IMMUNOBIOLOGY FOR SURGEONS

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FOREWORD

Recent developments have emphasized the importance of immunobiology in surgical practice and have forecast that the further expansion of many of the frontiers of surgery will depend on new knowledge and techniques provided by this rapidly growing science.

Significant and daring advances in clinical surgery followed the introduction of penicillin and other antibiotics during the past 25 years extending new and complex operations to a large number of patients, many of whom were debilitated by various anomalies, diseases, or injuries.

Unfortunately, however, the number and varieties of postoperative infections have not been reduced. This has made it necessary to examine the reasons antibiotic therapy has had a limited effect in preventing and controlling surgical infections. From this examination has come the recollection of the fundamental importance of the role of host resistance and the immune response.

One of the current expanding frontiers of surgery is the field of tissue and organ transplantation. Serious obstacles confronting its further development are two phenomena: tissue rejection and complicating infection. For breakthroughs in these areas we must look to scientific knowledge developed in the field of surgical immunology.

For these reasons, as well as for the general relationship of immunobiology to surgical practice, a text containing the important principles and concepts of surgical immunobiology should be of great value to surgeons. Dr. J. Wesley Alexander and Dr. Robert A. Good have collaborated to prepare such a text, and both are eminently qualified to do so. *Immunobiology for Surgeons* will be a welcome source of scientific facts and immunological methods useful to the surgeon who wishes to acquire a working knowledge in this field and to improve his surgical results.

Since our current knowledge and skill are dependent upon the scientific and technical contributions of so many, it is important that these be compiled and interpreted by experienced authorities. Only in this way can the expanding mass of scientific knowledge resulting from laboratory and clinical research be made applicable to clinical practice.

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PREFACE

Immunobiology is related to some aspect of virtually every surgical endeavor, and the rapid expansion of knowledge and publications in this field during recent years has made it difficult, if not impossible, for any busy surgeon to keep abreast. Pertinent information is published in many journals and books which are not surgically oriented, and we know of no attempt to present and correlate those aspects of immunobiology which are related to surgical practice. We have tried to achieve this goal, realizing the difficulties involved.

This book is not intended to be a definitive and complete text. Instead, the authors have attempted to present what they consider to be the important principles and concepts of surgical immunobiology, along with enough of an introduction to the language and methods of this burgeoning science to help the immunologically unsophisticated reader to become conversant with this field. It is our hope that the information presented will provide our reader with a solid foundation upon which his expanding experimental and clinical understanding can be built. In particular, we wish to provide a source of basic facts and interpretation for those young surgeons and students of the art to whom it has become obvious that a knowledge of immunobiology is a desirable and almost essential requisite for modern surgical practice.

To accomplish the goal of writing a relatively brief but still comprehensive book, we have deleted all mention of specific references with the exception of annotated suggestions for further reading. In general, the latter are comprehensive articles or reviews. The omission of extensive references in the text also serves to improve readability and, hopefully, to facilitate retention. We wish to slight no one and trust that our many unnamed contemporary colleagues who have been responsible for the original work described and digested in this volume will not be offended but rather will be indulgent of these purposes.

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Introduction

Immunology is a relatively new medical discipline which has developed symbiotically with bacteriology during the past century. In its older and classical meaning, it was the study of immunity, the processes by which organisms defend theselves against infection, and early immunologists dealt primarily with studies of antibody and the development of vaccines. It was later found that hypersensitivity reactions resulted from antigen-antibody interactions, and the study of allergic disorders became part of the immunologist's work. More recently, cellular immunity has been recognized as being important in processes which have to do with recognition phenomena, self-characterization, growth and development, heredity, aging, cancer, and transplantation. With this expansion, immunology has exceeded the limits of its original meaning, and immunobiology has become a preferable term for this expanding field.

Immunobiology has grown in an almost malignant fashion to embrace every discipline of medicine. Surgery has not escaped this invasion and has benefited immensely. Today, hardly a surgical patient can be treated without directly or indirectly involving immunobiological principles in some way. It is evident that surgeons should know a great deal about this exciting new discipline, but it covers such a broad area that learning all of it would be a formidable, if not impossible, task. To make things worse, the facts that surgeons would like to know and which would be helpful are buried in literally tons of publications, only a few of which seem to have the surgeon in mind. Our purpose in writing this book is to provide a short but comprehensive review of immunobiology as it applies to surgical practice.

HISTORICAL DEVELOPMENT OF SURGERY AND IMMUNOLOGY

The beginnings of surgical practice are lost in the annals of antiquity. Certainly, from the very beginning, man sustained wounds and injuries for which he treated himself and his fellow man. The development of surgery was unrecorded for many thousands of years, but initially it must have developed from what we would consider today to be witchcraft. Objective evidence of surgical treatment dates as far back as Neolithic times when trephining was practiced. Trephined skulls have been found in widely dispersed areas throughout the world giving evidence that this was a not uncommon operation of the prehistoric era.

The first written evidence of surgical practice was inscribed on a stone in Babylon about 2000 B.C. and consisted of enumeration of a series of penalties and regulations known as the Code of Hammurabi. The earliest scientific document that has been discovered is the Edwin Smith Papyrus, written about 1700 B.C. This document is a surgical treatise, which describes a series of case histories that provide us with a good insight into the state of surgical practice at that time. The document itself is felt to be a compilation of observations handed down from the period between 3000 and 2500 B.C.

It is interesting to observe how little surgical practice changed during that initial 3000 years (see inside front cover). By the time of the writings of Hippocrates, a great deal of experience and knowledge had accrued concerning certain surgical conditions, notably, fractures, dislocations, and wounds. Like the Egyptian surgeons, Hippocrates was well aware of the complications of infection and tetanus but, in addition, seemed to have a grasp of some of the modern concepts of wound healing and infection. He realized the desirability of primary healing without infection and also appreciated that free drainage of purulent discharges was essential. He preached that oil or greasy remedies were not good for fresh wounds, but, nevertheless, the practice of treating wounds in this manner was continued for many centuries.

Most surgeons up to and including the time of Ambroise Paré made their fame by caring for the injured during the time of war. Their practice must have been rather depressing, since approximately three out of every four persons injured in battle died, the primary causes being hemorrhage and sepsis. Even in the Franco-Prussian War, in the latter part of the nineteenth century, the mortality from gunshot wounds of the abdomen approached 100 per cent.

Throughout the history of mankind before the nineteenth century, advances in the practice of surgery came pitifully slowly. Immunology, on the other hand, was unknown, although the Chinese custom of inhaling crusts from smallpox lesions to prevent the development of smallpox infection in later life had been practiced since 1500 A.D. Jenner published his monumental work on vaccination for the prevention of smallpox in 1798, and in the following 150 years the growth of both immunology and surgery occurred at an increasingly rapid rate (see inside back cover).

One of the landmarks in surgical history was the development of anesthesia which, in many ways, permitted the development of antisepsis and asepsis in surgery. Prior to anesthesia, haste on the part of the surgeon was essential, and the meticulous operative care of today would have been unacceptable to the patient regardless of the risk involved. Although the use of anesthetic agents made operations more acceptable to the patient, it did not directly decrease mortality from infection. Infection was not only to be expected, it was felt to be desirable by most surgeons. From the lack of attention to the details of asepsis still given by a few, one might suspect that this belief survives.

By the time of Lister, the care of patients in Europe had gradually shifted from the home to hospitals, where overcrowding and unclean conditions prevailed. To be admitted for a major operative procedure or with a compound fracture meant almost certain death in some hospitals. The situation was not universally dismal, however, as the idea of disinfection and cleanliness had been developing over the preceding one hundred years. Both Oliver Wendell Holmes and Ignaz Semmelweis, a young Hungarian, connected the high mortality from puerperal sepsis to transmission of the disease by the unclean hands of attending physicians. Semmelweis developed nothing new, but he was responsible for the greatest amount of controversy concerning disinfection and cleanliness and for their final victory. Ironically, he died from blood poisoning in an insane asylum in Vienna in 1865, the same year that Joseph Lister first used carbolic acid as an antiseptic.

Lister, an Englishman, was disturbed by the observation that death from hospital gangrene was much more prevalent in patients treated in a hospital environment than in patients with similar lesions who were treated at home. As a result of studying Pasteur's work, which had shown that bacteria caused fermentation, he reasoned that bacteria might likewise cause fermentation in wounds. He was pondering what would be the best way to attack this problem when he had the good fortune to pass a sewage disposal plant and was struck by the fact that the disinfected sewage had lost its characteristic stench. After he found that carbolic acid was used to disinfect the sewage, he applied carbolic acid to the wounds of his patients with dramatic success. After two years of experimenting, he had accumulated indisputable evidence that the treatment had a remarkable effect in preventing hospital gangrene. His first work was published in 1867, but was not well received, and it took a number of years before wide acceptance was gained.

By the time Lister had started his experiments, Pasteur (1864) had shown that heat would kill bacteria, and from this observation grew the use of the term pasteurization. Pasteur also showed that chicken cholera and anthrax in animals could be prevented by vaccination and later made the outstanding contribution of vaccination for rabies. Koch (1878) made the observation that different types of bacteria could cause different types of wound infections. As a result of Lister's studies on antisepsis and the early observations of Pasteur and Koch, the period of antiseptic surgery emerged. In 1886, Von Bergman introduced the steam sterilizer, and in 1890, Halstead introduced rubber gloves, which, interestingly enough, were developed to protect the sensitive hands of his faithful scrub nurse, and later his wife, from the irritating effects of carbolic acid. Schemmelbusch published his book on aseptic technique in 1892, and Mikulicz introduced the mask in 1896, thus making the concept of aseptic technique almost complete by the beginning of the twentieth century. Surgical infection had by no means been eradicated, but, on the other hand, the mortalities from injury and operation fell remarkably during this period, and to have an operation no longer meant almost certain death. Partly because of this and partly because the use of anesthesia allowed surgeons to be slower and more precise, technical surgery developed at a rapid rate.

Aside from hospital gangrene and technical advances, there were other surgical problems to be solved, and immunology again extended a helping hand. In 1888, Roux and Yersin discovered diphtheria toxin and found that an antitoxin could be produced in animals which would neutralize its toxic effects. Von Behring and Kitasato (1890) showed that immunity to tetanus antitoxin could be passively transferred to another animal. Roux later used horse antitoxin for the treatment of human diphtheria with marked success (1894). Production of tetanus antitoxin was a natural outgrowth of these earlier observations, and, in 1914, equine tetanus antitoxin was used with great success for preventing the dreaded and highly fatal disease of tetanus which so frequently followed war wounds. Later (1923), Glenny and Ramon found that toxins could be made to lose their toxic property while still retaining their antigenic property, and, as a result of their observations, a highly effective immunizing agent was developed which virtually eliminated tetanus in our troops during World War II and subsequently.

Shock was another problem facing surgeons of the early twentieth century. It was believed by many that blood transfusions would be helpful in preventing death if they could be given with safety. Transfusion of blood from animals to humans was first attempted in the mid-seventeenth century and met with occasional success, but, more often, transfusions were disastrous. Transfusions of blood from one human to another were tried in the early nineteenth century with greater success, but this, too, was sometimes associated with severe and even fatal reactions. Karl Landsteiner, a quiet but brilliant laboratory investigator, came to the surgeon's rescue when he discovered the major blood group antigens in 1900 and described their interactions. As a direct result of his experiments, blood transfusions became possible as a safe procedure after appropriate typing and cross-matching. In 1914, citrate was used to prevent clotting. Stored blood was used for transfusions in World War I, but it was not until the period between World War I and World War II that blood banking became safe. Landsteiner described the blood groups M and N only a few years after the ABO system was found, but it was not until 1940 that Landsteiner and Weiner discovered the Rh factors. The development of thoracic and cardiovascular surgery could only follow Landsteiner's monumental discovery of the blood group antigens and adequate means for the safe transfusion of blood, even though most of the technical problems had been solved by the early twentieth century. The first successful pneumonectomy was not done until 1933 by Evarts Graham. The burgeoning success of cardiovascular and pulmonary surgery since that time has been evident to all.

Even this success would be considerably dampened if it were not for the studies of other immunologists. The great pioneer of immunochemistry, Paul Ehrlich, was the first to use quantitative measurements in immune reactions. Because of his interest in dyes, he introduced useful methods for examining the cells of blood and tissues, and he developed salvarsan, the first effective chemotherapeutic agent against any microorganism. The antibacterial action of pencillin was first observed by Alexander Fleming in 1928, but it was several years before its significance was realized. In 1932, Gerhard Domagk developed prontosil which was an effective antibacterial agent against *Streptococcus*. Later, the active ingredient was found to be sulfanilamide, and its action was found to be effective against a wide variety of organisms. It was used so enthusiastically that allergic and toxic reactions came to be a significant problem. The tedious process of isolation and purification of penicillin was accomplished in 1941, by Howard Florey and Ernst Chain. Penicillin received its first major trial in World War II during the North African campaign, and it was also at this time that blood transfusions reached a high point of safety and effectiveness. Few surgeons need to be reminded of the usefulness of antibiotic therapy in surgical practice, although use of these agents is sometimes abused.

The story does not stop there, for the classic studies of Medawar and his colleagues in 1944 and 1945 initiated a flurry of interest among surgeons in the problems of transplantation. A large number of immunologists more recently have been instrumental in providing diagnostic and therapeutic techniques in support of surgical problems, and these advances will be discussed at greater length elsewhere in this book.

It may be of interest to the reader to recall the background of some of the men who have been destined to change the face of surgical practice. Morton and Wells, who discovered anesthesia, were both dentists. Jenner and Koch both started their careers as country doctors. Landsteiner was a pathologist who devoted his full efforts to research on immunological problems. Pasteur was a chemist. Metchnikoff, about whom we will say more later, was a Russian biologist. Paul Ehrlich was a chemist; Fleming, a bacteriologist; Medawar, a zoologist; and Coombs, a veterinarian. Surgery owes a great debt to these pioneers, and we should be somewhat humbled by the observation that most of them were not even physicians, much less surgeons.

IMMUNOLOGY IN MODERN SURGERY

It is apparent from the foregoing brief historical review that the fundamental discoveries in immunology have profoundly influenced the development of surgery. Today, immunobiology has an even greater impact on surgery. Its principles are used in the treatment and prevention of infection and in understanding the processes of wound healing. Chemotherapeutic agents and other treatment modalities may modify the capacity of an individual to respond to infection or to an immunological stimulus. Drugs, themselves, may cause severe allergic reactions. Major operative procedures depend upon the availability of blood which is selected by immunological matching. Many of the diagnostic tests of value to surgical patients depend upon immunological reactions. Many diseases treated by surgical therapy have an abnormal immune response as their sole basis. In addition, there is a growing number of patients having immunological deficiencies in whom surgical treatment is necessary. A whole new area of surgical practice, organ transplantation, is now beginning to be made feasible through histocompatibility matching and manipulation of the immune response. Other major areas of disease, such as cancer and degenerative diseases, are closely related to immunological changes.

FUTURE OF IMMUNOBIOLOGY TO SURGICAL PRACTICE

Undoubtedly, surgeons will continue in future years to be concerned primarily with the operative care of patients. The surgeon of the future, however, will be faced with increasingly difficult and complex tasks related to the preservation and transplantation of living tissues, the prevention and treatment of infection, and the treatment of diseases such as ulcer and cancer by immunological manipulation. It may become possible to destroy selectively certain tissues, to give an individual a new set of immunological information, or to destroy that which he has. Although no one can predict the exact future course of events, it is obvious that immunobiology will continue to be of increasing importance in surgical practice.

SUMMARY

The major achievements in immunology during the past 150 years have profoundly influenced the development of surgical practice. Had it not been for these developments, surgical practice would have advanced little from the dark ages. Because of their relationship to infection, wound healing, cancer, transplantation, transfusions, and drug therapy, immunobiological principles are employed in the treatment of virtually every surgical patient in modern times. The field of immunobiology is a broad and complex one, but one which will have an ever-increasing importance in surgical practice. It is the purpose of this book to present a brief but comprehensive survey of immunobiology as it applies to surgical practice.

Suggestions for Further Reading

Burnet, F. M.: The Integrity of the Body. Harvard University Press, Cambridge, 1962. (A discussion of the scope of immunobiology in medicine is presented.)
Humphrey, J. H., and White, R. C.: Immunology for Students of Medicine. F. A. Davis Co., Philadelphia, 1963. (A good text of basic immunology with an excellent historical review.)
Richardson, R. G.: The Surgeon's Tale. Ruskin House, London, 1958. (A short and enjoyable history of surgery.)
Zimmerman, L. M., and Veith, I.: Great Ideas in the History of Surgery. Williams & Wilkins Co., Baltimore, 1961. (Biographies of major contributors to surgical science are presented.)

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Nonspecific Immunity

Immunity is usually meant to be synonymous with resistance, including not only resistance to infectious agents, but also to foreign particles, toxins, living cells, and cancer. Its success is based upon the ability of living organisms to recognize the foreignness of complex molecules which are unrelated to their own normal structure. Immunity may be acquired as a result of prior experience with a foreign substance, or it may be nonspecific, in which case it is genetically determined. Nonspecific, innate, or natural immunity will be considered in this chapter.

The genetic control of resistance to foreign substances encompasses an exceedingly broad body of knowledge which deals with basic cellular function, but since it is not our purpose to deal with the more esoteric aspects of cellular biology, we will confine ourselves to a discussion of those features which we feel may relate directly to clinical practice, realizing that what seems to be of practical significance to one individual is often deemed worthless by another. The basic concepts of nonspecific immunity can best be learned by studying nonspecific resistance to bacterial infection, since the concepts derived therefrom usually apply equally well to other aspects of nonspecific immunity.

THE INFLAMMATORY LESION

Requisite to an understanding of infection and wound healing is an understanding of the inflammatory lesion, without which defense against infection cannot take place, nor wounds heal. An inflammatory response can be elicited by numerous means, all of which, even physical trauma, are ultimately chemically mediated and somewhat similar in nature. Its development depends upon a continuing sequence of events which include alterations of the microvasculature, deposition of phagocytic cells, removal of noxious substances, and ultimate tissue repair.

The Vascular Response

Whether inflammation results from bacterial invasion, traumatic injury, or the introduction of noxious materials, the initial events in the microcircu-

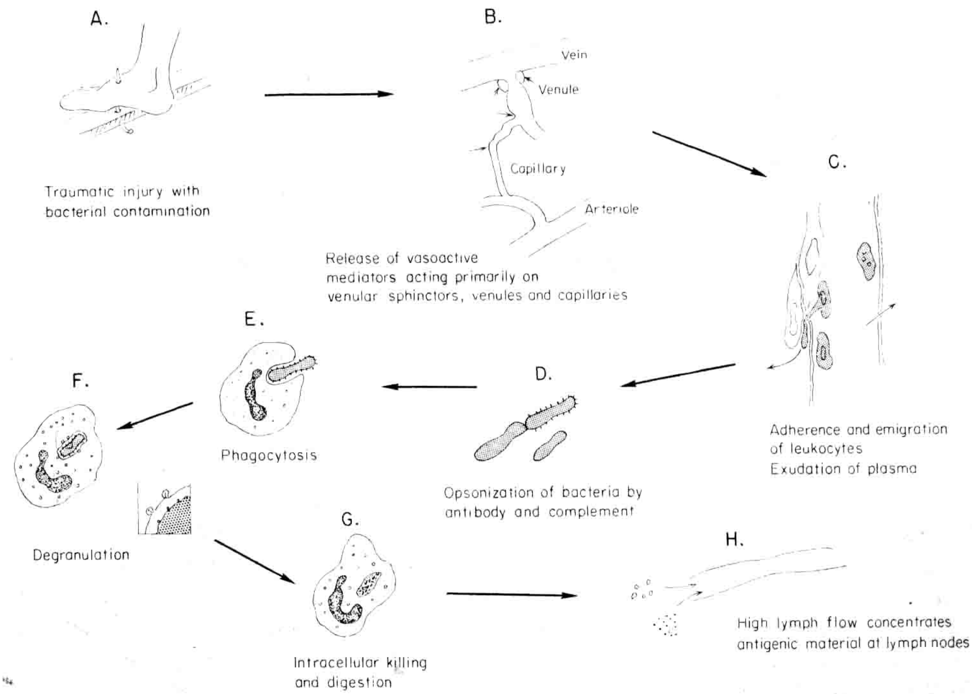

Figure 2–1. Schematic development of an inflammatory lesion following traumatic injury with bacterial contamination.

lation are similar. Attendant to injury, there is an immediate vascular response which reaches its peak in five to ten minutes and is accompanied by an increase in endothelial permeability. The chemical mediators of early inflammation produce constriction of the venular sphincters at the junction of venules with veins (Fig. 2-1A). This produces increased venular and capillary pressures, decreased rates of blood flow with stasis, hypoxia, and acidosis, increased permeability of the endothelium to plasma proteins, and exudation of fluids into the tissues (Fig. 2-1B). As a result of the exudation of plasma proteins and fluids from the intravascular to the extravascular compartment, there is an increase in lymphatic flow. The arterioles may be variably affected, and small arteriolar-venular shunts may become functional. In the established inflammatory lesion, total blood flow is usually significantly increased. Following the brief initial phase of increased permeability, or concurrent with it, is a more sustained phase which is characterized by adherence of blood phagocytes to the endothelium of the venules and capillaries. These leukocytes marginate because of the decreased rate of flow and become "sticky" upon contact with the activated endothelium. They exit from the blood vessels by emigrating through the spaces at intercellular junctions (Fig. 2-1C).

Many investigators have studied the phenomenon of sticking and emigration of leukocytes since it was described in 1824, but numerous prob-