Introduction to Immunology

John W. Kimball

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Preface

This book has grown out of a semester-long course in immunology that I taught for a number of years at Tufts University and presently teach at Harvard University. A course in genetics and one in biochemistry were prerequisites for the course at Tufts and are strongly recommended at Harvard. Because of these requirements, the course has been populated chiefly by advanced undergraduate biology majors and graduate students. But even with prerequisites, any class represents a considerable spectrum of ability and current preparation, and I often find it necessary to review topics in genetics, biochemistry and physiology. In writing this book, therefore, I decided not to assume any prior knowledge on the part of the reader other than the terminology and concepts one would expect to find in a reasonably rigorous introductory biology text. Specifically, I have used the contents of my own text, *Biology* (Fifth edition, Addison-Wesley, 1983) as the criterion by which to decide what additional background information is needed for the discussion of each topic. This should not suggest that a year of introductory biology is adequate preparation for this book. The serious student will need more background to properly appreciate the material. However, the inevitable lapses in memory ought to be able to be filled by referring to a comprehensive introductory text.

A glance at the table of contents will reveal the basic organization of topics. One of my aims in choosing this way of organizing the material was to reinforce the importance and distinctiveness of cell-mediated immune responses. Perhaps this approach will reduce the number of students who, even at the end of their course, still think of antibodies as the sole expression of immunity.

The virtually exponential growth in our knowledge of the immune system makes the writing of a text that is both manageable in size and accessible to the beginning student a challenging task. One approach to the task is to set out our current thinking as a series of succinct conclusions. But such an approach misses, I believe, not only the essence of the subject but the excitement as well. I have chosen instead to develop most of the topics around the experimental evidence for such tentative conclusions as we can now draw. This approach requires, of course, more lines of text than would a strict didactic presentation. Of necessity, then, I have had to be selective not only in what topics to

include but what experiments to describe to support them. Sometimes I have chosen the classic work that laid the foundations of the topic; sometimes recent work that provides a more complete view of the topic in a single set of experiments. In any case, I hope that you will not find my choices overly idiosyncratic.

It has been my experience that beginning students profit more from reading original research papers than from reading reviews. The majority of the experiments I describe are illustrated by figures, and the citations to the original work appear in the legend accompanying the illustration. Therefore, the list of references at the end of each chapter is not by any means to be considered comprehensive, but simply represents other material I felt appropriate that was not cited earlier in the chapter. A number of the papers cited are readily available to students in the excellent reprint collection prepared by Vicki L. Sato and Malcolm L. Gefter (*Cellular Immunology*, Addison-Wesley, 1981).

Another recurring problem is how close to approach the advancing edge of each subject. I have usually, perhaps rashly in some cases, carried the discussion into recent, less well-tested areas. I have done this because (1) I want students to sense the excitement of the new directions that the field is taking and (2) I want to prepare students to be able to read the current literature. Surely one of the greatest satisfactions of a teacher is to work with students to the point where they can sit down with a current journal article and be able to understand and evaluate it.

I am indebted to many people for the help that they have given me in preparing this book. Each of the following read large sections of the manuscript and gave many valuable suggestions for its improvement. Duane W. Sears, University of California, Santa Barbara; William D. Baxter, Bowling Green State University; Cynthia V. Sommer, University of Wisconsin, Milwaukee; Edward M. Hoffman, University of Florida; Charles A. Janeway, Jr., Yale University; David W. Thomas, Washington University; John Clausz, Carroll College; Roderick MacLeod, University of Illinois (who also tested some of the material with his students); and Ray L. Bratcher, Syracuse University. Although in some cases I decided not to follow a particular piece of advice, I assure them that I paid close attention to all their suggestions and, of course, absolve them of any responsibility for the final product. I am especially indebted to Lisa Steiner (MIT) for her meticulous and thoughtful appraisals and for steering me away from many pitfalls both syntactic and scientific.

I also want to thank all the students who took my course at Tufts in 1980–81. They were the guinea pigs for chapters 1–12 and helped me greatly by returning the manuscript chapters marked with suggestions for improvement.

Despite the best efforts of all concerned, I am sure that errors—of fact, of interpretation, of proofreading—still remain. I do hope that those who examine and/or use the book will communicate to me any suggestions that they have for its improvement.

All the drawings were prepared by Cynthia Phillips. Working under imminent deadlines, she cheerfully and speedily turned my rough ideas into clear and, I believe, pedagogically effective illustrations. I

also wish to thank the many colleagues who supplied me with their photographs and electron micrographs. Their names appear in the legend accompanying their work.

Every book is the product of a partnership between the author and the publisher. I am grateful to the many people at Macmillan involved in the creation of this book for the skill and spirit of cooperation that they brought to their tasks.

And, finally, my special thanks to A. M. Pappenheimer, Jr. ("Pap"), now Professor *Emeritus* at Harvard, who not only taught me how to do immunology, but taught me—by example rather than by precept—so much about standards and style in any scientific undertaking. This book is dedicated to him with the hope that it will partially balance the debt I owe to him.

J. W. K.

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I

Introduction

CHAPTER

1

The Nature of Immunity

1.1 What is an Immune Response?

An immune response can be defined as "altered reactivity to a specific molecular configuration that develops following contact with it." The altered reactivity might take the form of, for example, resistance to a second infection by measles virus or an allergic response to grass pollen. The specific molecular configuration would be the surface structure of a specific molecule, such as one found on a virus particle, pollen grain and so forth. This definition contains two critically important concepts. One is the concept of **specificity.** The other is the concept of **memory.**

SPECIFICITY

In order to qualify as immune, the response must meet the criterion of specificity. The investigator must be able to demonstrate that the

altered response occurs *only* with respect to the *same* molecular configuration encountered before.

Consider what happened in 1977 to people who encountered the influenza virus called A/Texas/77 for the first time. Following their recovery from the infection, these people were no longer susceptible to a second infection by the same virus. They were now immune. However, they were still fully susceptible to the "Russian" flu virus (A/USSR/77) circulating throughout the world at the same time. Their *selective reactivity* to one virus and not the other demonstrates specificity and qualifies their response as immune.

If, on the other hand, they had been exposed to the Russian flu virus while their illness was still in progress or in early convalescence, the second virus would not have caused disease. This is because when certain kinds of cells (for example, lymphocytes) become infected with a virus, they synthesize and secrete a protein called *interferon.* Interferon inhibits viral replication in cells and is thus an important antiviral agent. But interferon exerts its inhibitory effect on the multiplication of *all* types of viruses. Therefore, the interferon response fails to meet our definition of an immune response.

Memory

In order to qualify as immune, any subsequent response to an agent must be measurably different in its qualities from the initial response. The immunity that follows a bout with A/Texas/77 does not mean that the virus can never again enter the body. But if a second infection by the virus should occur, the defensive responses will be so swift that the virus will be unable to cause enough tissue damage to create noticeable symptoms. Only laboratory tests will be able to reveal the telltale traces of its re-entry. On the other hand, if phagocytic cells in the body proceed to scavenge invading microorganisms with the same speed and efficiency they displayed on their first encounter with that microorganism, then immunity has played no role in their response.

A third feature is often—but not always—a hallmark of immunity. Immunity to a specific molecular configuration will normally occur only if that configuration is not found in the body of the responding animal. In other words, the immune system usually responds only to "foreign" molecular configurations. Thus the immune system discriminates between "nonself" and "self." We shall, however, examine a number of violations of this principle in the following chapters. Immune response to "self" create a state of *autoimmunity.* Autoimmunity may result in pathological effects on the organism, as we shall see in Chapter 17.

You may have noticed that the terms "immune response" and "immunity" have not been used in precisely the same way. This is because some immune responses lead to a state of **immunological tolerance.** Immunological tolerance is a specific *hypo*responsiveness to a particular molecular configuration. It is also induced by contact. Thus immune responses can lead either to immunity (enhanced reactivity) or to tolerance (sharply decreased reactivity). Both show specificity and memory. Immunological tolerance is the topic of Chapter 15.

As you read the literature of immunology, you will occasionally encounter the expressions *natural immunity* and *nonspecific immunity.* "Natural immunity" is sometimes used to describe the innate lack of susceptibility of humans to many animal diseases. The basis of this innate protection is often obscure, but no evidence exists that it involves immunity as we have defined it. If you accept our definition of immune responses, then "nonspecific immunity" is a contradiction in terms. It refers to defense mechanisms, like interferon and some examples of phagocytosis, that are effective against a broad range of agents. Nonspecific host defense mechanisms such as these are important, but they fail to meet the criteria that we have established for immune responses.

No one knows just when humans first became aware of the existence of immunity. In his history of the Peloponnesian Wars, Thucydides wrote of a plague that swept Athens some 2,500 years ago. He mentions that whatever attention the sick received was "tended by the pitying care of those who had recovered, because they were themselves free of apprehension. For no one was ever attacked a second time or with a fatal result." Today we cannot tell what the pestilence was; perhaps it was typhus, perhaps plague. Regardless, these words, written two and one-half millenia ago, express the central concept of immunity.

1.2 The Duality of the Immune System

Two kinds of effector mechanisms mediate immune responses. Some immune responses are mediated by specific molecules, called **antibodies,** that are carried in the blood and lymph. Antibody-mediated immunity is called **humoral immunity.** Other immune responses are mediated by cells. All the leukocytes (white cells) of the blood participate in **cell-mediated immunity** (CMI). However, the *specificity* of the response depends upon a subset of lymphocytes called *T lymphocytes* or *T cells.* Most immune responses involve the activity and interplay of both the humoral and the cell-mediated branches of the immune system.

This duality of function in the immune system recurs as a theme throughout this book. It in fact provides a major organizational pattern to the topics discussed. Chapter 2 deals largely with humoral immunity. The basic features of cell-mediated immunity are considered in Chapter 3.

1.3 The Conquest of Smallpox

On October 26, 1977, Ali Maow Maalin came down with smallpox (variola) in the town of Merka in Somalia. Within a few weeks he was fully recovered. Since that time, not a case of smallpox (except as a result of one laboratory accident) has been discovered anywhere in

the world. By May of 1980, the World Health Organization (WHO) felt that it could confidently announce that smallpox had been completely eradicated. Smallpox certainly qualified as one of the greatest scourges of humanity. It regularly killed 25% and sometimes as many as 50% of its victims. Introduced into Europe around the sixth century A.D., smallpox rivaled plague in its ability to decimate entire populations. Introduced into the New World in the sixteenth century, smallpox devastated the native populations and played a far greater role than weaponry in the Spanish Conquest.

How was such a pestilence eradicated? Four factors were decisive:

1. The variola virus, which causes the disease, attacks only humans; no animal reservoirs have been found (as they have, for example, for the yellow fever virus and the plague bacillus).
2. With recovery from the disease, the virus is completely eliminated from the body. There are no smallpox "carriers" as there are for such diseases as typhoid fever and malaria.
3. An effective vaccine was available. The vaccine could quickly establish a strong (and reasonably long-lasting) immunity. Thus the chain of contagion could quickly be broken by vaccinating all possible contacts associated with a new case.
4. The WHO and the countries involved provided personnel, money and the determination to do the job. An effective vaccine had, as we shall see, been available since 1796 and had already rendered many parts of the world free of the disease during the first half of this century. But still the disease smouldered in Asia, Indonesia, Brazil and Africa. Only an heroic public health effort—a campaign that began in 1967—finally eliminated it worldwide.

VARIOLATION

The first effective attempts to cope with smallpox were made in some of the same regions—Asia, India, Africa—that were the last freed of the disease. The technique was to deliberately inoculate susceptible individuals (that is, those with no pockmarks to indicate that they had survived an earlier epidemic) with material taken from the

Year	1721	1764	1792
Population	10,700	15,500	19,300
Natural Smallpox			
Cases	5,759	699	232
Deaths	842	124	69
Deaths/1000 cases	146	177	298
Smallpox caused by Variolation			
Cases	130	4,977	9,152
Deaths	2	46	179
Deaths/1000 cases	15	9	20

Figure 1.1 *Smallpox in Boston. (From Blake, J. B., Public Health in the Town of Boston, 1630–1832, Harvard University Press, 1959.)*

pustules of victims having a mild case of the disease. This practice, called *variolation*, induced an active case in the recipient, but usually the case was less severe than if the disease had been contracted in the normal way (by inhalation as it turned out). Variolation was introduced into England and the American colonies early in the eighteenth century. For many years, the practice was accompanied by violent controversy. For one thing, it was not an entirely safe procedure. The variolated person often became quite ill and the mortality rate, although only a fraction of that for people who contracted the disease in the normal way, was nonetheless appreciable (Figure 1.1). But far more significant in terms of public acceptance was the fact that the variolated individual was fully contagious to others during the period of his brief, hopefully mild illness. Thus a family electing variolation could serve as the starting point of a fresh smallpox epidemic. Nonetheless, the practice gradually gained favor (Figure 1.1) until it was replaced—almost overnight—by vaccination.

VACCINATION

Edward Jenner (Figure 1.2), was a Gloucestershire physician who introduced the practice that led to the elimination of smallpox. Jenner's success was grounded on two observations:

1. The regional folk belief that if a milkmaid had ever contracted cowpox, she would not contract smallpox.
2. The inability to successfully variolate those who had had an earlier case of cowpox. Cowpox is a disease characterized by pustules on the teats and udders of cows. Persons in close contact with cows frequently contracted the disease and suffered a mild and transient infection.

Jenner systematically exploited these observations. First he deliberately induced cowpox in his human subjects by inoculating them with material from cowpox pustules. Then he showed that these individuals could not be variolated. Jenner's procedure, which we call *vaccination* (L. *vacca*, cow) quickly replaced variolation as a public health measure because:

1. Any reaction it induced was far milder than the disease induced by variolation.
2. The vaccinated subject was not contagious to others.

Jenner's was the first safe and successful attempt to artificially induce an active immunity. Many successful attempts have followed since Jenner's day, but the principles that guided him are still followed: to develop a harmless (or as harmless as possible) preparation that will, upon introduction into the body, induce a response that will protect the individual from a harmful pathogenic agent. Because of Jenner's priority and his success, the term *vaccine* is used today for all such preparations. The administration of a vaccine is called *immunization*.

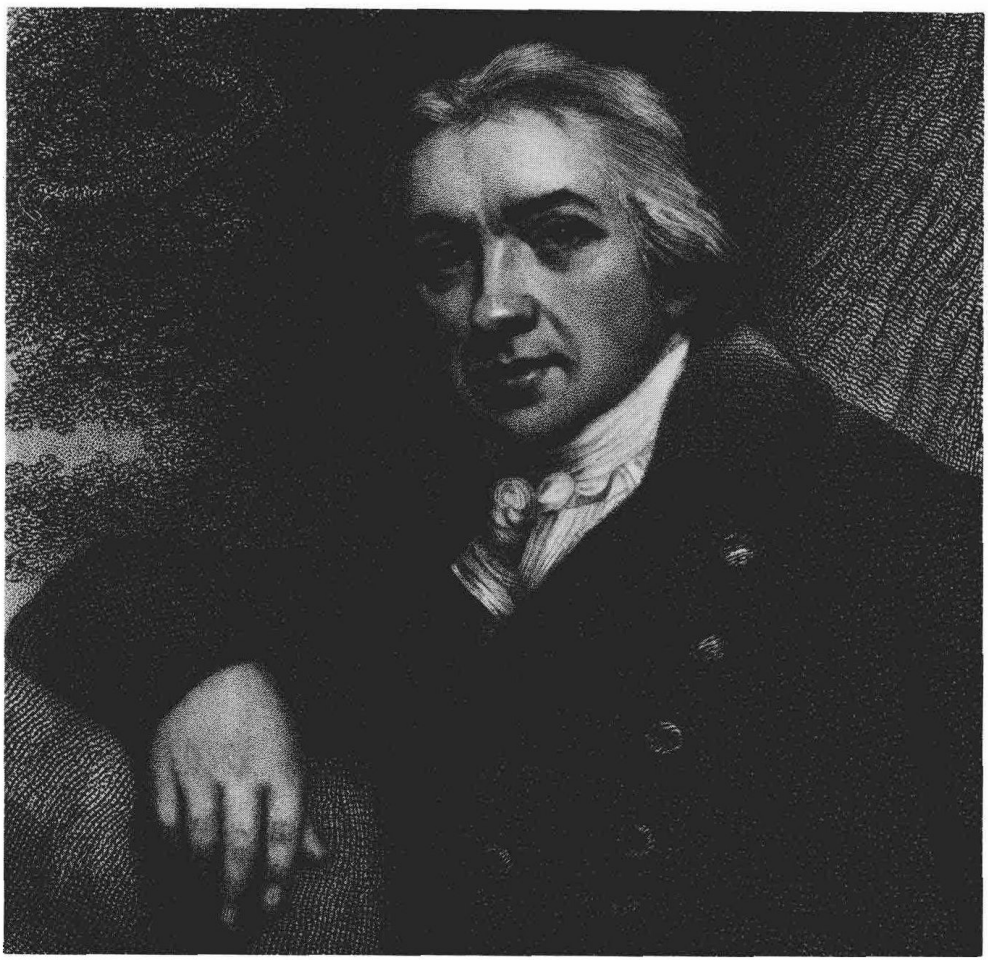

Figure 1.2 *Edward Jenner, 1749–1823. Engraved by J. R. Smith. (Courtesy of the Boston Athenaeum.)*

The virus used in today's smallpox vaccine is called the *vaccinia virus*. It is probably not cowpox virus but rather a highly-attenuated form of smallpox (variola) virus. Just when the switch occurred is lost in the obscurity of the years since Jenner's day.

Jenner knew nothing of viruses, lymphocytes or antibodies. His success was based on empirical methods of observation and clinical trials. Today we know a great deal more about the machinery of immunity. And much of this knowledge intersects with fundamental knowledge about the properties of cells and molecules. But as you read the chapters that follow, never lose sight of the incalculable benefits that the ability to manipulate the immune system has brought to humanity. Jenner himself wrote of vaccination: "the annihilation of smallpox must be the final result of this practice." One hundred and eighty-two years later, his prediction appears to have been fulfilled at last.

Other afflictions await. For some, such as polio and tetanus, the knowledge and tools are already at hand. What is now needed is money and commitment. For other goals, such as a vaccine for malaria, successful organ transplants, perhaps even specific and effective tumor therapy, more knowledge is needed.

1.4 Antigens

An antigen is a substance that when introduced into an animal with a functioning immune system, can elicit a specific immune response. If the response leads to a state of immunity, the antigen is said to be *immunogenic*. An antigen that produces a state of specific tolerance is called a *tolerogen*.

Proteins are highly immunogenic when injected into an animal for whom they are not normal ("self") constituents. Thus bovine serum albumin (BSA), which is a normal component of cow serum, is strongly immunogenic in mice but not in cows. Chicken ovalbumin (OVA), the major protein in the white of the egg, and keyhole limpet hemocyanin (KLH), the oxygen-carrying pigment of this marine gastropod, are other examples of protein antigens frequently used in immunological studies.

Polysaccharides and nucleic acids can also serve as antigens, although nucleic acids tend to be only weakly immunologic. Conjugated proteins, such as nucleoproteins, glycoproteins and lipoproteins, are strongly immunogenic thanks largely to the protein portion of the molecule. Conversely, small molecules, those with molecular weights below about 2000, *by themselves* do not elicit the formation of antibodies. For example, injections of steroid hormones like testosterone, drugs like digitalis and morphine, or nucleotides like cyclic AMP do not induce antibody formation. But if these same molecules are first coupled with an immunogenic antigen such as a protein, antibodies will be elicited to the complex, and a *subset* of these antibodies will bind specifically to the small molecule. Thus while only macromolecules are immunogenic, the antibodies produced in response to the antigen react with (bind to) only certain portions of the antigen. These portions are called **antigenic determinants** (or "epitopes".) Covalently bound to a macromolecular "carrier," small molecules such as testosterone and morphine can serve as—or be part of—an antigenic determinant.

To take another example, dinitrobenzene is not by itself immunogenic. However, when covalently coupled to a protein (to the epsilon amino groups of its lysine residues), the resulting dinitrophenyl complex (for example, DNP-BSA) is immunogenic. Injections of DNP-BSA into a rabbit induce the formation of a broad spectrum of antibody molecules, subsets of which react with different antigenic determinants on the molecules, and *one* subset of which binds specifically to ("recognizes") those determinants of which DNP is a part (Figure 1.3). This latter subset of antibody molecules will also bind to molecules of DNP that have been coupled to ovalbumin (DNP-OVA), but none of the antibodies will bind to OVA alone. A molecule that is not immunogenic by itself but can serve as part of an antigenic determinant on an immunogenic molecule (the "carrier") is called a **hapten.**

The universe of antigenic determinants is immense, perhaps limitless. Probably no molecular configuration exists that, when presented to the appropriate animal in an appropriate fashion, cannot elicit the