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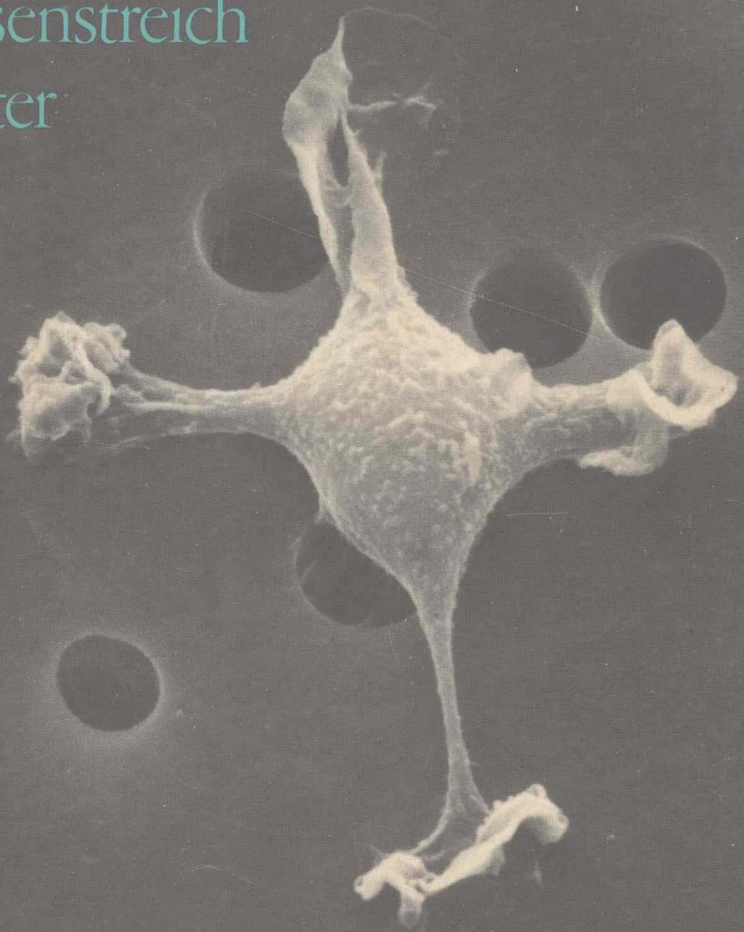

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To the many investigators
from Louis Pasteur, Robert Koch, Elie Metchnikoff, Paul Ehrlich on,
who discovered the cells and factors responsible
for immunological and inflammatory reactions,
that have made this book possible.

Preface

The study of the processes that underly host defense against foreign substances has become ever more compartmentalized as our knowledge has increased. Immunologists study the specific immune reactions of the host to an antigenic stimulus, which primarily involve lymphocytes and immunoglobulins. In contrast, students of inflammatory reactions investigate the non-specific inflammatory reactions that are mediated by polymorphonuclear leukocytes, macrophages, complement enzymes, prostaglandins, and kinins. Moreover, even within these broad categories, specialization is the rule therefore many investigators study only a specific cell type or factor.

Although such specialization is an extremely efficient means of producing rapid progress in a small area, it is clear to most of us that these processes to not occur in isolation, but are mechanistically interrelated and also occur in a close temporal relationship, either simultaneously or sequentially. The more we know about these systems, the more we realize how they interact with each other. For example histamine and serotonin which are released in acute inflammatory reactions influence lymphocyte-dependent delayed hypersensitivity whereas some lymphocyte products result in "nonspecific inflammation." Thus cells and their products participate both in immunologically mediated and nonspecific inflammatory processes.

For these reasons, we felt that it was important that the processes of immunity and inflammation be considered as an integral unit rather than as isolated subjects. We felt that this approach would give the working scientist some new insights, and the beginning student a less fragmented, better structured framework on which to build his knowledge.

With this in mind, we organized a post-graduate course focusing on the mechanisms of host defense at the National Institutes of Health that included lectures from a number of related disciplines not usually considered together. Although each area was taught by specialized investigators the common theme of interaction between diverse biological systems was stressed. This course has proved to be popular and informative for student and instructors alike. However, in the course of organizing and giving the course, one noted a conspicuous absence of a single book that used this approach or included the diversity of subjects under one cover that we considered to be essential. Because of this, we decided such a text would be useful, and this book is the result.

The contents of the book are a combination of classical subjects covered in text books on immunology and inflammation. Thus, there are chapters on T- and B-lymphocytes, macrophages, immunoglobulins, complement, and on inflammatory cells such as neutrophils,

eosinophils, and basophils, as well as chapters concerning important molecules such as acute phase proteins, kinins, prostaglandins, interferon and lymphokines modulating inflammation. However, we have also included chapters on other important interactions that are often over looked, or studied in isolation such as the effects of hormones on inflammation and the effect of inflammatory processes in tissue repair. In addition to a thorough discussion of each topic, we have tried to emphasize the interrelationships and interactions of cells and factors that serve to culminate in immunity and inflammation. In order to keep this volume to a manageable size some topics, such as platelets, that did not warrant a separate chapter were briefly considered in a number of the chapters.

We would like to thank all the contributors for their work and cooperation, our colleagues for their many helpful suggestions, Drs. Stanley Cohen and Gerald Weissman for their constructive critiques of this volume and the secretarial and editorial assistance that made this book possible.

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Immunity and Inflammation

Joost J. Oppenheim, M.D. and Michael Potter, M.D.

The cardinal signs of inflammation, rubor, calor, dolor, and tumor, represent the manifestations of the basic vascular and cellular responses of the mammalian organism to infection, tissue injury, and intrusion of foreign materials. These inflammatory responses serve to maintain the integrity of the host by eliminating dead tissue, microbes, toxins, and inert foreign substances (Figure 1). It is the purpose of this chapter to delineate the role of immunity in the various types of inflammatory reactions. We will classify inflammatory responses as either nonimmunological, when they only involve vascular changes and nonlymphocytic inflammatory cells, or as immunological, when they involve lymphocyte dependent reactions. Inflammation and immunity are closely interrelated, and in vertebrate species most inflammatory responses have an immunological component. Furthermore, the effector mechanisms of inflammation and immunity are virtually identical. Immunity provides a mechanism for focusing inflammatory reactions on a specific target and thus has enabled inflammatory reactions to evolve into a more efficient, effective, and rapid host defense response. Immunity can either preempt or suppress the inflammatory response to a foreign substance or, alternatively, mobilize an inflammatory reaction that at times may be excessive and even self destructive. Conversely, nonimmunological stimulants can have adjuvant effects and markedly augment immunologically mediated host reactions.

Historical Overview

Historically, the concepts that inflammation and immunity participate in host defense were developed independently of one another. The close interrelationship of these two processes has been discovered in a piecemeal fashion during the past century.

Rudolph Virchow, the father of cellular pathology, recognized in 1858 that inflammation represents the host response to an exogenous insult.

> Whilst until quite recently it was the custom to look upon inflammation as a real entity, as a process everywhere identical in its essence, after I made my investigations no alternative remained but to divest the notion of inflammation of all that was ontological

From the National Institute of Dental Research, National Institutes of Health, Bethesda, Maryland, and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

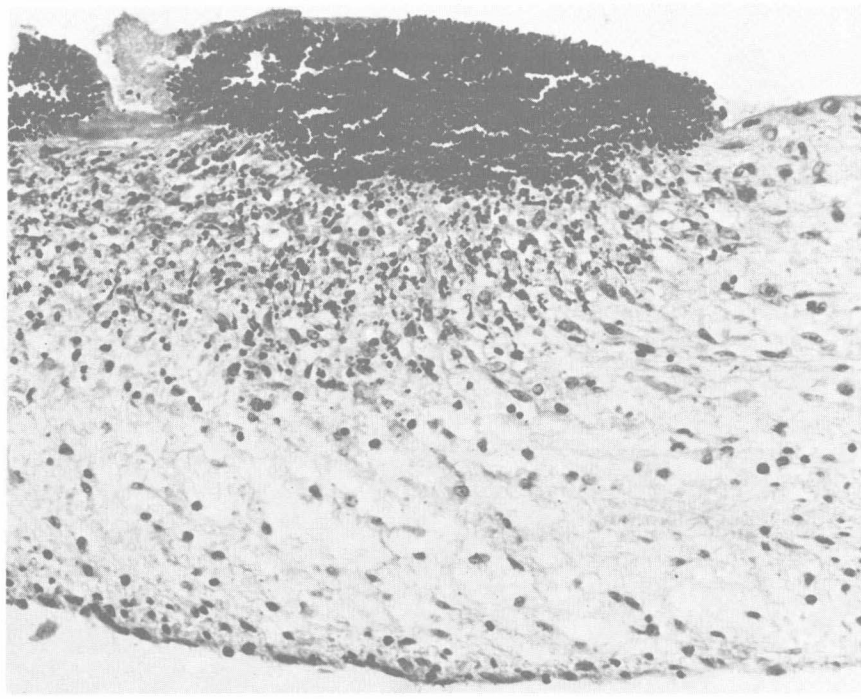

Figure 1. Yeast vegetation on wall of right atrium following central venous catheter related septic episode. Note chronic mononuclear inflammatory cell response to the organisms. (Courtesy of A. Anderson.)

in it, and no longer to look upon the processes but only to regard it as one differing in its form and course. We cannot imagine inflammation to take place without an irritating stimulus (irritament) and the first question is, what conception we are to form of such a stimulus.

Virchow explains the term "irritament":

The term irritament (Reiz which however, sometimes means irritant; stimulus) is intended to express the change (mechanical or chemical, palpable anatomical or molecular) which takes place in a tissue in consequence of the action of an irritant—a change therefore, which is of a fairly passive nature (lesion) and which (subsequently) provokes changes in the neighboring parts not directly altered by the irritant. The consequence of which is their action or reaction.

Virchow then thought of inflammation as host reactions to irritants but not as a nosological entity. Inflammation was a process that could vary in form and course.

Julius Cohnheim in 1867 described the pathophysiology of inflammation as being induced by touching the cornea of a frog's eye with a stick of lunar caustic, and he correlated the changes with histologic sections. He found that the edge of the necrotic site became infiltrated with white blood cells. He developed a vital stain for phagocytic cells and was able to trace the origin of the cells from lymph to blood to inflammatory site. Cohnheim's research focused attention on vascular changes in inflammation and their consequences: the transudation of fluids and the migration of white blood cells into inflammatory sites. What remained to be described was the kinds of cells that occupied an inflammatory site and their function.

The first natural forms of inflammation to be studied in great depth were associated with infections by microorganisms. Robert Koch in 1877 and Louis Pasteur in 1879 isolated the pathogens of ovine anthrax and fowl cholera. These were exciting findings that led quickly to one of the most momentous discoveries in all of medicine: a rediscovery of Edward Jenner's (1798) principle of immunization by Louis Pasteur. For the first time, an isolated propagatable organism that induced immunity was available for detailed study. No finding better illustrates Pasteur's famous saying "chance favors the prepared mind" as did the study of fowl cholera.

The causative agent of fowl cholera was a small gram-negative coccobacillus, now in the *Pasteurella* group. Pasteur, Chamberland, and Roux succeeded in isolating and culturing the organism in a chicken broth medium. They were able to transmit the disease with cultured organisms, and all chickens infected with the cultured organisms administered even in the minutest doses died within 2 to 4 days. In late summer of 1879, the work on fowl cholera came to a temporary halt for the summer vacation. The cultures apparently were not passaged during this period but had remained viable. When work resumed, organisms from the old cultures now failed to transmit the virulent disease. So attempts were quickly made to reestablish virulent organisms. During this period of testing, normal chickens were used, but some "economy minded" person probably threw in a few of the birds that had been inoculated with the old non-virulent cultures. For the first time some chickens survived the fatal disease. Pasteur questioned the source of these survivors and discovered they had been inoculated previously with the nonvirulent cultures. He then recognized he had rediscovered a new means to induce immunity that was related to Jenner's vaccination reported 81 years earlier. A series of interesting experiments followed.

Three quotes from Pasteur's original article on fowl cholera give the facts succinctly.

> Par certain changement dans le mode de culture on peut faire que le microbe infectieux soit diminué dans sa virulence.
>
> La diminution dans la virulence se traduit dans les cultures par un faible retard dans le développement du microbe; mais au fond il y a identité de nature entre les deux variétés du virus. Sous le premier de ses états, l'état très infectieux, le microbe inoculé peut tuer vingt fois sur vingt. Sous le second de ses états il provoque vingt fois sur vingt la maladie et non la mort. . . .
>
> Il me paraitrait superflu de signaler les principales conséquences des faits que je viens d'avoir l'honneur d'exposer devant l'Académie. Il en est deux cependant qu'il n'est peut-être pas sans utilité de mentionner: c'est d'une part, l'espoir d'obtenir des cultures artificielles de tous les virus, de l'autre une idée de recherche des virus vaccins des maladies virulentes qui ont désolé à tant de reprises et désolent encore tous les jours l'humanité et qui sont une des grandes plaies de l'Agriculture dans l'élevage des animaux domestiques (Pasteur 1880).[1]

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[1] "By a certain change in the mode of culture one can bring about a diminution in the virulence of the infectious microbe. The diminution in virulence is reflected in the cultures by a slight delay in the development of the microbe but basically the nature of the two varieties of virus are identical. In the first of these states, the very infectious state, the inoculated microbe can kill twenty times out of twenty. In the second state it provokes an illness twenty times out of twenty but no death.

It would seem to me to be superfluous to point out the principle consequences of the facts that I have the honor to present to the Academy. There are two however, that seem to me to be worth mentioning. One is the hope of obtaining artificial cultures of all viruses, the other the idea of seeking viral vaccines for the virulent diseases which have so grievously desolated and still desolate humanity day after day and which are one of the great scourges of agriculture in breeding domestic animals." (Pasteur 1880)