Basic & Clinical Immunology

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4th edition

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Preface

As the fourth edition of *Basic & Clinical Immunology* goes to the printer, we are pleased to note that it has achieved a wide readership both in the USA and overseas. Spanish, Italian, and Portuguese editions have been published, and translations are going forward in French, German, Japanese, and Serbo-Croatian. We intend to continue biennial editions in order to keep pace with the rapid advances in this vast field.

Major changes have been made in the fourth edition. The book has been reorganized into 3 sections: Basic Immunology, Immunologic Laboratory Tests, and Clinical Immunology. Several new chapters have been added, including Chapter 5, Immunoglobulins II: Gene Organization and Assembly; Chapter 6, The Human Major Histocompatibility HLA Complex; Chapter 8, Cellular Interactions in the Expression and Regulation of Immunity; Chapter 10, Phagocytic Cells: Chemotaxis and Effector Functions of Macrophages and Granulocytes; Chapter 12, Immune Mechanisms in Tissue Damage; Chapter 13, Autoimmunity; Chapter 14, Clinical Transplantation; Chapter 17, Tumor Immunology; Chapter 20, Effects of Sex Hormones, Nutrition, and Aging on the Immune Response; and Chapter 21, Reproductive Immunology.

We continue to solicit comments and suggestions from our readers for improvements and for correction of any errors they may find.

The clinical chapters focus on primary immunologic diseases or on disorders with important immunopathologic characteristics. These discussions are not intended to serve as a manual of clinical treatment; where specific medications or drug dosages are mentioned, the physician should also consult more comprehensive medical texts.

It is hoped that this book will serve as a text for medical students, house officers, graduate students, practicing physicians, and others interested in learning more about the field. Immunologists from both basic and clinical disciplines should find it a comprehensive review.

–The Editors

San Francisco
July, 1982

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Spanish Edition: *El Manual Moderno, S.A., Av. Sonora 206, 06100 Mexico, D.F.*
Italian Edition: *Piccin Editore, Via Altinate, 107, 35100 Padua, Italy*
Portuguese Edition: *Editora Guanabara Koogan, S.A., Travessa do Ouvidor, 11-ZC-00, 20,040 Rio de Janeiro - RJ, Brazil*

International Standard Book Number: *0-87041-223-X*
Library of Congress Catalogue Card Number: *82-82063*

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Table of Contents

SECTION II. IMMUNOLOGIC LABORATORY TESTS

SECTION III. CLINICAL IMMUNOLOGY

Section I. Basic Immunology

The Historical Background of Immunology | 1

Pierre Grabar, DSc

Immunology is a relatively young branch of medical science. Many observations of importance to immunology were made by microbiologists around the turn of this century, usually in the course of active research in bacteriology and infectious diseases. For many years immunology was studied as part of microbiology, and progress in the field consisted mainly of application of what had been learned about immunologic phenomena to the problems of the diagnosis and control of bacterial infections. Some of the most important advances were made possible by the introduction of chemical techniques in the elucidation of the nature of antigens and antibodies.

The explosive increase in fundamental information has made immunology an independent branch of science. *Zeitschrift für Immunitätsforschung* began publication in 1909 and the *Journal of Immunology* in 1916. There are now 27 national member societies in the International Union of Immunological Societies. This chapter will outline some of the contributions by pioneers in immunology which have led to the current state of the art. Where appropriate, reference is made to relevant chapters in this book.

The term **immune** derives from Latin *immunis*, ie, exempt from "charges" (taxes, expenses). However, for nearly a century the term immunity has denoted resistance to possible attack by an infectious agent. Resistance to second attacks of certain diseases had been observed even in ancient times. Attempts to protect against variola (smallpox) were made in ancient China before our era and in western Asia by inoculation (variolation) using vesicle fluid from persons with mild forms of smallpox, or by purposely seeking out contact with diseased individuals. Lady Mary Wortley Montagu (1721) introduced into England from Turkey the process of **variolation**, or inoculation with unmodified smallpox virus. It was quite dangerous, since disease and death often resulted. Similarly, an ancient Greek king of Pontus, Mithridates VI, tried to protect himself against the effects of poison by administering small amounts of poisonous substances on multiple occasions—a procedure that came to be called **mithridatism.**

A Portuguese army officer, Serpa Pinto, who traveled through central Africa in the middle of the last century, related how local "wizards" protected people against snake bites by treatment with a mixture of snake heads and ant eggs. At the beginning of this century, the same procedure was employed by specialists called "djoekas" among the black population of Dutch Guiana. It is interesting that ants contain formol, which is now used for the detoxification of toxins and venoms.

EARLY IMMUNOLOGY

The first effective—though still empirical—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. Jenner introduced vaccination with cowpox in 1796 as a means of protecting against smallpox. The term **vaccination** (L *vacca* cow) was introduced to replace the term variolation.

The scientific approach was not applied to the study of immunologic phenomena until almost a century later as a consequence of work on microbes by Louis Pasteur (1822–1895) and his collaborators. They investigated the possibility of protecting against infection by vaccinations with attenuated strains of microorganisms. Their first observation (1878–1880) was that a culture of *Pasteurella aviseptica* (then called chicken cholera) which had been left in the laboratory during vacation lost its virulence for chickens, and that animals inoculated with this culture were protected against the virulent strain. Pasteur concluded that this culture contained attenuated microbes and, to honor the work of Jenner (nearly 100 years before), extended the term vaccination to denote conferring immunity by injection of attenuated strains of organisms. The idea of using attenuated strains of microorganisms was confirmed by Pasteur when he studied vaccination against anthrax (1881). Research on the mechanisms of protective effects led Richet and Héricourt to the observation (1888) that the blood of an animal immunized with staphylococci conferred partial protection against subsequent inoculation with these microorganisms. The next year, Charrin and Roger observed that the serum of an animal immunized with *Pseudomonas aeruginosa* (then called *Bacterium aeruginosum* among other names) agglutinated a suspension of this microbe.

In 1889, Pfeiffer, a pupil of Koch, used cross-

immunization of guinea pigs with 2 similar microbes (*Vibrio cholerae* and *V metchnikovii*) to show that it was possible to distinguish them immunologically, since immunization against one did not protect against the other. The specificity of the protective effects of immunization had already been observed, but this example showed how extremely fine the specificity could be in some cases.

"CELLULAR IMMUNITY" THEORY

In 1882 in Messina, the Russian zoologist Elie Metchnikoff (1845–1916) studied the role of motile cells of a transparent starfish larva in protection against foreign intruders. He introduced a rose thorn into these larvae and noted that a few hours later the thorn was surrounded by motile cells. This experiment can be considered the starting point of cellular immunology. It had already been established by Koch and Neisser that bacteria can be found in leukocytes, but it was thought that this was the result of bacterial invasion of the leukocytes. Metchnikoff showed that the leukocytes had in fact engulfed the microorganisms. In 1883, Metchnikoff observed that *Daphnia*, a tiny transparent metazoan animal, can be killed by spores of the fungus *Monospora bicuspidata* and that in some instances these spores are attacked by blood cells and can be destroyed in these cells, thereby protecting the animal against the invaders. In 1884, he extended these observations to the leukocytes of rabbits and humans, using various bacteria. He noted that the engulfment of microorganisms by leukocytes, which he called **phagocytosis,** is greatly enhanced in animals recovering from an infection or after vaccination with a preparation of these microorganisms. He therefore concluded that phagocytosis was the main defense mechanism of an organism. He later showed the existence of 2 types of circulating cells capable of phagocytosis—the polymorphonuclear leukocytes and the macrophages—as well as certain fixed cells capable of phagocytosis, and proposed the general term **phagocytes** for all of these cells (Chapter 7).

The **cellular immunity** theory of Metchnikoff, who worked at the Pasteur Institute in Paris from 1887, was accepted with enthusiasm by some but was criticized by several other pathologists. The inflammatory reaction had been described by Celsus as early as the first century AD, but before Metchnikoff it had been studied only in mammals. Pathologists such as Virchow (1871) agreed that inflammation was due to changes in the connective tissue cells induced by various agents, particularly by abnormal deposits of metabolic products. Cohnheim (1873) and his collaborator Arnold (1875) considered inflammation to be a local vascular lesion due to a noxious agent which allowed blood cells to penetrate into tissues. Metchnikoff, who had observed the same accumulation of motile cells in lower animals with no circulatory vessels, asserted that diapedesis in higher animals was a process of active penetration of these cells through the walls of the vessels (1892). In his opinion, inflammation resulted from an enzymatic digestion process due to ingestion of the noxious agent by the motile phagocytes.

"HUMORAL" THEORY

Metchnikoff's theory came under severe criticism somewhat later by those who observed immunity in the absence of cells. Fodor in 1886 was apparently the first to observe 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, which was considered the first proof of humoral immunity. In 1894, Calmette observed the same neutralizing activity of snake venom antiserum.

An important humoral defense mechanism described by Pfeiffer and Isaeff (1894) has come to be called the **Pfeiffer phenomenon.** Cholera vibrios injected into the peritoneum of previously immunized guinea pigs lose mobility, are clumped, are no longer stainable, and are later phagocytosed by leukocytes, but they are also lysed in the absence of cells.

A theory of immunity due to humoral factors provoked intense debate between Metchnikoff and the supporters of this new theory, mainly from the laboratory of Robert Koch (1843–1910). At the time of Pfeiffer's discovery, a young Belgian, Jules Bordet (1870–1961), was engaged in the study of agglutination reactions in Metchnikoff's laboratory at the Pasteur Institute. He became interested in the Pfeiffer phenomenon and in 1895 showed that both bacteriolysis and lysis of red cells (which he described in 1898) required 2 factors: one, which he called **sensitizer,** was thermostable and specific; the other, which he called **alexine,** was thermolabile and nonspecific. The factor designated alexine by Bordet came to be called **cytase** by Metchnikoff and **complement** by Ehrlich (Chapter 11). Bordet believed that his "alexine" possessed enzymatic activity and that it consisted of several components.

It is of interest that Bordet's studies of humoral factors were performed in Metchnikoff's laboratory and were in contradiction to the master's theories. Later, both theories gained general acceptance and it was established that humoral factors originated from lymphoid cells.

During this period, the term **antigen** was introduced to designate any substance (then mainly microbes or cells) capable of inducing a reaction against itself and the illogical term **antibody** (both being "anti-") to designate the factor present in the serum possessing this activity. At first, various special names were used to indicate each observed antibody activity, such as **agglutinins, precipitins, sensitizers,** and **opsonins.** The first observation of agglutination is de-

*The particle von was added later to Behring's name after he became famous—about the time he received the Nobel Prize.

scribed above. The precipitin reaction was described later—in 1897 by Kraus with microbial culture supernates and the serum of immunized animals, and in 1899 by Tchistovitch with serum protein antigens and by Bordet with milk antigens and serum of animals injected with these fluids. The precipitin reaction was introduced by Wassermann and Uhlenhuth into forensic medicine for the identification of blood or meat.

Resolution of Conflicting Theories

In 1895, Denys and Leclef observed the fixation of antibodies present in an antistreptococcus serum by these organisms and called them **bacteriotropins.** Neufeld and Rimpau had also demonstrated similar in vitro fixation. In 1903, Wright and Douglas, after a careful study of Metchnikoff's observation that phagocytosis of microbes is facilitated by the serum of an immunized animal, used washed cells to demonstrate that the immune serum contained an active factor they called **opsonin.** They proposed the term **opsonization** for the activity, and this phenomenon acted as a "bridge" between the apparently contradictory humoral and cellular theories.

During this same period, Paul Ehrlich (1854–1915) studied the neutralization of toxins by immune serum, using the highly toxic vegetable poisons abrin and ricin, which could be extracted easily in sufficient quantity. These studies enabled him to establish a technique for the evaluation of the antitoxic activity of diphtheria antiserum (1897).

EHRLICH'S "SIDE-CHAIN" THEORY

Ehrlich was interested in the theoretic aspects of immunologic phenomena and in 1896 elaborated his **side-chain theory** to explain the appearance of antibodies in the circulation. He considered it an "enhancement" of a normal mechanism and suggested that cells capable of forming antibodies possessed on their surface membranes specific side chains which were receptors for antigens. He proposed that binding of antigen to the side chains provoked new synthesis of these side chains, which were liberated into serum as antibodies. He expressed the specificity of the reaction of antigens and antibodies as a "key [antigen] in a lock [antibody]" and thought that this reaction was of a chemical nature. During the next few years, he tried to substantiate his theory with various arguments, but the theory was not generally accepted. It was criticized by Bordet, who felt that the antigen-antibody reaction was of colloid nature; by Gruber; and particularly by Arrhenius and Madsen, who insisted on the reversibility of the reaction and on different proportions of reactants in specific precipitates. Nevertheless, Ehrlich's general theory, with modifications and additions, has been taken into consideration by many authors, and his hypothesis on the existence of specific receptors on immunocompetent cells has recently been completely vindicated.

Isoantibody

In 1875, L. Landois published his monograph *Blood Transfusion*. He noted the effects of blood transfusions between members of different species and observed it was preferable to work within a single species. He also stated, however, that there were differences within a single species, since a recipient's own cells could be hemolyzed by serum from a nonidentical donor of the same species.

The term **isoantibody** or **isohemagglutinin** was introduced by Bordet, who observed in 1898 that the serum of rabbits injected with red cells of another species agglutinated the red cells whereas rabbit red cells injected into rabbits were not agglutinated. However, in 1902, Landsteiner used the agglutination reaction to demonstrate several different antigenic specificities of red cells in the same species—the blood groups A, B, and O in humans—which became the basis of blood transfusion (Chapter 27). Later, he also discovered Rh specificity, using rhesus monkey blood. The term isoantibody is no longer used for antibodies to antigenic determinants specific for other species. It is now used to indicate antibody in an individual to antigenic determinants in other genetically nonidentical members of the same species, eg, anti-A antibody (isohemagglutinin) in blood group B humans (see Chapter 27).

Ehrlich also observed that the plant toxins abrin and ricin agglutinate red cells. Landsteiner and Raubitchek in 1907 extended these observations, using particularly *Papilionaceae* (a family of beans). These plant-derived hemagglutinins were later termed **lectins** by W.C. Boyd.

Hypersensitivity

At the close of the 19th century, all of the immunologic phenomena observed to that time supported the view that they were defense mechanisms. Apparent contradictions were the observations of Landsteiner and, particularly, the discovery of anaphylaxis by Charles Richet and Portier in 1902. It had already been shown, particularly by Wassermann and von Dugern, that second challenge of a previously immunized organism with the same antigen increased the antibody activity in its serum. Thus, the fact of immunologic memory had to be explained. The discovery of Charles Richet and Portier was absolutely unexpected. They studied the toxic activity of the tentacles of Actinaria by injecting a glycerin extract into dogs. The first injection, in small doses, had no direct observable effect, and they thought the animals were protected. But a second injection resulted in shock—often lethal for the animals. They proposed the term **anaphylaxis** for this phenomenon (Chapters 18 and 28). The next year, Arthus described what is now called the **Arthus phenomenon,** ie, the local necrotic lesion produced by injecting antigen into a previously immunized animal (Chapter 12). This reaction is specific, whereas an analogous but nonspecific reaction was described by Sanarelli and by Shwartzman many years later—the **Shwartzman phenomenon.**

AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

——— QUID MORIS CERTIUS IPSIS
SENSIBUS ESSE POTEST, QUO VERA AC FALSA NOTEMUS.
LUCRETIUS.

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AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1798.

Figure 1–1. Face plate from first edition (1798) of Jenner's *Inquiry Into the Causes and Effects of . . . the Cow pox.*

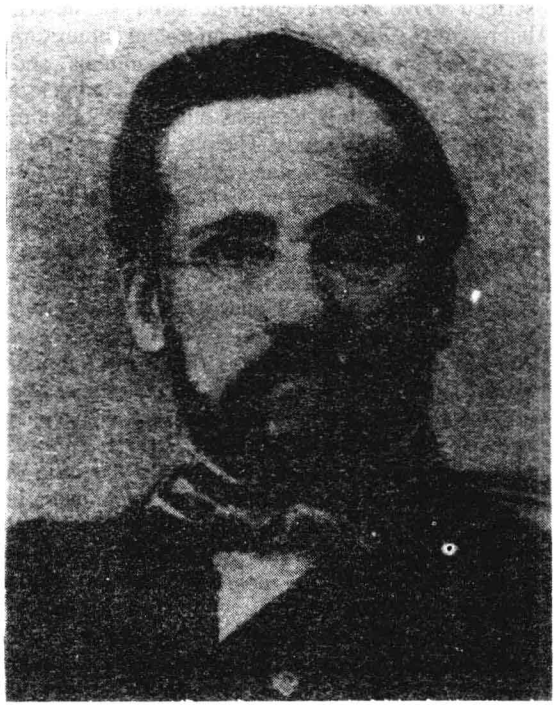

Figure 1–2. Louis Pasteur (1822–1895). (Courtesy of the Museum of the Pasteur Institute, Paris.)

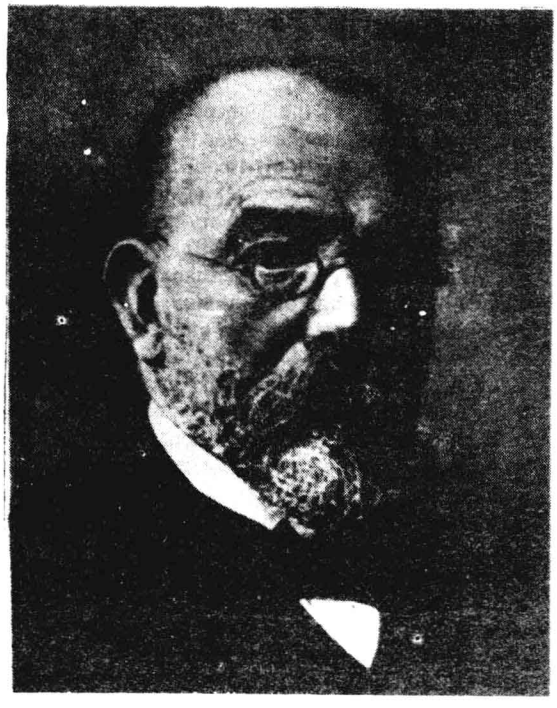

Figure 1–3. Robert Koch (1843–1910). (Courtesy of the Museum of the Pasteur Institute, Paris.)

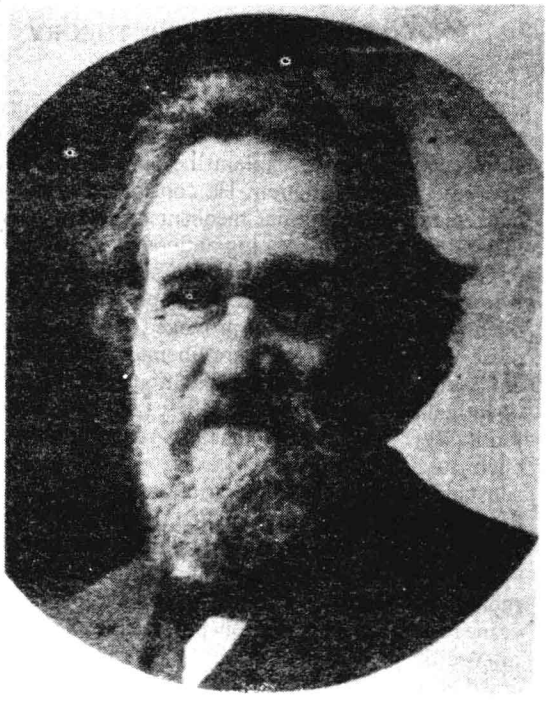

Figure 1–4. Elie Metchnikoff (1845–1916). (Courtesy of the Rare Book Library, the University of Texas Medical Branch, Galveston.)

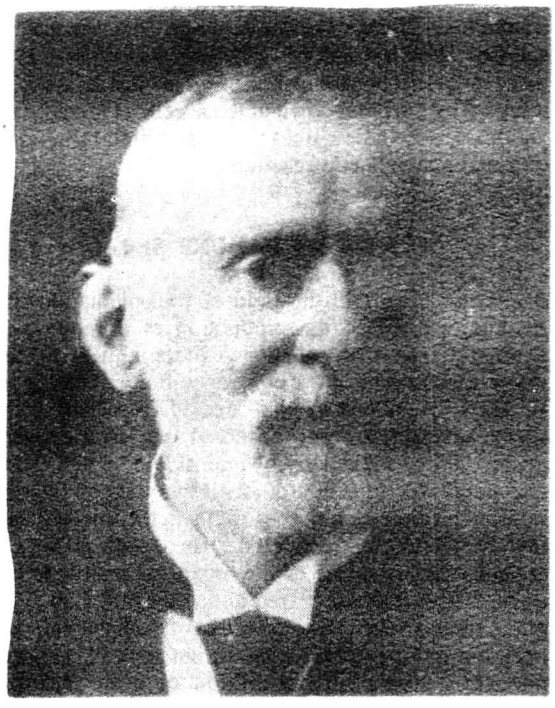

Figure 1–5. Paul Ehrlich (1854–1915). (Courtesy of the Museum of the Pasteur Institute, Paris.)

Figure 1–6. Emil von Behring (1854–1917). (Courtesy of the Museum of the Pasteur Institute, Paris.)

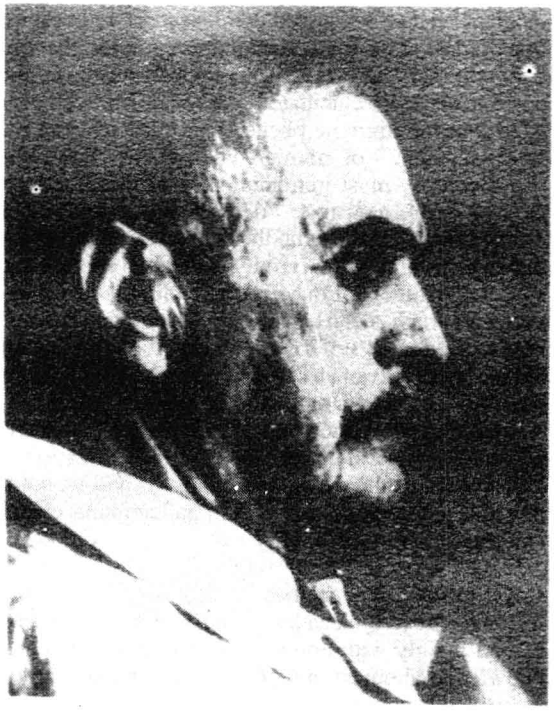

Figure 1–7. Karl Landsteiner (1868–1943). (Courtesy of the Museum of the Pasteur Institute, Paris.)

Figure 1–8. Jules Bordet (1870–1961). (Courtesy of the Museum of the Pasteur Institute, Paris.)

At the beginning of the 20th century, von Pirquet, working in Vienna, studied **serum sickness,** the delayed reaction that occurred following a second injection of a heterologous antistreptococcus serum, and observed that this **hypersensitivity reaction** (von Pirquet and Schick, 1905) sometimes appeared rapidly (Chapter 12). He suggested that this reaction had a direct connection with the presence in the animal of antibodies to the injected serum. In the course of his research on tuberculosis, he observed that a cutaneous reaction appeared more rapidly after a second injection than after the first. He developed the scratch test for tuberculin sensitivity, and in 1906 he proposed the term **allergy** for modified immune reactivity. Since then, this term has been generalized to denote all sensitization phenomena, whereas the better and earlier term **generalized anaphylaxis** is used to denote **anaphylactic shock.**

Another series of investigations on anaphylactic reactions was initiated by Theobald Smith and Otto (1906) and, more successfully, by Rosenau and Anderson in Washington (1909). These investigations showed (1) that the secondary reaction provoked in guinea pigs by the injection of diphtheria toxin and antiserum (this mixture was used at that time for vaccination) was due not to the toxin but rather to antibodies against the antiserum; (2) that the sensitizing time was about 10 days; and (3) that passive sensitization with the serum of a sensitized animal was sufficient to provoke a secondary reaction to the antigen. It was thought that the relatively long time required for sensitization to develop was due to fixation of antibodies to cells. Schultz had demonstrated in 1910 that a contractile reaction occurs in vitro following contact of the antigen with a strip of intestine of a previously sensitized animal. This reaction was also studied by H. Dale with uterine smooth muscle and is now called the **Schultz-Dale reaction** (Chapter 18).

Hay fever was a recognized disease entity for a long time, but until the beginning of this century it was believed to be due to toxic substances in pollen. Experimental "desensitization" was attempted by inoculation of small amounts of pollen to neutralize the supposed toxin (Besredka, 1907; Noon and J. Freeman, 1911). Shortly thereafter, Wolff-Eisner suggested that hay fever might be a hypersensitivity reaction, a concept proved correct in 1921 by Prausnitz and Küstner with different antigens. The term Prausnitz-Küstner (PK) reaction is therefore used to denote the test for passive transfer of reactivity to an allergen (Chapter 18). A similar phenomenon in experimental animals, the **passive cutaneous anaphylaxis (PCA) reaction,** which allows a semiquantitative estimation of antibodies, was described much later—in 1949—by Biozzi, Mene, and Ovary (Chapter 18).

The role of histamine and related substances in inflammatory and anaphylactic reactions is discussed in Chapters 18 and 28, but it is appropriate to cite a few of the more important contributions. Dale and Laidlaw in 1910 showed the similarities between the reactions provoked by histamine and those associated with anaphylaxis. Lewis (1927) explained the "triple response" in skin reactions, and Riley and West (1953) discovered that histamine is present in mast cells and is released by the breakdown of these cells. These observations opened a new field of research into inflammatory and anaphylactic reactions.

ANTITISSUE IMMUNE SERA

Early efforts in the field of transplantation immunology included the production of immune sera against tissue components (Lindemann) and the discovery of tissue and species specificity of antigens. In 1902, Metchnikoff and Besredka prepared antileukocyte antisera and observed that such antisera possessed cytotoxic activity against leukocytes. They also noted that injection of small amounts of antisera induced proliferation of these cells in the injected animal. Metchnikoff envisaged the use of such antisera to enhance the resistance of the organism against infections. Bogomoletz prepared antisera against all lymphoid tissues. The cytotoxic effect of such antisera has been the starting point for the recent use of "antilymphocyte antisera" for inhibition of graft rejection (Woodruff, Starzl). In either case, variable results are obtained because of the multiplicity of antigens on the injected cells and the consequent variety of antibody specificities in the resultant antisera.

The first 3 decades—until 1910—of active development of immunology as a separate branch of medical science witnessed the discovery and description of most of the fundamental immunologic phenomena, although the mechanisms underlying those phenomena were not elucidated. Although Ehrlich postulated that the immune phenomena must represent an "enhancement" of normal mechanisms, they were considered by most immunologists of the time to be part of the organism's "defense apparatus." This opinion gained force from the general assumption that the organism will react only against foreign ("not self") constituents, and Ehrlich's phrase *horror autotoxicus* emphasized his view that the organism would not react against "self" components, though he admitted the possibility of an autoreaction when the "normal regulatory mechanisms" were disturbed (Chapter 13). Actually, at that time, Metalnikoff, in Metchnikoff's laboratory, had demonstrated autosensitization in guinea pigs to their own spermatozoa, and we know now that autoantibodies exist in small amounts even in "normal" sera (see below).

Development of Vaccines

The next 3 decades—until 1940—were concerned mainly with applications and development of knowledge about immunologic phenomena, particularly in the preparation of immune sera, diagnostic reagents for clinical study of infectious disease, and vaccination programs. A few examples are Haffkine's experiments with cholera vaccination in India in 1892, using himself and his collaborators as control subjects;

the use of an attenuated strain of *Mycobacterium tuberculosis,* BCG (bacille Calmette-Guérin, 1908–1921); and vaccination against bacterial toxins using detoxified preparations. Several workers tried to develop a nontoxic but still immunogenic preparation by treating bacterial toxins with various chemicals. Formol was used by Eisler and Löwenstein (1915) for tetanus toxin and by Glenny (1921) for diphtheria toxin, but their preparations were not completely detoxified. Ramon in 1924 developed a method called optimal flocculation for the quantitative measurement of toxins and antitoxins which resulted in a satisfactory method of detoxification. He obtained preparations which he called **anatoxins,** now generally called **toxoids,** as proposed by Ehrlich years before.

In 1916, LeMoignic and Pinoy introduced lipid (as adjuvant) vaccines, and in 1935 Ramon obtained some good results with various other adjuvants to increase the production of antitoxins in horses, although these produced lesions at the site of the injection. These were precursors of the current main adjuvant, Freund's complete adjuvant (1947), used to augment immune responses (Chapter 19).

IMMUNOCHEMISTRY

Important progress was made during the second period of immunologic studies when the principles of chemistry were applied to immunologic research. Although Ehrlich had suggested years earlier that immunologic reactions must have a chemical basis and although Arrhenius, studying antigen-antibody reactions, introduced the term immunochemistry in 1904, the applications of chemical theory and methodology truly began only during this second period.

Among the most productive applications of chemistry to immunology were the studies of Landsteiner and his collaborators (Prasek, Lampl, van der Scheer, Chase). Space does not permit discussion of their many achievements, and only one will be mentioned. In 1903, Obermayer and Pick suggested that antigens possessed the properties of immunogenicity and a capacity to react with antibodies. Subsequently, Landsteiner and his co-workers, as well as others, observed that these properties could be altered by chemical treatment of antigens (Chapter 3). This initiated in 1914 Landsteiner's studies with artificial conjugated antigens. Various chemical groupings were attached to proteins, and the specificity of these groupings was demonstrated in serologic reactions. In 1921, Landsteiner coined the term **haptens** for those specific groupings which by themselves were incapable of provoking the formation of antibodies but were still responsible for specific reaction with antibodies (Chapter 3). Similar studies were later performed by Haurowitz and Breinl (1931), who introduced groupings containing arsonate, which facilitated their recognition. Landsteiner's book *The Specificity of Serological Reactions,* published in German in 1933 and in English in 1936, had a great influence on further research, as did Wells's book *The Chemical Aspects of Immunity* (1925) and Marrack's text *The Chemistry of Antigens and Antibodies* (1935).

Immunologic Tolerance

An important observation made by Felton (1942) showed that if mice are injected with very small amounts of pneumococcal polysaccharide they are protected against infection by the corresponding microbe, but if the injection is made with large quantities of polysaccharide the mice can be infected. This **Felton phenomenon** was also called immunologic unresponsiveness and is now known as **immunologic tolerance.** The multiple mechanisms involved in this phenomenon are discussed in Chapter 13.

Identification of Immunoglobulins

Felton was probably also the first to obtain purified preparations of antibodies, using horse antisera to pneumococci and precipitating the euglobulin fraction rich in antibodies. The practical isolation of pure antibodies from such sera was achieved by Heidelberger and Kendall (1936) by dissociation of specific precipitates with concentrated salt reagents. As a result of studies by Heidelberger and Pedersen with Svedberg's ultracentrifuge (1937) and by Tiselius and Kabat with electrophoresis in liquid media (1938), it became clear that antibodies belong to that globulin fraction of the serum proteins possessing slow mobility, at that time designated γ-globulins (Chapter 4).

In parallel with the development of immunochemistry, studies on the cellular aspects of immunology had been performed mainly by hematologists and pathologists who confirmed the role of white blood cells in the formation of antibodies. Pfeiffer and Marx found that antibodies, which they called sensitizers or fixators, appear earlier in the spleen, lymph nodes, and bone marrow than in the blood. The lymphatic system, which came to be called the reticuloendothelial system, was progressively studied and various cells were described (Chapter 7).

This period of development of the field of immunology also witnessed the isolation of the components of complement, studies on their respective activities, and identification of several specific subgroups among human and animal red cells.

RECENT PERIOD OF IMMUNOLOGY

The period of development of the discipline of immunology beginning just before World War II is characterized by the emergence of an enormous amount of new data. Space limitations preclude even brief mention of much of this work. Moreover, it is not the aim of this chapter to show the recent development and current status of our knowledge. Therefore, only a few examples of some recent fundamental findings are briefly mentioned here.

Owen observed in 1945 that bovine dizygotic twins possess double serologic specificities. Medawar