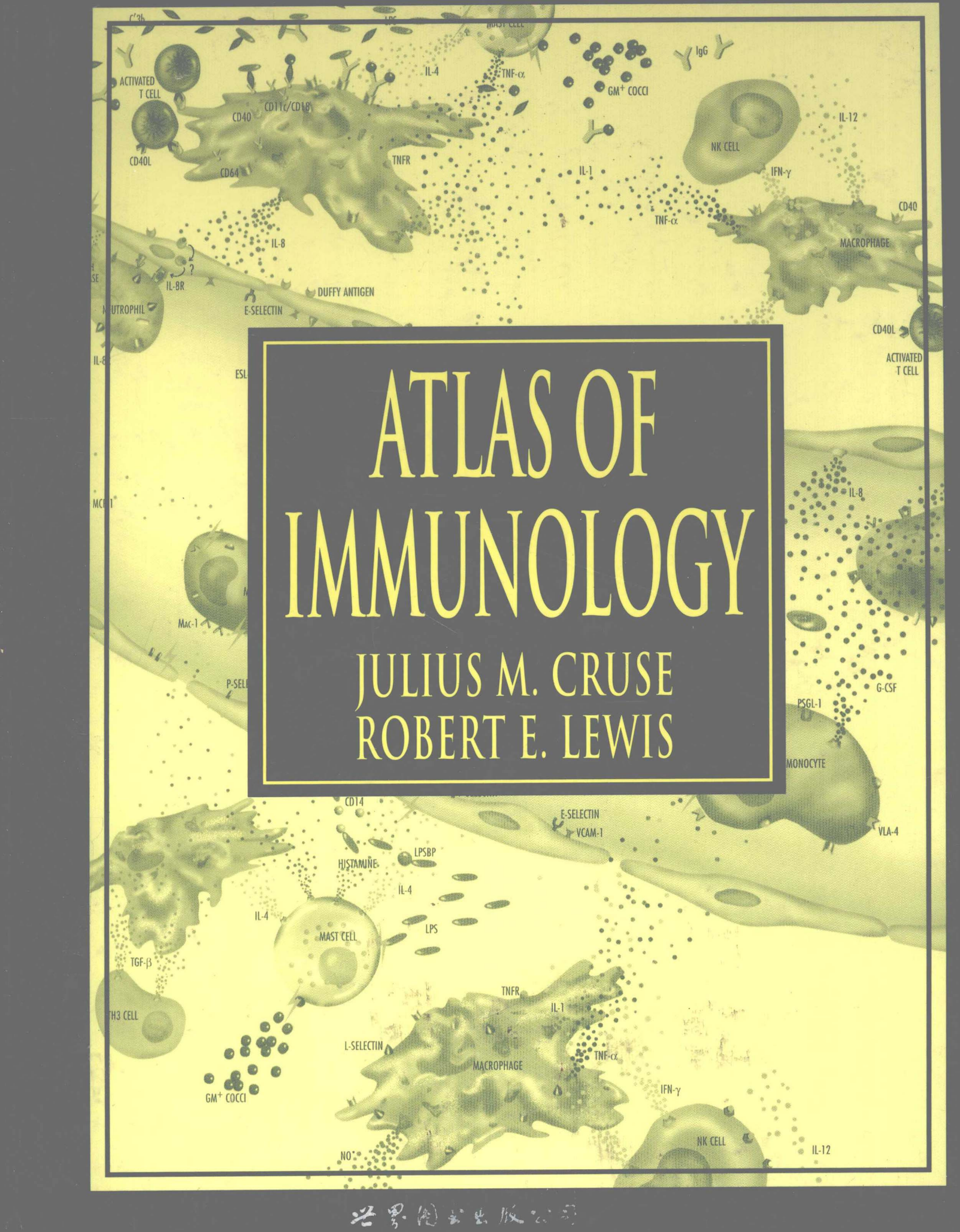

ATLAS OF IMMUNOLOGY

JULIUS M. CRUSE
ROBERT E. LEWIS

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ATLAS OF IMMUNOLOGY

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Earl R. Wilson

Martha Lyles Wilson

Hyman F. McCarty, Jr.

Mary Ann McCarty

... truly persons of vision whose philanthropy and unselfish dedication to their fellow human beings in establishing the Mississippi Methodist Rehabilitation Center, the Wilson Research Foundation, and advancing medical education at the University of Mississippi Medical Center have inspired all of us who are beneficiaries of their generosity to create a better community, state and nation through medical research and improved patient care.

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Dr. Cruse is a member of numerous professional societies which include the American Association of Immunologists (Historian), the American Society for Investigative Pathology, the American Society for Histocompatibility and Immunogenetics (Member of Council, formerly Chairman [1987-1995], Publications Committee 1987-1995), the Societe Francaise d'Immunologie, the Transplantation Society, the Society for Experimental Biology and Medicine, among many others. He is a Fellow of the American Academy of Microbiology and a Fellow of the Royal Society of Health (U.K.).

Dr. Cruse's research has centered on transplantation and tumor immunology, autoimmunity, MHC genetics in the pathogenesis of AIDS, and neuroendocrine immune interactions. He has received many research grants during his career and is presently funded by the Wilson Research Foundation for neuroendocrine-immune system interactions in spinal cord injury and stroke patients. He is the author of more than 250 publications in scholarly journals and 35 books, and has directed dissertation and thesis research for more than 40 graduate students during his career. He is the founding editor of the journals *Immunologic Research, Pathobiology and Transgenics*.

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Dr. Lewis is a member of numerous professional societies which include the American Immunologists, the American Society for Investigative Pathology, the Society for Experimental Biology and Medicine, the American Society for Microbiology, the Canadian Society for Immunology, the American Society for Histocompatibility and Immunogenetics (Vice Chairman, Publications Committee), among numerous other scientific organizations. He is a Fellow of the Royal Society of Health of Great Britain. Dr. Lewis has been the recipient of a number of research grants in his career and is currently funded by the Wilson Research Foundation for his research on neuroendocrine–immune system interaction in spinal cord injury and stroke patients.

Dr. Lewis has authored or co-authored more than 100 papers and 125 abstracts and has made numerous scientific presentations at both the national and international levels. In addition to neuroendocrine-immune interactions, his current research also includes immunogenetic aspects of AIDS progression. Dr. Lewis is a founder and editor of *Immunologic Research, Pathobiology* and *Transgenics*.

Preface

The *Atlas of Immunology* is designed to provide a pictorial reference and serve as a primary resource for the most up-to-date and thorough illustrated treatise available in the complex science of immunology. The book contains more than 1,000 illustrations and depicts essentially every concept of importance in understanding the subject matter of immunology. It is addressed to immunologists and nonimmunologists alike, including students, researchers, practitioners, and basic biomedical scientists. Use of the book does not require prior expertise. Some of the diagrams illustrate basic concepts, whereas others are designed for the specialist interested in a more detailed treatment of the subject matter of immunology. The group of illustrations is relatively complete and eliminates the need to refer to another source. The subject matter ranges from photographs of historical figures to molecular structures of recently characterized cytokines, the major histocompatibility complex molecules, immunoglobulins, and molecules of related interest to immunologists.

The subject matter is divided into chapters that follow an outline that correlates with a standard immunology textbook. This provides for a logical and sequential presentation and gives the reader ready access to each part of the subject matter as it relates to the other parts of the publication. These descriptive illustrations give the reader a concise and thorough understanding of basic immunological concepts that often intersect the purview of other basic and clinical scientific disciplines. A host of new illustrations, such as cellular adhesions molecules, is presented in a manner that facilitates better understanding of their role in intercellular and immune reactions. Figures that are pertinent to all of the immunological subspecialties, such as transplantation, autoimmunity, immunophysiology, immunopathology, antigen presentation, the T-cell receptor, to name a few, may be found in this publication. Those individuals with a need for ready access to a visual image of immunological information will want this book to be readily available in their bookshelf. No other publication provides the breadth or detail of illustrated immunological concepts as may be found in the *Atlas of Immunology.*

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We express genuine appreciation to Mary Blaine, Dana Roe, Smaroula Dilioglou, and Jean Henderson for their dedicated efforts in helping us to complete this publication in a timely manner and making valuable editorial contributions. We also appreciate the constructive criticisms of Patsy Foley, B.S., M.T., C.H.T., Paula Hymel, B.S., M.T., C.H.T., Elisa Rodabough, B.S., M.T., C.H.T., Maxine Crawford, B.S., Kathy VanLandingham, B.S., M.T., C.H.T., and Susan Touchstone, B.S., M.T., S.B.B., C.H.T., C.H.S. We thank doctoral candidates Martha Brackin and Andrew Achord for constructive criticisms and William Buhner for scanning selected figures. We are most grateful to Joanna Arentz, of R&D Corp. for providing the artwork for the cover illustration and sharing with us a number of schematic diagrams of immunological molecules and concepts owned by R&D. We would also like to commend the individuals at CRC Press — Liz Covello, Acquiring Editor, Gerry Jaffe, Production Manager, Life Sciences and Forensics, Becky McEldowney, former Marketing Manager, Gary Bennett, Prepress Manager, and all members of their staff for their professionalism and unstinting efforts to bring this book to publication. To these individuals, we offer our grateful appreciation.

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Contents

1

History of Immunology

The metamorphosis of immunology from a curiosity of medicine associated with vaccination to a modern science focused at the center of basic research in molecular medicine is chronicled here. The people and events that led to this development are no less fascinating than the subject itself. A very great number of researchers in many diverse areas of medicine and science contributed to building the body of knowledge we now possess. It will be possible to name only a few but we owe a debt to them all. We are standing on the shoulders of giants, and in remembering their achievements we come to understand better the richness of our inheritance.

Resistance against infectious disease agents was the principal concern of bacteriologists and pathologists to establish the basis of classical immunology in the latter half of the nineteenth and early twentieth centuries. Variolation was practiced for many years prior to Edward Jenner's famous studies proving that inoculation with the cowpox could protect against subsequent exposure to smallpox. This established him as the founder of immunology. He contributed the first reliable method of conferring lasting immunity to a major contagious disease. Following the investigations by Louis Pasteur on immunization against anthrax, chicken cholera and rabies, and Robert Koch's studies on hypersensitivity in tuberculosis, their disciples continued research on immunity against infectious disease agents. Emil von Behring and Paul Ehrlich developed antitoxin against diphtheria while Elie Metchnikoff studied phagocytosis and cellular reactions in immunity. Hans Buchner described a principle in the blood later identified by Jules Bordet as alexine or complement. Bordet and Octave Gengou went on to develop the complement fixation test that was useful to assay antigen-antibody reactions. Karl Landsteiner described the ABO blood groups of man in 1900 followed by his elegant studies establishing the immunochemical basis of antigenic specificity.

Charles Robert Richet and Paul Jules Portier, in the early 1900s, attempted to immunize dogs against toxins in the tentacles of sea anemones but inadvertently induced a state of hypersusceptibility which they termed anaphylaxis. Since that time, many other hypersensitivity and allergic phenomena that are closely related to immune reactions have been described. Four types of hypersensitivity reactions are now recognized as contributory mechanisms in the production of immunological diseases. From the early 1900s until the 1940s, immunochemistry was a predominant force maintaining that antibody was formed through a template mechanism. With the discovery of immunological tolerance by Peter Medawar in the 1940s, David Talmage's cell selection theory and Frank Burnet's clonal selection theory of acquired immunity, it became apparent that a selective theory based on genetics was more commensurate with the facts than was the earlier template theory of the immunochemists. With the elucidation of immunoglobulin structure by Rodney Robert Porter and Gerald Edelman, among others, in the late 1950s and 1960s, modern immunology emerged at the frontier of medical research. Jean Baptiste Dausset described human histocompatibility antigens and transplantation immunology develop into a major science making possible the successful transplantation of organs. Bone marrow transplants became an effective treatment for severe combined immunodeficiency and related disorders. The year 1960 marked the beginning of a renaissance in cellular immunology, and the modern era dates from that time. Many subspecialties of immunology are now recognized and include such diverse topics as molecular immunology (immunochemistry), immunobiology, immunogenetics, immunopathology, tumor immunology, transplantation, comparative immunology, immunotoxicology, immunopharmacology, among others. Thus, it is apparent that immunology is only at the end of the beginning and has bright prospects for the future as evidenced by the exponential increase in immunologic literature in recent years.

In 1948, Astrid Elsa Fagraeus established the role of the plasma cell in antibody formation. The fluorescence antibody technique developed by Albert Coons was a major breakthrough for the identification of antigen in tissues and subsequently demonstrated antibody synthesis by individual cells. While attempting to immunize chickens in which the bursa of Fabricius had been removed, Bruce Glick et al. noted that antibody production did not take place. This was the first evidence of bursa-dependent antibody formation. Robert A. Good immediately realized the significance of this finding for immunodeficiencies of childhood. He and his associates in Minneapolis and J.F.A.P. Miller in England went on to show the role of the thymus in the immune response, and various investigators began to search for bursa equivalence in man and other animals. Thus, the immune system of many species was found to have distinct bursa-dependent, antibody-synthesizing and thymus-dependent

cell-mediated limbs. In 1959, James Gowans proved that lymphocytes actually recirculate. In 1966, Tzvee Nicholas Harris et al. demonstrated clearly that lymphocytes could form antibodies. In 1966 and 1967, Claman et al., Davis et al. and Mitchison et al. showed that T and B lymphocytes cooperate with one another in the production of an immune response. Various phenomena such as the switch from forming one class of immunoglobulin to another by B cells were demonstrated to be dependent upon a signal from T cells activating B cells to change from IgM to IgG or IgA production. B cells stimulated by antigen in which no T cell signal was given continued to produce IgM antibody. Such antigens were referred to as thymus-independent antigens and others requiring T cell participation as thymus-dependent antigens. Mitchison et al. described a subset of T lymphocytes demonstrating helper activity, i.e., helper T cells. In 1971, Gershon and Condo described suppressor T cells. Suppressor T cells have been the subject of much investigation but have eluded confirmation by the techniques of molecular biology. Baruj Benacerraf et al. demonstrated the significant role played by gene products of the major histocompatibility complex in the specificity and regulation of T cell-dependent immune response. Jerne described the network theory of immunity in which antibodies formed against idiotypic specificities of antibody molecules followed by the formation of anti-idiotypic antibodies constitutes a significant additional immunoregulatory process for immune system function. This postulate has been proven valid by numerous investigators. Tonegawa et al. and Leder et al. identified and cloned the genes that code for variable and constant regions of immunoglobulin molecules leading to increased understanding of the origin of diversity in antibody-combining sites. In 1975, George Kohler and Cesar Milstein successfully produced monoclonal antiodies by hybridizing mutant myeloma cells with antibody producing B cells (hybridoma technique). The B cells conferred the antibody-producing capacity while the myeloma cells provided the capability for endless reproduction. Monoclonal antibodies are the valuable homogeneous products of hybridomas that have widespread application in diagnostic laboratory medicine.

Smallpox cartoon, artist unknown From the Clement C. Fry Collection. Yale Medical Library, contributed by Jason S. Zielonka, published in *J. Hist. Med.* 27-447-7, 1972. Legend translated: Smallpox disfigured father says, "How shameful that your pretty little children should call my children stupid and should run away, refusing to play with them as friends…" Meanwhile, the children lament: "Father dear, it appears to be your fault that they're avoiding us. To tell the truth, it looks as though you should have inoculated us against smallpox."

L. Gillray Cowpox Cartoon The Cowpox or the wonderful effects of the new inoculation 1802. Courtesy of the National Library of Medicine.

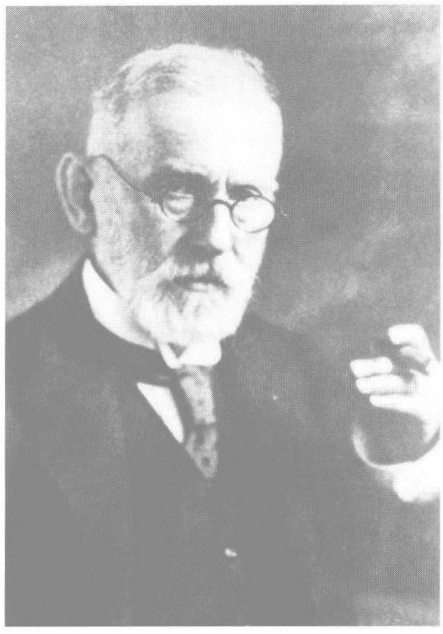
Lady Mary Wortley Montagu (1689–1762) Often credited as the first to introduce inoculation as a means of preventing smallpox in England in 1722. After observing the practice in Turkey where her husband was posted as Ambassador to the Turkish court, she had both her young son and daughter inoculated and interested the Prince and Princess of Wales in the practice. Accounts of inoculation against small pox are found in her *Letters*, 1777. Robert Halsband authored a biography *The Life of Lady Mary Wortley Montagu*. Clarendon, Oxford, 1956.

Edward Jenner (1749–1822) Often is termed the founder of immunology for his contribution of the first reliable method of conferring lasting immunity to a major contagious disease. He studied medicine under John Hunter and for most of his career was a country doctor in Berkeley in Southern England. Although it was common knowledge in the country that an eruptive skin disease of cattle, cowpox, and a similar disease in horses called grease conferred immunity to smallpox on those who cared for the animals and caught the infection from them, Jenner carefully observed and recorded 23 cases. The results of his experiments were published, establishing his claim of credit for initiating the technique of vaccination. He vaccinated an 8-year-old boy, James Phipps with matter taken from the arm of the milkmaid, Sara Nelmes, who was suffering from cowpox. After the infection subsided, he inoculated the child with smallpox and found that the inoculation had no effect. His results led to widespread adoption of vaccination in England and elsewhere in the world leading ultimately to eradication of smallpox.

Louis Pasteur (1822–1895) French. Father of Immunology. One of the most productive scientists of modern times, Pasteur's contributions included the crystallization of L- and O-tartaric acid, disproving the theory of spontaneous generation, studies of diseases in wine, beer and silkworms, and the use of attenuated bacteria and viruses for vaccination. He used attenuated vaccines to protect against anthrax, fowl cholera and rabies. He successfully immunized sheep and cattle against anthrax, terming the technique vaccination in honor of Jenner. He produced a vaccine for rabies by drying the spinal cord of rabbits and using the material to prepare a series of 14 injections of increasing virulence. A child's (Joseph Meister's) life was saved by this treatment. *Les Maladies des Vers a Soie*, 1865; *Etudes sur le Vin*, 1866; *Etudes sur la Biere*, 1876; *Oeuvres*, 1922–1939.

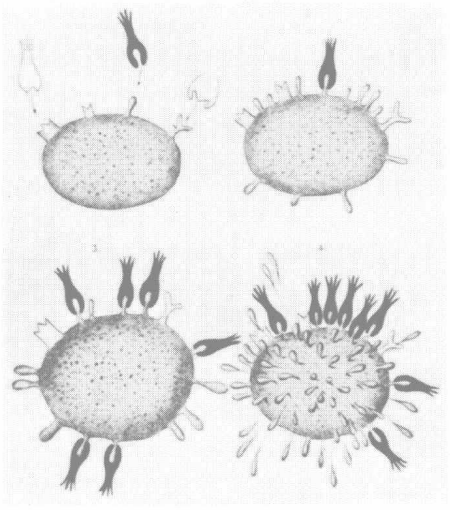
Robert Koch (1843–1910) German Bacteriologist awarded the Nobel Prize in 1905 for his work on tuberculosis. Koch made many contributions to the field of bacteriology. Along with his postulates for proof of etiology, Koch instituted strict isolation in culture methods in bacteriology. He studied the life cycle of anthrax and discovered both the cholera vibrio and the tubercle bacillus. The Koch phenomenon and Koch-Weeks bacillus both bear his name.

Elie (Ilya) Metchnikoff (1845–1916) Born at Ivanovska, Ukraine, where he was a student of zoology with a very special interest in comparative embryology. He received a Ph.D. degree at the University of Odessa where he also served as Professor of Zoology. He studied phagocytic cells of starfish larvae in 1884 in a marine laboratory in Italy. This served as the basis for his cellular phagocytic theory of immunity. On leaving Russia for political reasons, Pasteur offered him a position at the Institute Pasteur in Paris where he extended his work on the defensive role of phagocytes and championed his cellular theory of immunity. He also made numerous contributions to immunology and bacteriology. He shared the 1908 Nobel Prize for medicine or physiology with Paul Ehrlich "In recognition for their work on immunity." *Lecons sur le Pathologie de l'Inflammation*, 1892; *L'Immunite dans les Maladies Infectieuses*, 1901; *Etudes sur la Nature Humaine*, 1903.



Paul Ehrlich (1854–1915) Born in Silesia, Germany, and graduated Doctor of Medicine from the University of Leipzig. His scientific work included three areas of investigation. He first became interested in stains for tissues and cells and perfected some of the best ones to demonstrate the tubercle bacillus and for leukocytes in blood. His first immunological studies were begun in 1890 when he was an assistant at the Institute for Infectious Diseases under Robert Koch. After first studying the antibody response to the plant toxins abrin and ricin, Ehrlich published the first practical technique to standardize diphtheria toxin and antitoxin preparations in 1897. He proposed the first selective theory of antibody formation known as the "side chain theory" which stimulated much research by his colleagues in an attempt to disprove it. He served as Director of his own institute in Frankfurt am Main where he published papers with a number of gifted colleagues including Dr. Julius Morgenroth on immune hemolysis and other immunological subjects. He also conducted a number of studies on cancer and devoted the final phase of his career to the development of chemotherapeutic agents for the treatment of disease. He shared the 1908 Nobel prize with Metchnikoff for their studies on immunity. Fruits of these labors led to treatments for trypanosomiasis and syphilis (Salvarsan) — "The magic bullet". *Collected Studies on Immunity, 1906; Collected Papers of Paul Ehrlich*, Vol 3, 1957.

Svante Arrhenius (1859–1927) Photographed with Paul Ehrlich, 1903. Coined the term "immunochemistry" and hypothesized that antigen-antibody complexes are reversible. He was awarded the Nobel Prize for chemistry, 1903. Book: *Immunochemistry.* MacMillan Publishers, New York, 1907.



DIAGRAMMATIC REPRESENTATION OF THE SIDE-CHAIN THEORY
(PLATES I AND II)

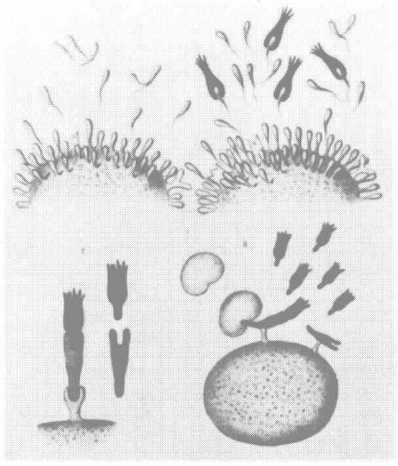
Fig. 1 "The groups [the haptophore group of the side-chain of the cell and that of the food-stuff or the toxin] must be adapted to one another, *e.g.*, as male and female screw (PASTEUR), or as lock and key (E. FISCHER)."

Fig. 2 ". . . the first stage in the toxic action must be regarded as being the union of the toxin by means of its haptophore group to a special side-chain of the cell protoplasm."

Fig. 3 "The side-chain involved, so long as the union lasts, cannot exercise its normal, physiological, nutritive function . . ."

Fig. 4 "We are therefore now concerned with a defect which, according to the principles so ably worked out by . . . Weigert, is . . . [overcorrected] by regeneration."

Side-Chain Theory



DIAGRAMMATIC REPRESENTATION OF THE SIDE-CHAIN THEORY
(*cont.*)

Fig. 5 ". . . the antitoxins represent nothing more than the side-chains reproduced in excess during regeneration and therefore pushed off from the protoplasm—thus coming to exist in a free state."

Fig. 6 [The free side-chains (circulating antitoxins) unite with the toxins and thus protect the cell.]

Fig. 7 ". . . two haptophore groups must be ascribed to the 'immune-body' [haemolytic amboceptor], one having a strong affinity for a corresponding haptophore group of the red blood corpuscles, . . . and another . . . which . . . becomes united with the 'complement' . . ."

Fig. 8 "If a cell . . . has, with the assistance of an appropriate side-chain, fixed to itself a giant [protein] molecule . . . there is provided [only] one of the conditions essential for the cell nourishment. Such . . . molecules . . . are not available until . . . they have been split into smaller fragments. This will be . . . attained if . . . the 'tentacle' . . . possesses . . . a second haptophore group adapted to take to itself ferment-like materia . . ."

Side-Chain Theory

Ehrlich side chain theory The first selective theory of antibody synthesis developed by Paul Ehrlich in 1900. Although elaborate in detail, the essential feature of the theory was that cells of the immune system possess the genetic capability to react to all known antigens and that each cell on the surface bears receptors with surface haptophore side chains. On combination with antigen, the side chains would be cast off into the circulation and new receptors would replace the old ones. These cast-off receptors represented antibody molecules in the circulation. Although far more complex than this explanation, the importance of the theory was in the amount of research stimulated to try to disprove it. Nevertheless, it was the first effort to account for the importance of genetics in immune responsiveness at a time when Mendel's basic studies had not even yet been "rediscovered" by De Vries.

Jules Bordet (1870–1961) Belgian. Physician who graduated Doctor of Medicine from the University of Brussels. He was preparateur in Metchnikoff's laboratory at the Institut Pasteur from 1894–1901 where he discovered immune hemolysis and elucidated the mechanisms of complement-mediated bacterial lysis. He and Gengou described complement fixation and pointed to its use in the diagnosis of infectious diseases. Their technique was subsequently used by von Wassermann to develop a complement fixation test for syphilis which enjoyed worldwide popularity. His debates with Paul Ehrlich on the nature of antigen-antibody-complement interactions stimulated much useful research. He was awarded the Nobel Prize in Medicine or Physiology for his studies on immunity, 1919. Book: *Traite de l'Immunite dans les Maladies Infectieuses*, 1920.