THE IMMUNE SYSTEM

Peter Parham

Stanford University

The Immune System is derived from *Immunobiology* by Charles A. Janeway, Jr., Paul Travers and Mark Walport; also published by Garland Publishing and Current Trends.

Garland Publishing
New York and London

Current Trends
London

Distributors:

Inside North America: Garland Publishing, a member of the Taylor & Francis Group, 29 West 35th Street, New York, NY 10001-2299, US.
Outside North America: Garland Publishing, a member of the Taylor & Francis Group, 11, New Fetter Lane, London EC4P 4EE, UK.

ISBN: 0 8153 3043 X (paperback) Garland
ISBN: 0 8153 3848 1 (paperback) International Student Edition

A catalog record for this book is available from the British Library.

Library of Congress Cataloging-in-Publication Data

Parham, Peter, 1950-
The immune system / Peter Parham
p. cm.

Includes index.
ISBN 0-8153-3043-X (pbk.)
1. Immune system. 2. Immunopathology. I. Title.

QR181 .P335 2000
616.07'9 21--dc21
99-042006

This book was produced using QuarkXpress 4.0 and Adobe Illustrator 7.0.

Printed in United States of America.

Published by Current Trends, part of Elsevier Science London, 84 Theobalds Road, London, WC1X 8RR, UK and Garland Publishing, a member of the Taylor & Francis Group, 29 West 35th Street, New York, NY 10001-2299, US.

Elements of the Immune System and their Roles in Defense 1

Immunology is the study of the physiological mechanisms that humans and other animals use to defend their bodies from invasion by other organisms. The origins of the subject lie in the practice of medicine and in historical observations that people who survived the ravages of epidemic disease were untouched when faced with that same disease again—they had become **immune** to infection. Infectious diseases are caused by microorganisms, which have the advantage of reproducing and evolving much more rapidly than do their human hosts. During the course of an infection, the microorganism can pit enormous populations of its species against an individual *Homo sapiens*. In response, the human body invests heavily in cells dedicated to defense, which collectively form the **immune system**.

The immune system is crucial to human survival. In the absence of a working immune system, even minor infections can take hold and prove fatal. Without intensive treatment, children born without a functional immune system die in early childhood from the effects of common infections. However, in spite of their immune systems, all humans suffer from infectious disease, especially when young. This is because the immune system takes time to build up a strong response to an invading microorganism, time during which the invader can multiply and cause disease. To provide **protective immunity** for the future, the immune system must first do battle with the microorganism. This places people at highest risk during their first infection with a microorganism and, in the absence of modern medicine, leads to substantial child mortality as witnessed in the developing world. When entire populations face a completely new infection, the outcome can be catastrophic, as experienced by indigenous Americans whose populations were decimated by European diseases to which they were suddenly exposed after 1492.

In medicine the greatest triumph of immunology has been **vaccination**, or **immunization**, a procedure whereby severe disease is prevented by prior exposure to the infectious agent in a form that cannot cause disease. Vaccination provides the opportunity for the immune system to gain the experience needed to make a protective response with little risk to health or life. Vaccination was first used against smallpox, a viral scourge that once ravaged populations and disfigured the survivors. In Asia, small amounts of smallpox virus had been used to induce protective immunity for hundreds of years before 1721, when Lady Mary Wortley Montagu introduced the method into western Europe. Subsequently, in 1796, Edward Jenner, a doctor in rural England, showed how inoculation with cowpox virus offered protection against the related smallpox virus with less risk than the earlier methods. Jenner called his procedure vaccination, after *vaccinia*, the name given to the mild disease produced by cowpox, and he is generally credited with its invention. Since his time, vaccination dramatically reduced the incidence of smallpox worldwide with the last cases being seen by physicians in the 1970s (Figure 1.1).

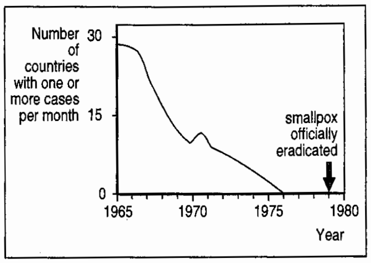

Figure 1.1 The eradication of smallpox by vaccination. In 1979, after 3 years in which no case of smallpox was recorded, the World Health Organization announced that the virus had been eradicated. Since then there has been debate as to whether all laboratory stocks of the virus should be destroyed. One view is that the stocks could be used for nefarious purposes and should therefore be destroyed. The other view is that the virus might not have been eradicated and that if the disease returns, well characterized laboratory stocks will be required to renew study of the disease and its prevention.

Effective vaccines have been made from only a fraction of the agents that cause disease and of those some are of limited availability because of their cost. Most of the widely used vaccines were first developed many years ago by processes of trial and error, before very much was known about the workings of the immune system. That approach is no longer so successful for making new vaccines, perhaps because all the easily won vaccines have been obtained. But deeper understanding of the mechanisms of immunity is spawning new ideas for vaccines against infectious diseases and even against other types of disease such as cancer. Much is now known about the molecular and cellular components of the immune system and what they can do in the laboratory. Current research aims at understanding their contributions to fighting infections in the world at large. The new knowledge is also being used to find better ways of manipulating the immune system to prevent the unwanted immune responses that cause allergies, autoimmune diseases, and rejection of organ transplants.

In the first part of this chapter we consider the microorganisms that infect human beings and the defenses they must overcome to start an infection. These include physical barriers, chemical barriers, and the fixed defenses of innate immunity that are ready and waiting to halt infections before they can barely start. Also described are the individual cells and tissues of the immune system and how they integrate their functions with the rest of the human body. The second part of the chapter focuses on the more flexible and forceful defenses of adaptive immunity. These mechanisms are only brought into play if and when an infection is established. The adaptive response is always targeted to the specific problem at hand and is made and refined during the course of the infection. When successful, it clears the infection and provides long-lasting immunity that prevents its recurrence.

Defenses facing invading pathogens

The purpose of the vertebrate immune system is to recognize invading foreign organisms, to prevent their spread, and ultimately to clear them from the body. It consists of billions of cells of various types, which interact with the infectious agent and with each other to fight the infection. With very few exceptions, the cells of the immune system derive originally from the bone marrow, but at some time in their life they leave that site to circulate in the blood, to enter other tissues, and to form part of specialized **lymphoid** tissues. This part of the chapter introduces the cells and tissues of the immune system and some of the molecules through which they carry out their functions. But first we shall consider the organisms and infections that the immune system evolved to protect us against.

1-1 Pathogens are infectious organisms that cause disease

Numerous species of microorganism colonize the human body in large numbers and rarely produce symptoms of disease, for example the benign strains of the bacterium *Escherichia coli* that normally inhabit the gastrointestinal tract. However, for some microorganisms, such as the influenza virus or the typhoid bacillus, infection habitually causes a disease. Any organism with the potential to cause disease is known as a **pathogen**. This definition includes not only microorganisms that generally cause disease if they enter the body, but also ones that can

The immune system protects against four classes of pathogen		
Type of pathogen	**Examples**	**Diseases**
Bacteria	*Salmonella enteritidis* *Mycobacterium tuberculosis*	Food poisoning Tuberculosis
Viruses	Variola Influenza HIV	Smallpox Flu AIDS
Fungi	*Epidermophyton floccosum* *Candida albicans*	Ringworm Thrush, systemic candidiasis
Parasites protozoa worms	*Trypanosoma brucei* *Leishmania donovani* *Plasmodium falciparum* *Ascaris lumbricoides* *Schistosoma mansoni*	Sleeping sickness Leishmaniasis Malaria Ascariasis Schistosomiasis

Figure 1.2 The four kinds of pathogen that cause human disease. Examples of the types of pathogen are listed, along with the diseases they cause.

colonize the human body to no ill effect for much of the time but cause illness if the body's defenses are weakened or if the organism gets into the 'wrong' place. The latter kinds of microorganism are known as **opportunistic pathogens**.

Pathogens can be divided into four kinds: **bacteria**, **viruses**, and **fungi**, which are each a group of related microorganisms, and internal **parasites**, a less precise term used to embrace a heterogeneous collection of unicellular protozoa and multicellular invertebrates, mainly worms (Figure 1.2). In this book we consider the functions of the human immune system principally in the context of controlling infections. For some pathogens, this necessitates their complete elimination, but for others it is sufficient to limit the size and location of the pathogen population within the host. Figure 1.3 gives examples of pathogens from the four classes.

Over evolutionary time, the relationship between a pathogen and its human hosts can change, affecting the severity of the disease produced. Most pathogenic organisms have evolved special adaptations that enable them to invade their hosts, replicate in them and be transmitted. However, the rapid death of its host is rarely in a microbe's interest, because this destroys both its home and its source of food. Consequently, those organisms with the potential to cause severe and rapidly fatal disease often tend to evolve towards an accommodation with their hosts. In complementary fashion, host populations have evolved a degree of in-built genetic resistance to common disease-causing organisms, as well as acquiring lifetime immunity to endemic diseases as a result of infection in childhood. Because of the interplay between host and pathogen, the nature and severity of infectious diseases in the human population are always changing.

Influenza is a good example of a common viral disease that, although severe in its symptoms, is usually overcome successfully by the immune system. The fever, aches, and lassitude that accompany infection can be overwhelming, and it is difficult to imagine overcoming foes or predators at the peak of a bout of influenza. However, despite the severity of the symptoms, most strains of influenza do not pose any great danger to healthy people in populations in which influenza is endemic. Warm, well-nourished, and otherwise healthy individuals usually recover in a couple of weeks and take it for granted that their immune systems will accomplish this task. Pathogens new to the human population, in contrast, often cause high mortality—between 60% and 75% in the case of the Ebola virus.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

WHAT WILL YOU BUILD? | **sales@docketalarm.com** | **1-866-77-FASTCASE**

fastcase®
Smarter legal research.