpox inoculation.

Pasteur extended these findings to other diseases, demonstrating that it was possible to attenuate a pathogen and administer the attenuated strain as a vaccine. In a now classic experiment performed in the small village of Pouilly-le-Fort in 1881, Pasteur first vaccinated one group of sheep with anthrax bacteria (*Bacillus anthracis*) that were attenuated by heat treatment. He then challenged the vaccinated sheep, along with some unvaccinated sheep, with a virulent culture of the anthrax bacillus. All the vaccinated sheep lived and all the unvaccinated animals died. These experiments marked the beginnings of the discipline of immunology. In 1885, Pasteur administered his first vaccine to a human, a young boy who had been bitten repeatedly by a rabid dog (Figure 1-2). The boy, Joseph Meister, was inoculated with a series of attenuated rabies virus preparations. The rabies vaccine is one of very few that can be successful when administered shortly after exposure, as long as the virus has not yet reached the central nervous system and begun to induce neurologic symptoms. Joseph lived, and later became a caretaker at the Pasteur Institute, which was opened in 1887 to treat the many rabies victims that began to flood in when word of Pasteur's success spread; it remains to this day an institute dedicated to the prevention and treatment of infectious disease.

FIGURE 1-2 Wood engraving of Louis Pasteur watching Joseph Meister receive the rabies vaccine. [*Source: From Harper's Weekly 29:836; courtesy of the National Library of Medicine.*]

Vaccination Is an Ongoing, Worldwide Enterprise

The emergence of the study of immunology and the discovery of vaccines are tightly linked. The development of effective vaccines for some pathogens is still a major challenge, discussed in greater detail in Chapter 17. However, despite many biological and social hurdles, vaccination has yielded some of the most profound success stories in terms of improving mortality rates worldwide, especially in very young children.

In 1977, the last known case of naturally acquired smallpox was seen in Somalia. This dreaded disease was eradicated by universal application of a vaccine similar to that used by Jenner in the 1790s. One consequence of eradication is that universal vaccination becomes unnecessary. This is a tremendous benefit, as most vaccines carry at least a slight risk to persons vaccinated. And yet in many cases every individual does not need to be immune in order to protect most of the population. As a critical mass of people acquire protective immunity, either through vaccination or infection, they can serve as a buffer for the rest. This principle, called **herd immunity**, works by decreasing the number of individuals who can harbor and spread an infectious agent, significantly decreasing the chances that susceptible individuals will become infected. This presents an important altruistic consideration: although many of us could survive infectious diseases for which we receive a vaccine (such as the flu), this is not true for everyone. Some individuals cannot receive the vaccine (e.g., the very young or immune compromised), and vaccination is never 100% effective. In other words, the susceptible, nonimmune individuals among us can benefit from the pervasive immunity of their neighbors.

However, there is a darker side to eradication and the end of universal vaccination. Over time, the number of people with no immunity to the disease will begin to rise, ending herd immunity. Vaccination for smallpox largely ended by the early to mid-1970s, leaving well over half of the current world population susceptible to the disease. This means that smallpox, or a weaponized version, is now considered a potential bioterrorism threat. In response, new and safer vaccines against smallpox are still being developed today, most of which go toward vaccinating U.S. military personnel thought to be at greatest risk of possible exposure.

In the United States and other industrialized nations, vaccines have eliminated a host of childhood diseases that were the cause of death for many young children just 50 years ago. Measles, mumps, chickenpox, whooping cough (pertussis), tetanus, diphtheria, and polio, once thought of as an inevitable part of childhood are now extremely rare or nonexistent in the United States because of current vaccination practices (Table 1-1). One can hardly estimate the savings to society resulting from the prevention of these diseases. Aside from suffering and mortality, the cost to treat these illnesses and their aftereffects or sequelae (such as paralysis, deafness, blindness, and mental retardation) is immense and dwarfs the costs of immunization. In fact, recent estimates suggest

TABLE 1-1	Cases of selected infectious disease in the United States before and after the introduction of effective vaccines		
	ANNUAL CASES/YR	CASES IN 2010	
Disease	**Prevaccine**	**Postvaccine**	**Reduction (%)**
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Rubeola (measles)	503,282	26	99.99
Mumps	152,209	2,612	98.28
Pertussis ("whooping cough")	147,271	27,550	81.29
Paralytic polio	16,316	0	100
Rubella (German measles)	47,745	5	99.99
Tetanus ("lockjaw")	1,314 (deaths)	26 (cases)	98.02
Invasive *Haemophilus influenzae*	20,000	3,151	84.25

SOURCE: Adapted from W. A. Orenstein et al., 2005. *Health Affairs* **24:**599 and CDC statistics of Notifiable Diseases.

that significant economic and human life benefits could be realized by simply scaling up the use of a few childhood vaccines in the poorest nations, which currently bear the brunt of the impact of these childhood infectious diseases. For example, it is estimated that childhood pneumonia alone, caused primarily by vaccine-preventable *Streptococcus pneumoniae* (aka, pneumococcus) and *Haemophilus influenzae* type b (aka, Hib), will account for 2.7 million childhood deaths in developing nations over the next decade if vaccine strategies in these regions remain unchanged.

Despite the many successes of vaccine programs, such as the eradication of smallpox, many vaccine challenges still remain. Perhaps the greatest current challenge is the design of effective vaccines for major killers such as malaria and AIDS. Using our increased understanding of the immune system, plus the tools of molecular and cellular biology, genomics, and proteomics, scientists will be better positioned to make progress toward preventing these and other emerging infectious diseases. A further issue is the fact that millions of children in developing countries die from diseases that are fully preventable by available, safe vaccines. High manufacturing costs, instability of the products, and cumbersome delivery problems keep these vaccines from reaching those who might benefit the most. This problem could be alleviated in many cases by development of future-generation vaccines that are inexpensive, heat stable, and administered without a needle. Finally, misinformation and myth surrounding vaccine efficacy and side effects continues to hamper many potentially life-saving vaccination programs (see Clinical Focus Box on p. 5).

Immunology Is About More Than Just Vaccines and Infectious Disease

For some diseases, immunization programs may be the best or even the only effective defense. At the top of this list are infec-tious diseases that can cause serious illness or even death in unvaccinated individuals, especially those transmitted by microbes that also spread rapidly between hosts. However, vaccination is not the only way to prevent or treat infectious disease. First and foremost is preventing infection, where access to clean water, good hygiene practices, and nutrient-rich diets can all inhibit transmission of infectious agents. Second, some infectious diseases are self-limiting, easily treatable, and nonlethal for most individuals, making them unlikely targets for costly vaccination programs. These include the common cold, caused by the Rhinovirus, and cold sores that result from Herpes Simplex Virus infection. Finally, some infectious agents are just not amenable to vaccination. This could be due to a range of factors, such as the number of different molecular variants of the organism, the complexity of the regimen required to generate protective immunity, or an inability to establish the needed immunologic memory responses (more on this later).

One major breakthrough in the treatment of infectious disease came when the first antibiotics were introduced in the 1920s. Currently there are more than a hundred different antibiotics on the market, although most fall into just six or seven categories based on their mode of action. Antibiotics are chemical agents designed to destroy certain types of bacteria. They are ineffective against other types of infectious agents, as well as some bacterial species. One particularly worrying trend is the steady rise in antibiotic resistance among strains traditionally amenable to these drugs, making the design of next-generation antibiotics and new classes of drugs increasingly important. Although antiviral drugs are also available, most are not effective against many of the most common viruses, including influenza. This makes preventive vaccination the only real recourse against many debilitating infectious agents, even those that rarely cause mortality in healthy adults. For instance, because of the high mutation rate of the influenza virus, each year a new flu vaccine must

BOX 1-1

Vaccine Controversy: What's Truth and What's Myth?

Despite the record of worldwide success of vaccines in improving public health, some opponents claim that vaccines do more harm than good, pressing for elimination or curtailment of childhood vaccination programs. There is no dispute that vaccines represent unique safety issues, since they are administered to people who are healthy. Furthermore, there is general agreement that vaccines must be rigorously tested and regulated, and that the public must have access to clear and complete information about them. Although the claims of vaccine critics must be evaluated, many can be answered by careful and objective examination of records.

A recent example is the claim that vaccines given to infants and very young children may contribute to the rising incidence of autism. This began with the suggestion that thimerosal, a mercury-based additive used to inhibit bacterial growth in some vaccine preparations since the 1930s, was causing autism in children. In 1999 the U.S. Centers for Disease Control and Prevention (CDC) and the American Association of Pediatricians (AAP) released a joint recommendation that vaccine manufacturers begin to gradually phase out thimerosal use in vaccines. This recommendation was based on the increase in the number of vaccines given to infants and was aimed at keeping children at or below Environmental Protection Agency (EPA)–recommended maximums in mercury exposure. However, with the release of this recommendation, parent-led public advocacy groups began a media-fueled campaign to build a case demonstrating

what they believed was a link between vaccines and an epidemic of autism. These AAP recommendations and public fears led to a dramatic decline in the latter half of 1999 in U.S. newborns vaccinated for hepatitis B. To date, no credible study has shown a scientific link between thimerosal and autism. In fact, cases of autism in children have continued to rise since thimerosal was removed from all childhood vaccines in 2001. Despite evidence to the contrary, some still believe this claim.

A 1998 study appearing in *The Lancet,* a reputable British medical journal, further fueled these parent advocacy groups and anti-vaccine organizations. The article, published by Andrew Wakefield, claimed the measles-mumps-rubella (MMR) vaccine caused pervasive developmental disorders in children, including autism spectrum disorder. More than a decade of subsequent research has been unable to substantiate these claims, and 10 of the original 12 authors on the paper later withdrew their support for the conclusions of the study. In 2010, *The Lancet* retracted the original article when it was shown that the data in the study had been falsified to reach desired conclusions. Nonetheless, in the years between the original publication of the *Lancet* article and its retraction, this case is credited with decreasing rates of MMR vaccination from a high of 92% to a low of almost 60% in certain areas of the United Kingdom. The resulting expansion in the population of susceptible individuals led to endemic rates of measles and mumps infection, especially in several areas of Europe, and is credited with thou-

sands of extended hospitalizations and several deaths in infected children.

Why has there been such a strong urge to cling to the belief that childhood vaccines are linked with developmental disorders in children despite much scientific evidence to the contrary? One possibility lies in the timing of the two events. Based on current AAP recommendations, in the United States most children receive 14 different vaccines and a total of up to 26 shots by the age of 2. In 1983, children received less than half this number of vaccinations. Couple this with the onset of the first signs of autism and other developmental disorders in children, which can appear quite suddenly and peak around 2 years of age. This sharp rise in the number of vaccinations young children receive today and coincidence in timing of initial autism symptoms is credited with sparking these fears about childhood vaccines. Add to this the increasing drop in basic scientific literacy by the general public and the overabundance of ways to gather such information (accurate or not). As concerned parents search for answers, one can begin to see how even scientifically unsupported links could begin to take hold as families grapple with how to make intelligent public health risk assessments.

The notion that vaccines cause autism was rejected long ago by most scientists. Despite this, more work clearly needs to be done to bridge the gap between public perception and scientific understanding.

Gross, L. 2009. A broken trust: Lessons from the vaccine–autism wars. *PLoS Biology* **7**:e1000114.
Larson, H.J., et al. 2011. Addressing the vaccine confidence gap. *Lancet* **378**:526.

be prepared based on a prediction of the prominent genotypes likely to be encountered in the next season. Some years this vaccine is more effective than others. If and when a more lethal and unexpected pandemic strain arises, there will be a race between its spread and the manufacture and administration of a new vaccine. With the current ease of worldwide travel, present-day emergence of a pandemic strain of influenza could dwarf the devastation wrought by the 1918 flu pandemic, which left up to 50 million dead.

However, the eradication of infectious disease is not the only worthy goal of immunology research. As we will see later, exposure to infectious agents is part of our evolutionary history, and wiping out all of these creatures could potentially cause more harm than good, both for the host and the environment. Thanks to many technical advances allowing scientific discoveries to move efficiently from the bench to the bedside, clinicians can now manipulate the immune response in ways never before possible. For example, treatments to boost, inhibit,

or redirect the specific efforts of immune cells are being applied to treat autoimmune disease, cancer, and allergy, as well as other chronic disorders. These efforts are already extending and saving lives. Likewise, a clearer understanding of immunity has highlighted the interconnected nature of body systems, providing unique insights into areas such as cell biology, human genetics, and metabolism. While a cure for AIDS and a vaccine to prevent HIV infection are still the primary targets for many scientists who study this disease, a great deal of basic science knowledge has been gleaned from the study of just this one virus and its interaction with the human immune system.

Immunity Involves Both Humoral and Cellular Components

Pasteur showed that vaccination worked, but he did not understand how. Some scientists believed that immune protection in vaccinated individuals was mediated by cells, while others postulated that a soluble agent delivered protection. The experimental work of Emil von Behring and Shibasaburo Kitasato in 1890 gave the first insights into the mechanism of immunity, earning von Behring the Nobel Prize in Physiology or Medicine in 1901 (Table 1-2). Von Behring and

TABLE 1-2	Nobel Prizes for immunologic research		
Year	**Recipient**	**Country**	**Research**
1901	Emil von Behring	Germany	Serum antitoxins
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff Paul Ehrlich	Russia Germany	Role of phagocytosis (Metchnikoff) and antitoxins (Ehrlich) in immunity
1913	Charles Richet	France	Anaphylaxis
1919	Jules Bordet	Belgium	Complement-mediated bacteriolysis
1930	Karl Landsteiner	United States	Discovery of human blood groups
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	F. Macfarlane Burnet Peter Medawar	Australia Great Britain	Discovery of acquired immunological tolerance
1972	Rodney R. Porter Gerald M. Edelman	Great Britain United States	Chemical structure of antibodies
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	George Snell Jean Dausset Baruj Benacerraf	United States France United States	Major histocompatibility complex
1984	Niels K. Jerne Cesar Milstein Georges E. Köhler	Denmark Great Britain Germany	Immune regulatory theories (Jerne) and technological advances in the development of monoclonal antibodies (Milstein and Köhler)
1987	Susumu Tonegawa	Japan	Gene rearrangement in antibody production
1991	E. Donnall Thomas Joseph Murray	United States United States	Transplantation immunology
1996	Peter C. Doherty Rolf M. Zinkernagel	Australia Switzerland	Role of major histocompatibility complex in antigen recognition by T cells
2002	Sydney Brenner H. Robert Horvitz J. E. Sulston	South Africa United States Great Britain	Genetic regulation of organ development and cell death (apoptosis)
2008	Harald zur Hausen Françoise Barré-Sinoussi Luc Montagnier	Germany France France	Role of HPV in causing cervical cancer (Hausen) and the discovery of HIV (Barré-Sinoussi and Montagnier)
2011	Jules Hoffman Bruce Beutler Ralph Steinman	France United States United States	Discovery of activating principles of innate immunity (Hoffman and Beutler) and role of dendritic cells in adaptive immunity (Steinman)
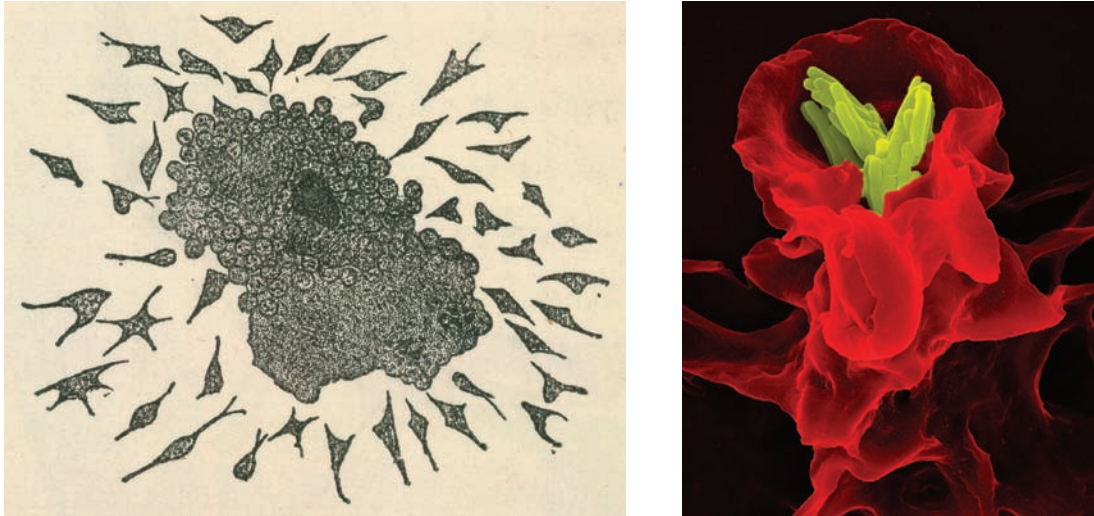
FIGURE 1-3 Drawing by Elie Metchnikoff of phagocytic cells surrounding a foreign particle (left) and modern image of a phagocyte engulfing the bacteria that cause tuberculosis (right). Metchnikoff first described and named the process of phagocytosis, or ingestion of foreign matter by white blood cells. Today, phagocytic cells can be imaged in great detail using advanced microscopy techniques. *[Drawing reproduced by permission of The British Library:7616.h.19,* Lectures on the Comparative Pathology of Inflammation delivered at the Pasteur Institute in 1891, *translated by F. A. Starling and E. H. Starling, with plates by Il'ya Il'ich Mechnikov, 1893, p. 64, fig. 32. Photo courtesy Dr. Volker Brinkmann/Visuals Unlimited, Inc.]*

Kitasato demonstrated that serum—the liquid, noncellular component recovered from coagulated blood—from animals previously immunized with diphtheria could transfer the immune state to unimmunized animals.

In 1883, even before the discovery that a serum component could transfer immunity, Elie Metchnikoff, another Nobel Prize winner, demonstrated that cells also contribute to the immune state of an animal. He observed that certain white blood cells, which he termed **phagocytes**, ingested (phagocytosed) microorganisms and other foreign material (Figure 1-3, left). Noting that these phagocytic cells were more active in animals that had been immunized, Metchnikoff hypothesized that cells, rather than serum components, were the major effectors of immunity. The active phagocytic cells identified by Metchnikoff were likely blood monocytes and neutrophils (see Chapter 2), which can now be imaged using very sophisticated microscopic techniques (Figure 1-3, right).

Humoral Immunity

The debate over cells versus soluble mediators of immunity raged for decades. In search of the protective agent of immunity, various researchers in the early 1900s helped characterize the active immune component in blood serum. This soluble component could neutralize or precipitate toxins and could agglutinate (clump) bacteria. In each case, the component was named for the activity it exhibited: antitoxin, precipitin, and agglutinin, respectively. Initially, different serum components were thought to be responsible for each activity, but during the 1930s, mainly through the efforts of Elvin Kabat, a fraction of serum first called gamma globulin (now **immunoglobulin**) was shown to be responsible for all these activities. The soluble active molecules in the immunoglobulin fraction of serum are now commonly referred to as **antibodies**. Because these antibodies were contained in body fluids (known at that time as the body *humors*), the immunologic events they participated in was called **humoral immunity**.

The observation of von Behring and Kitasato was quickly applied to clinical practice. **Antiserum**, the antibody-containing serum fraction from a pathogen-exposed individual, derived in this case from horses, was given to patients suffering from diphtheria and tetanus. A dramatic vignette of this application is described in the Clinical Focus box on page 8. Today there are still therapies that rely on transfer of immunoglobulins to protect susceptible individuals. For example, emergency use of immune serum, containing antibodies against snake or scorpion venoms, is a common practice for treating bite victims. This form of immune protection that is transferred between individuals is called **passive immunity** because the individual receiving it did not make his or her own immune response against the pathogen. Newborn infants benefit from passive immunity by the presence of maternal antibodies in their circulation. Passive immunity may also be used as a preventive (prophylaxis) to boost the immune potential of those with compromised immunity or who anticipate future exposure to a particular microbe.

While passive immunity can supply a quick solution, it is short-lived and limited, as the cells that produce these antibodies are not being transferred. On the other hand, administration

Passive Antibodies and the Iditarod

In 1890, immunologists Emil Behring and Shibasaburo Kitasato, working together in Berlin, reported an extraordinary experiment. After immunizing rabbits with tetanus and then collecting blood serum from these animals, they injected a small amount of immune serum (cell-free fluid) into the abdominal cavity of six mice. Twenty-four hours later, they infected the treated mice and untreated controls with live, virulent tetanus bacteria. All of the control mice died within 48 hours of infection, whereas the treated mice not only survived but showed no effects of infection. This landmark experiment demonstrated two important points. One, it showed that substances that could protect an animal against pathogens appeared in serum following immunization. Two, this work demonstrated that immunity could be passively acquired, or transferred from one animal to another by taking serum from an immune animal and injecting it into a nonimmune one. These and subsequent experiments did not go unnoticed. Both men eventually received titles (Behring became von Behring and Kitasato became Baron Kitasato). A few years later, in 1901, von Behring was awarded the first Nobel Prize in Physiology or Medicine (see Table 1-2).

These early observations, and others, paved the way for the introduction of passive immunization into clinical practice. During the 1930s and 1940s, **passive immunotherapy**, the endowment of resistance to pathogens by transfer of antibodies from an immunized donor to an unimmunized recipient, was used to prevent or modify the course of measles and hepatitis A. Subsequently, clinical experience and advances in the technology of immunoglobulin preparation have made this approach a standard medical practice. Passive immunization based on the transfer of antibodies is widely used in the treatment of immunodeficiency and some autoimmune diseases. It is also used to protect individuals against anticipated exposure to infectious and toxic agents against which they have no immunity. Finally, passive immunization can be life-saving during episodes of certain types of acute infection, such as following exposure to rabies virus.

Immunoglobulin for passive immunization is prepared from the pooled plasma of thousands of donors. In effect, recipients of these antibody preparations are receiving a sample of the antibodies produced by many people to a broad diversity of pathogens—a gram of intravenous immune globulin (IVIG) contains about 10^{18} molecules of antibody and recognize more than 10^7 different antigens. A product derived from the blood of such a large number of donors carries a risk of harboring pathogenic agents, particularly viruses. This risk is minimized by modern-day production techniques. The manufacture of IVIG involves treatment with solvents, such as ethanol, and the use of detergents that are highly effective in inactivating viruses such as HIV and hepatitis. In addition to treatment against infectious disease, or acute situations, IVIG is also used today for treating some chronic diseases, including several forms of immune deficiency. In all cases, the transfer of passive immunity supplies only temporary protection.

One of the most famous instances of passive antibody therapy occurred in 1925, when an outbreak of diphtheria

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of a vaccine or natural infection is said to engender **active immunity** in the host: the production of one's own immunity. The induction of active immunity can supply the individual with a renewable, long-lived protection from the specific infectious organism. As we discuss further below, this long-lived protection comes from memory cells, which provide protection for years or even decades after the initial exposure.

Cell-Mediated Immunity

A controversy developed between those who held to the concept of humoral immunity and those who agreed with Metchnikoff's concept of immunity imparted by specific cells, or **cell-mediated immunity**. The relative contributions of the two were widely debated at the time. It is now obvious that both are correct—the full immune response requires both cellular and humoral (soluble) components. Early studies of immune cells were hindered by the lack of genetically defined animal models and modern tissue culture techniques, whereas early studies with serum took advantage of the ready availability of blood and established biochemical techniques to purify proteins. Information about cellular immunity therefore lagged behind a characterization of humoral immunity.

In a key experiment in the 1940s, Merrill Chase, working at The Rockefeller Institute, succeeded in conferring immunity against tuberculosis by transferring white blood cells between guinea pigs. Until that point, attempts to develop an effective vaccine or antibody therapy against tuberculosis had met with failure. Thus, Chase's demonstration helped to rekindle interest in cellular immunity. With the emergence of improved cell culture and transfer techniques in the 1950s, the **lymphocyte** was identified as the cell type responsible for both cellular and humoral immunity. Soon thereafter, experiments with chickens pioneered by Bruce Glick at Mississippi State University indicated the existence of two types of lymphocytes: **T lymphocytes (T cells)**, derived from
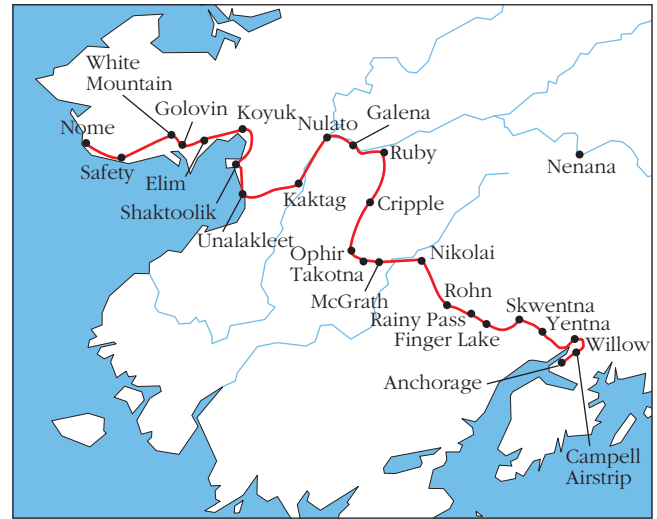
BOX 1-2

FIGURE 1
(left) Leonhard Seppala, the Norwegian who led a team of sled dogs in the 1925 diphtheria antibody run from Nenana to Nome, Alaska. (right) Map of the current route of the Iditarod Race, which commemorates this historic delivery of lifesaving antibody. *[Source: Underwood & Underwood/Corbis.]*

was diagnosed in what was then the remote outpost of Nome, Alaska. Lifesaving diphtheria-specific antibodies were available in Anchorage, but no roads were open and the weather was too dangerous for flight. History tells us that 20 mushers set up a dogsled relay to cover the almost 700 miles between Nenana, the end of the railroad run, and remote Nome. In this relay, two Norwegians and their dogs covered particularly critical territory and withstood blizzard conditions: Leonhard Seppala (Figure 1, left), who covered the most treacherous territory, and Gunnar Kaasen, who drove the final two legs in whiteout conditions, behind his lead dog Balto. Kaasen and Balto arrived in time to save many of the children in the town. To commemorate this heroic event, later that same year a statue of Balto was placed in Central Park, New York City, where it still stands today. This journey is memorialized every year in the running of the Iditarod sled dog race. A map showing the current route of this more than 1000-mile trek is shown in Figure 1, right.

the *t*hymus, and **B lymphocytes (B cells)**, derived from the *b*ursa of Fabricius in birds (an outgrowth of the cloaca). In a convenient twist of nomenclature that makes B and T cell origins easier to remember, the mammalian equivalent of the *b*ursa of Fabricius is *b*one marrow, the home of developing B cells in mammals. *We now know that cellular immunity is imparted by T cells and that the antibodies produced by B cells confer humoral immunity.* The real controversy about the roles of humoral versus cellular immunity was resolved when the two systems were shown to be intertwined and it became clear that both are necessary for a complete immune response against most pathogens.

How Are Foreign Substances Recognized by the Immune System?

One of the great enigmas confronting early immunologists was what determines the specificity of the immune response for a particular foreign material, or **antigen**, the general term for any substance that elicits a specific response by B or T lymphocytes. Around 1900, Jules Bordet at the Pasteur Institute expanded the concept of immunity beyond infectious diseases, demonstrating that nonpathogenic substances, such as red blood cells from other species, could also serve as antigens. Serum from an animal that had been inoculated with noninfectious but otherwise foreign (nonself) material would nevertheless react with the injected material in a specific manner. The work of Karl Landsteiner and those who followed him showed that injecting an animal with almost any nonself organic chemical could induce production of antibodies that would bind specifically to the chemical. These studies demonstrated that antibodies have a capacity for an almost unlimited range of reactivity, including responses to compounds that had only recently been synthesized in the laboratory and are otherwise not found in nature! In addition, it was