IMMUNOLOGY, BIOCHEMISTRY, AND BIOTECHNOLOGY

Immunology: Clinical, Fundamental, and Therapeutic Aspects

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Preface

Diagnostics and therapeutic immunology has expanded tremendously in recent years. T. S. Eliot once said, "Where is the knowledge we have lost in information?" Many books (elementary and advanced) have been published on immunological sciences trying to keep pace with the voluminous information available in this area that necessitated various subdivisions in immunology—immunogenetics, clinical immunology, etc. The present book discusses the clinical, fundamental, and therapeutic effects of immunology. Each chapter begins with the basic terminologies, and their explanations, then takes the reader to a much higher level of complexity so that he can appreciate some of the latest achievements of this decade. Thus, the book is useful for people who are beginning to understand immunology yet advanced enough for researchers who are venturing to find new niches in research.

The book begins with fundamentals of immunology and proceeds to explore the subject at increasing levels of detail. The first section delves into the present "state of the art" knowledge of the immune system and immunoglobulins, and its development over the years. Crystallographic structure of immunoglobulin is presented in Chapter 3, which contains the latest findings on this topic. This basic foundation, interwoven with use of immunology in biology (immunobiology), is detailed in the second section. The third section presents the immunological mechanisms that protect human beings against infectious disease and cancer. In addition, this section covers immune deficiency diseases. The fourth section presents drugs of immune origin, especially derived interleukins and immunoregulatory drugs. This area is still in its infancy but the next decade will see the tremendous potential offered by such drugs. This section is included to encourage researchers to develop drugs that are compatible with the immune systems.

The book is designed to give a glance at various aspects of immunology impacting upon the field of biomedicine, both from the basic and clinical view point, and should be of interest to biologists, biochemists, pharmaceutical scientists, immunologists, and biotechnologists, both in industry and academia. The book is directed to students as well as advanced researchers who might be exploring areas away from the beaten path in immunology. It may also be used as a textbook for advance study in immunology.

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Bhanu P. Ram
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Contents

SECTION I

BASIC IMMUNOLOGICAL CONSIDERATIONS

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CHAPTER 1

Immunology: Yesterday, Today, and Tomorrow

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Introduction

The field of immunology has expanded tremendously in recent years because of the unprecedented development of new concepts in answer to fundamental scientific questions and the introduction of powerful technologies that have both diagnostic and therapeutic impact. In previous years, immunology was considered part of microbiology, and research in the field investigated problems related to the diagnosis and treatment of infectious diseases. Following significant scientific advances, however, immunology developed into its own science, apart from those of microbiology, pathology, biochemistry, and molecular biology, which nursed its original development. Recently, moreover, with its ever expanding research applications and technologies, the field of immunology has provided important information of use to physicians and scientists in many disciplines, including neonatology, nephrology, genetics, medicine, and surgery. Immunology is currently at the forefront of the medical sciences and has become a most exciting, challenging, and promising field!

The term "immune" derives from the Latin *immunis*, which means "free or exempt from taxes or expenses". In the most classical sense, then, immunology, or the study of the immune system, is concerned with the mechanisms or processes that protect the host from damage caused by invading microorganisms. Moreover, the immune system functions to maintain homeostasis between the internal body milieu and the external environment. Under normal conditions, the immune system

effectively defends the host against foreign substances, such as pathogenic microbial agents, as well as native cells that have undergone neoplastic transformation. Defective functioning of the immune system results in disease. It is now well recognized that not all immune responses are helpful to the host. For example, the interaction of the immune system and the environment may produce injury to target cells, termed hypersensitivity or allergy. Likewise, target cells may be directly damaged via autoimmune mechanisms. When immunologic surveillance fails, the manifestations may be those of malignant disease. Bellanti,[1] therefore, has characterized the three functions of the immune system as defense, homeostasis, and surveillance.

Thus, the field of immunology includes contributions from both basic and clinical research investigations. The current text, therefore, has been developed to include contributions from workers in the spheres of both basic and clinical sciences. The first two sections of this text, "Basic Immunological Considerations" and "Immunobiology," reflect contributions from basic scientists, whereas Sections III and V, "Clinical Immunology" and "Drugs of Immune Origin," review the application of basic immunological principles to clinical problems and drug development.

Brief History

The origin of immunology lies buried in the past and is derived primarily from the study of resistance to infection. It was known from centuries that individuals acquired immunity against a particular disease, eg, smallpox, following recovery from the disease. The first effective immunization was performed by Edward Jenner, an English Physician (1749–1823), who observed that persons who got well after infection with cowpox were protected against smallpox. The enhancement and further development of preventative immunization almost a century later was made possible by Louis Pasteur, who coined the term "vaccine" (from *vacca*: L, cow) in honor of Jenner's contribution. Pasteur's research led to the development of germ theory. He developed techniques to grow microorganisms in vitro. The organisms (living, heat killed, and attenuated) were used as vaccines for the disease they caused. It was observed by Pasteur that old cultures (attenuated) of fowl cholera organism, when inoculated into fowl, produced no disease, although the fowls were found to be resistant to subsequent infection with the organism and were strongly immune.

Humoral Immunity

Robert Koch (1843–1910), while attempting to develop a vaccine for tuberculosis, observed the phenomenon known today as delayed hypersensitivity or cell-mediated immunity. Fodor in 1886 observed a direct action of an immune serum on microbes during the course of his studies on anthrax bacilli. Behring and Kitasato (1890) demonstrated the neutralizing antitoxic activity of sera from animals immunized with diphtheria or tetanus toxin. They injected the serum from animals and demonstrated that normal animals became resistant to the disease. Thus, they concluded

that blood (serum) of resistant animals contained a substance, antitoxin, that could neutralize the toxic effect of bacteria.

Rudolf Kraus (1897) demonstrated that a bacterial filtrate became clouded with a precipitate when mixed with serum from immune animals. The immune serum (antiserum) thus contained precipitins. At the same time it was also discovered that an antiserum reacted not only with bacterial products but also with the bacteria themselves. Pfifer observed that certain antisera dissolved bacterial cells (lysis). Gruber and Durham reported that certain other antisera glued bacteria together (agglutination). These reactions as well as others (opsonins, reagins, conglutinins) occurred because of the presence of substances in the serum that were later termed "antibodies." Substances stimulating the appearance of antibodies were then designated "antigens." Yet another serum factor involved in the immune reaction, which was distinctly different from antibodies, was discovered by Hans Buchner in 1893. Confirming Buchner's observation, Bordet observed that goat antiserum to vibro cholerae lysed bacteria when fresh, but when the serum has been heated at 58°C for 1 h, it lost its lysing activity. However, this lysing activity of the serum was regained when some fresh serum from nonimmunized guinea pig was added to the heated serum. It was concluded that goat serum contained two kinds of substances: (1) specific thermostable antibodies, and (2) heat-liable alexin, which was later renamed complement.

Antibodies

Initially, it was believed by microbiologists that antibodies could be produced only against microorganisms. However, it became clear that antibodies could be produced virtually against any molecule—big or small. In addition, the antibodies were found to be very specific in that they reacted with the substance they were produced against.

Later it became apparent that antibodies were proteins. Lloyd D Felton and GH Bailey were the first to isolate the pure antibody generated against pure polysaccharide from pneumococcal bacteria. Fractionation of the serum in ammonium sulfate gave a precipitate and a soluble portion, which were termed, respectively, "globulin" (thought to be related to hemoglobin) and "albumin" (resembling egg white). It was not until the development of an electrophoresis apparatus by Arne W Tiselius that the serum proteins were separated under electric current, yielding peaks with globulin activity. Globulins with antibody activity were designated "immunoglobulins" by JF Heremans.

What makes antibodies manage to distinguish so many antigens with great specificity? This was explained by Paul Ehrlich in 1900 by his theory of stereoscopic complementarity of two kinds of molecule. The antibody molecule is shaped to fit a particular antigen, and only that antigen, like a key and lock.

Karl Landsteiner and his collaborators explained the antigenicity of small molecules. He later termed these molecules "haptens." By conjugating haptens to proteins, he studied the immune response of such conjugates. He concluded that haptens had to be attached to a carrier (protein) to elicit antibody response. The

contribution of chemistry to immunology led Svante Arrhenius in 1907 to suggest the name "immunochemistry," denoting a combination of the two, which is accepted today.

Cellular Immunity

At around the turn of the century, there emerged two different points of view of immunology, from which two lines of thought later developed: (1) the humoral theory of immunity, that is mediated by soluble substance (antibodies) present in body fluids, and (2) the cellular theory of immunity, whose emphasis is the biologic effects of intact cells involved in the host's response to foreignness. The Russian zoologist Elie Metchnikoff was the founder of the cellular theory of immunity. His theory held that the body's scavanger cells, the phagocytes, were the primary detectors of foreign material as well as its primary defense system. Now, it is established that both cellular and humoral factors are involved in understanding the principles underlying the immunologic processes that result in tissue injury.

The realization that cellular and humoral immunity are governed by different organs has led some immunologists to speculate that there are two different kinds of lymphocytes—one processed by the bursa and involved primarily in the humoral immunity, and the other processed by the thymus and involved primarily in cellular immunity. William A Ford, Malcolm AS Moore, and some other investigators observed that there were indeed two pathways of lymphocyte development. One passes through the thymus and leads to thymus-derived lymphocytes or T cells, and the other passes through the bursa, leading to bursa-derived lymphocytes, or B cells. Thus, removal of thymus not only inhibits cellular immunity but depresses antibody response by preventing helper T cells (T_H) from maturing.

Recent Periods in Immunology

Discovery of B and T cells made a big impact on immunological understanding. The increasing importance of blood grouping in medicine led to a search for more blood groups in humans and animals. This made geneticists aware of the possibilities that immunological methods had to offer for the study of inheritance. This led to the development of a new branch of immunology, termed "immunogenetics" by M Robert Irwin in 1936. Slowly other new branches of immunology started emerging. An overview of related fields is presented in Figure 1-1.

Present Concepts in Immunology

Two fundamental aspects of immunology persist today; to wit, (1) immunologic phenomena are considered "defense mechanisms" and (2) the organism, under normal conditions, does not react against its own constituents.

In his presidential address to the American Association of Immunologists, William Paul[2] has characterized two centuries in the development of immunology. The first period, from 1880 to the present, marked the century of immunological

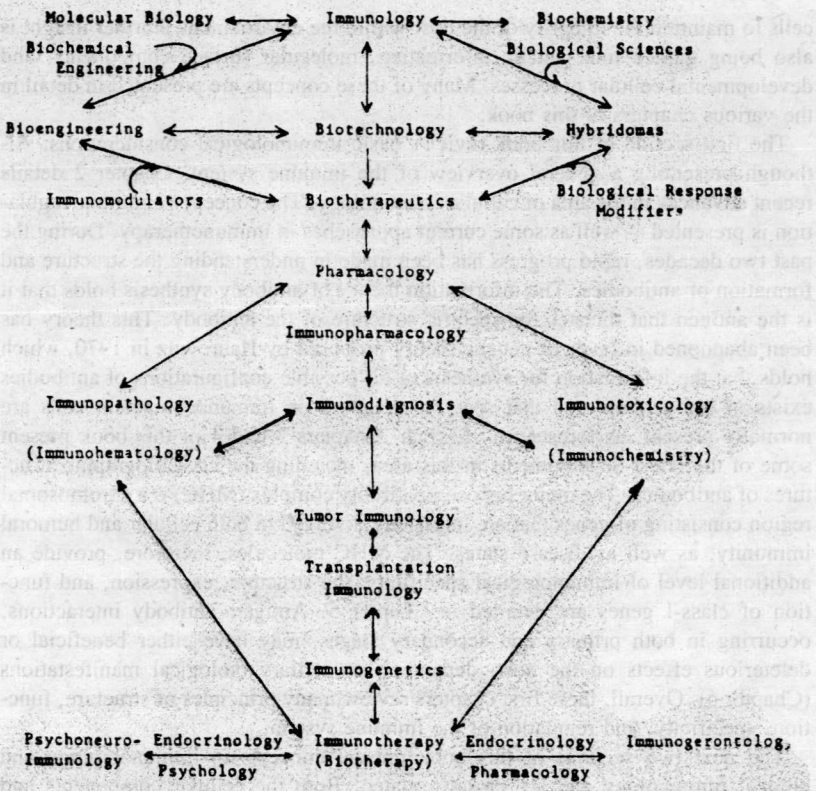

Figure 1-1. A multidisciplinary approach to immunology. (Courtesy Professor Albert Awad of Ohio Northern University.)

specificity. The second century of immunology, beginning in the 1980s, is proposed to be the century of immunological regulation and the physiology of the immune system. The new era of molecular immunoregulation has already dawned as evidenced by the proliferation of research and published material in this area. Important concepts include the recognition that antibody production requires the cooperation of helper T and B cells as well as current understanding of the function of helper and suppressor cells and idiotype–anti-idiotype interactions. In addition, soluble products of the immune system, including cytokines, interleukens, and hematopoietic growth factors, are important regulators of the immune system and may ultimately suggest new pharmacologic mechanisms for the treatment of disease. With regard to the physiology of the immune system, current knowledge is accumulating to elucidate basic biochemical mechanisms of cell function, and to establish cooperative cellular and molecular interactions as the basis for the transmission of information between cells. This network of communicating cells involves a molecular language that controls the development and function of other