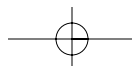
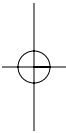
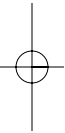
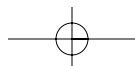
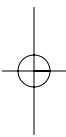
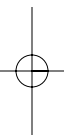
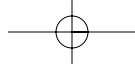


S E C T I O N

I

Immunologic Basis of Autoimmunity





C H A P T E R

1

Autoimmunity: A History of the Early Struggle for Recognition

ARTHUR M. SILVERSTEIN

Institute of the History of Medicine, Johns Hopkins Medical School, Baltimore, Maryland, USA

THE SEARCH FOR AUTOANTIBODIES	4
<i>Horror Autotoxicus</i>	4
Nature of Ehrlich's "Contrivances"	4
CHALLENGES TO THE THESIS	4
Lens Autoantibodies	4
Paroxysmal Cold Hemoglobinuria	5
Sympathetic Ophthalmia	5
The Wassermann Antibody	5
THE SHIFT TO IMMUNOCHEMISTRY	6
THE RETURN OF IMMUNOBIOLOGY	6
CONCLUDING REMARKS	8

"... 1955–1965 [was] the decade marked by the question, Does autoimmunity exist?"

(Rose and Mackay, 1985)

It is one of the curious situations in science that certain well-demonstrated facts are refused entry into the body of accepted knowledge, and may become so effaced from the collective memory that they must be rediscovered many years later in order to gain acceptance. Such was the case in immunology with Donath and Landsteiner's (1904) discovery that paroxysmal cold hemoglobinuria is an autoimmune disease, or with Clemens von Pirquet's (1910) explanation of immune complex disease. Sometimes the cause of this selective amnesia is merely an earlier pronouncement by a respected leader in the field; sometimes it lies in an inability to fit the new finding into the working paradigm that guides thought in the field, as the historian of science Thomas Kuhn (1970) has suggested. In the end, it may be that Ludwik Fleck (1979) was right when he proposed that acceptance of a fact in science depends less upon its truth than upon its acknowledgment by the leaders in the discipline (whom Fleck called the *Denkkollektiv*). However, the

truth in science ultimately emerges, although sometimes it takes a very long time.

The earliest discoveries in immunology were made in the context of the battle to ward off infectious diseases. These included Louis Pasteur's (1880) preventive vaccines, Ilya Metchnikoff's (1884) bacteria-eating phagocytes, and Behring and Kitasato's (1890) curative antidiphtheria and antitetanus sera. It seemed evident that these efficient mechanisms for the protection of the body were Darwinian adaptations designed to prevent or control infectious disease: a widespread view in the 1890s even after it was demonstrated that specific antibodies might be formed against such innocuous antigens as egg albumin, bovine serum proteins, and sheep red cells. It seemed unthinkable at the time that mechanisms designed to prevent disease might turn the tables and cause disease. So well established did this concept of a benign immune system become that demonstrations that antibodies might cause disease were either disregarded entirely, or else ascribed to "aberrant" antibodies acting under the influence of a "misdirected" immunity (Silverstein, 1989). This was how the early discoveries of serum sickness, hay fever, asthma, and a variety of immunopathologic phenomena were treated by mainstream immunology during the first half of the 20th century.

It is beyond the scope of this chapter to discuss the entire history of the unwillingness to accept that the immune response might lead to a variety of harmful outcomes (which we now describe under the rubric "immunopathology"). We shall limit the present discussion to the way that a subset of the whole, autoimmune diseases, was regarded (or rather disregarded) during the first half of the 20th century. This sample should provide an adequate representation of the way that early immunologists dealt with the paradox presented by the almost oxymoronic word *immunopathology*.

THE SEARCH FOR AUTOANTIBODIES

Horror Autotoxicus

A new mechanism that functions to mediate immunity was discovered by Richard Pfeiffer (1894)—the destruction of bacteria by humoral antibodies. Jules Bordet (1899) showed that not only were bacteria lysed by thermostable antibody and a thermolabile substance that he called *alexine* (later termed *Komplement* by Paul Ehrlich), but that mammalian erythrocytes could be hemolysed specifically by the same two agents. Here was a technique that would see broad application in many areas of immunology (Silverstein, 1994), not least in connection with the question of whether the individual could form antibodies against his/her own self.

Two consequences of Bordet's report were immediately apparent. Karl Landsteiner (1900) became interested in red cells and discovered blood groups in humans (for which he received the Nobel Prize in 1930). Then Paul Ehrlich and Julius Morgenroth launched a series of studies of immune hemolysis in order to develop additional support for Ehrlich's side-chain theory of how antibodies are produced and how they function (Ehrlich, 1897; 1900). It is Ehrlich's interpretation of his hemolysis experiments that would play a major role in the early history of autoimmunity. These hemolysis experiments are described and analyzed in detail by Silverstein (2002).

During the course of these experiments, Ehrlich and Morgenroth immunized many different species with the red cells of other species. They also immunized animals with the red cells of other members of their own species, and even tried to immunize animals with their own red cells. In every case, they were able to demonstrate the production of xenohemolysins and isohemolysins, but autohemolysins were never observed. This led inexorably and logically to the conclusion that animals could not make autotoxic antibodies to any self-antigens, a postulate that Ehrlich named *horror autotoxicus*. Indeed, he would conclude that, "It would be dysteleological in the highest degree, if under these circumstances self-poisons of the parenchyma—autotoxins—were formed" (Ehrlich, 1902).

But Ehrlich was not the only one who responded to Bordet's publication on immune hemolysis. If red cells could stimulate an immune response, why not other tissues and organs? In no time, attempts were undertaken to immunize animals with all types of cells and tissue extracts, especially at the Pasteur Institute in Paris, where Bordet had worked. As expected, cytotoxic xenoantibodies against a variety of tissues were reported; indeed, volume 14 of the *Annales de l'Institut Pasteur* was largely devoted to these studies, including a review of antitissue antibodies by Metchnikoff (1900). Most surprising was the report by Metalnikoff (1900) that some animals were able to form antibodies against their own spermatozoa. But while these

autoantibodies could destroy the sperm *in vitro*, they seemed to have no effect *in vivo* on the viable sperm in the immunized animal.

Ehrlich was not impressed. He commented that these are not "autocytotoxins within our meaning," since they do not cause disease (Ehrlich and Morgenroth, 1901). Here was the true meaning of *horror autotoxicus*: not that autoantibodies cannot be formed, but that they are prevented "by certain contrivances" from exerting any destructive action (Goltz, 1980). Due in part to Ehrlich's worldwide prestige and to the fact that an autoantibody seemed so obviously counter-intuitive, *horror autotoxicus* found broad acceptance as a guiding principle. Indeed, so firm was the conviction that autoimmune disease was impossible that everyone soon forgot Ehrlich's suggestion that an autoantibody might exist without causing disease. It would be some 80 years before the important distinction would be made between autoimmunity and autoimmune disease (Rose and Mackay, 1985).

Nature of Ehrlich's "Contrivances"

Paul Ehrlich was nothing if not logical. He proposed one of his typical thought-experiments to examine the possible outcomes (Ehrlich and Morgenroth, 1900). Suppose the existence of a self-antigen α . Then, since antibody formation results from the interaction of antigen with preformed cell receptors according to the side-chain theory (the first selection theory), two possibilities are seen:

1. The host possesses no anti- α cell receptors. Therefore, no autoantibody response and thus no disease can occur. (Here is, in embryo, Burnet's later clonal deletion idea.)
2. The host does possess anti- α cell receptors on its cells. Therefore, autoanti- α is formed. But the host also possesses the self-antigen α on its cells, with which the anti- α may react to stimulate the formation of anti-anti- α . (Remember, Ehrlich knew nothing about lymphocytes, and conceived that all cells possess receptors and may form antibodies.) But the specific site on the anti-antibody should be identical with that on the original antigen, since they both should react specifically with the antibody combining site. Thus, Ehrlich proposed that a self-regulating equilibrium would be established between autoantibody and antigen (= anti-antibody) to suppress the development of autoimmune disease. [Here was a regulatory network theory 70 years before Niels Jerne's (1974) idiotypic-anti-idiotypic theory.]

CHALLENGES TO THE THESIS

Lens Autoantibodies

The initial flurry of interest in antitissue antibodies quickly subsided as the implications of *horror autotoxicus*

gained broad acceptance. But in 1903, Paul Uhlenhuth (1903) demonstrated the existence of organ-specific antigens by showing that the proteins of the lens are unique to that tissue; they are found nowhere else in the body. Moreover, these antigens are shared by the lenses of different species. Ophthalmologists seized upon this finding to suggest that an immune response to an individual's own lens might be responsible for the development of senile cataract (Römer, 1905). They showed further that an intraocular inflammation may be induced by the experimental rupture of the lens in the eye of a lens-immunized animal (Krusius, 1910).

Here were observations that would fascinate both ophthalmic clinicians and a later generation of immunopathologists interested in the possible workings of autoimmune disease. First, there was this early preview of what would later be called the "sequestered antigen" concept. Since "self"-antigens by definition cannot elicit an immune response, then such antigens as do must be "foreign," that is, isolated from the immunologic apparatus of the host, like sperm and lens. Secondly, Römer and Gebb (1912) concluded that if indeed disease does result from the formation of autoantibodies, this would represent a most unusual occurrence and must be considered as an aberration due to a malfunction of Ehrlich's "contrivances." Here they showed that, unlike a future generation, they understood Ehrlich's "law of immunity research" completely.

Interest in the possibility that autoimmunity to lens might lead to disease did not disappear in the years that followed. But whereas the initial studies had been done in the context of the new immunology and were known to all workers in the field, further work was restricted to ophthalmologists and eye departments. Thus a broad clinical study led Verhoeff and Lemoine (1922) to identify numerous cases of lens-induced inflammatory disease, to which they gave the name *phacoanaphylaxis*. Thenceforth, the description would appear routinely in textbooks of ophthalmic pathology, and clinical diagnoses would be made.

Paroxysmal Cold Hemoglobinuria

Fast on the heels of the lens antigen demonstration came an even more convincing case involving erythrocyte antigens. Paroxysmal cold hemoglobinuria (PKH) was a rare disease presenting with signs of intravascular red cell lysis and a resulting hemoglobinuria, following exposure of the patient to the cold. Donath and Landsteiner (1904; 1906) published reports that reproduced *in vitro* all features of the disease. They demonstrated beyond question that it was due to a peculiar autoantibody in the patient's serum that affixes to his/her own red cells only in the cold, and mediates hemolysis with complement when the sensitized cells are rewarmed.

It was clear from the outset that Landsteiner understood fully the implications of this discovery and its meaning for Ehrlich's *horror autotoxicus*. Indeed, even Ehrlich's student Hans Sachs (1909) gave a somewhat grudging acceptance of the phenomenon and its interpretation. But again, the implication seemed to be that this was an unusual exception to the regular scheme, and the implications of PKH as the prototypical autoimmune disease soon almost vanished.

Sympathetic Ophthalmia

It had always seemed odd to clinicians that after traumatic injury to one eye, the second eye might spontaneously develop a blinding inflammatory disease, even years later. Soon after the discovery of cytotoxic antibodies, the proposal was advanced that sympathetic ophthalmia might be caused by the formation of "autocytotoxins" (Santucci, 1906). This concept was picked up and given broad currency by one of the foremost ophthalmologists of the day, Elschnig (1910a; 1910b) of Prague. As with autoimmunity to lens, work on the immunology of sympathetic ophthalmia continued, but in ophthalmology departments. Woods (1921; 1933) reported the presence of antiuveal antibodies in patients with perforating injuries of the globe, and uveal pigment was implicated as the causative antigen (Woods, 1925; Friedenwald, 1934).

The Wassermann Antibody

The discovery of the role of complement in immune hemolysis was soon followed by the finding that *any* antigen-antibody interaction would fix complement non-specifically (Bordet and Gengou, 1901). The ability to measure this uptake using a hemolytic assay meant that antibody could be titered if specific antigen were available. With the recent identification of *Treponema pallidum* as the cause of syphilis, a serologic test for this disease was sought. But since the organism could not be grown in culture, von Wassermann et al. (1906) and, independently, Detré (1906) used extracts of tissues from syphilitic patients as the antigen, and a valuable diagnostic test was born.

Most perplexing, however, was the report from many laboratories that positive tests for syphilis might be obtained also using extracts of normal tissues as antigen. This ran counter to the prevailing view that only *specific* antigen can interact with antibody to fix complement. It appeared necessary, therefore, to conclude that the "Wassermann antigen," being native, must be measuring an autoantibody rather than an antitreponemal antibody. This suggestion was made by Weil and Braun (1909) who speculated that the Wassermann antibody is an autoantibody specific for the tissue breakdown products generated in the syphilitic lesions. They suggested further that these autoantibodies exacerbate the disease, and that the brain lesions in tertiary

syphilis (paresis) may represent an autoimmune disease directed against neural antigens. (A century later, the antigen involved in the Wassermann reaction has been identified as a lipid, named cardiolipin, but why these antibodies are formed is still a mystery as is their role in the disease process.)

THE SHIFT TO IMMUNOCHEMISTRY

Despite all these hints that autoimmune diseases might exist, interest in the question waned in mainstream immunology—indeed almost disappeared—for some 40 years, from just before the First World War to the mid to late 1950s. This was due in part to the continuing sway of Ehrlich's *horror autotoxicus*. But there was another factor at play: the change in the overall direction of the field of immunology.

During the quarter century prior to the First World War, immunology had been concerned chiefly with medical problems, and was pursued almost exclusively by physicians. It had achieved notable successes in the prevention of infectious diseases (vaccine development), their cure (serotherapy), and their diagnosis (serology). It had even begun to define several immunogenic diseases (anaphylaxis, serum sickness, hay fever, and asthma). But most of the easy problems had been solved, and further successes in these areas became disappointingly rare. Vaccines were sought, generally unsuccessfully, for the remaining great scourges of mankind: syphilis, tuberculosis, typhus, and the many serious tropical diseases. Few diseases were caused by exotoxins like diphtheria and tetanus, and thus new serotherapeutic approaches were rare. Yet other forces were at work. The Wassermann test and its offshoots became so widespread for the diagnosis of disease that it moved from the immunologic research laboratory to the clinic. A new discipline, serology, arose and soon became independent of the mother discipline, immunology. In the same way, experimental anaphylaxis and its human disease relations, hay fever and asthma, stimulated the interest of clinicians, who soon took over work in this field and called their new discipline "allergy."

When in a science one research direction reaches the point of severely diminishing returns, its practitioners will usually move to more productive pursuits. So it was with immunology, beginning shortly after the end of the First World War. Karl Landsteiner (1962) started working with haptens, and soon devoted himself almost entirely to a chemically-oriented study of the structural basis of immunologic specificity and cross-reactions. Then, Michael Heidelberger (Heidelberger and Avery, 1923) studied the immunochemistry of pneumococcal polysaccharides and introduced a variety of quantitative methods for the estima-

tion of antigens and antibodies, best typified by the popular text written by his students, *Quantitative Immunochemistry* (Kabat and Mayer, 1949). For more than three decades, the field was devoted largely to studies of structure, specificity, and the thermodynamics of antigen-antibody interactions. The texts and monographs were primarily chemically oriented, and the practitioners were either chemically trained or at least chemically oriented. Even the theories of antibody formation that guided the field, Breinl and Haurowitz's (1930) and Pauling's (1940) antigen-instruction concept, were chemical (i.e., nonbiologic and non-Darwinian) in spirit. It was easy to assume that a protein might be synthesized according to external instruction; for the chemist, molecules have no evolutionary history.

Given the continuing influence of Ehrlich's dictum, and the generally nonmedical orientation of the most prominent immunologic investigators, it is not surprising that autoantibodies and autoimmune diseases were not among the most popular topics in the research laboratory. This is not to say, however, that there was no work along these lines. As we have seen, ophthalmologists reported findings in lens-induced disease and in sympathetic ophthalmia, but these were published in specialty ophthalmic journals. In the early 1930s, Rivers et al. published a series of papers on the production of an experimental autoimmune encephalomyelitis (EAE) (Rivers et al., 1933; Rivers and Schwentker, 1935). While these studies are viewed today as important milestones in autoimmunity research, they attracted little attention at the time among immunologists.

The contemporary view of autoimmunity during the 1940s and early 1950s is perhaps best exemplified by the position of Ernest Witebsky, who was trained in immunology by Ehrlich's student Hans Sachs and was himself a disease-oriented physician. He could say as late as 1954 at the celebration of the centenary of the birth of Ehrlich that, "The validity of the law [sic] of *horror autotoxicus* certainly should be evident to anyone interested in blood transfusion and blood disease. Autoantibodies—namely, antibodies directed against receptors of the same individual—are not formed" (Witebsky 1954). This was said by the individual who, only 2 years later with his student Noel Rose, would help refocus interest on autoimmunity with the demonstration of the production of experimental autoimmune thyroiditis (Rose and Witebsky, 1956; Witebsky et al., 1957).

THE RETURN OF IMMUNOBIOLOGY

During the late 1930s and 1940s, a series of observations began to challenge the assumptions that had guided recent thought and experiment in immunology. How could the enhanced booster antibody response, or the change with time of the specificity and affinity of the antibodies formed,

be explained in chemical terms? How to explain the persistence of antibody formation in the apparent absence of antigen? Even more troubling was the lack of relationship between immunity to certain viral diseases and the titer of antiviral antibodies. Here were basic biologic questions that demanded answers—questions with which current theory was unable to cope, and for which it could not even provide experimental approaches. But even more difficult questions arising from biology and medicine would pose further challenges.

Peter Medawar's (1945) experiments showed that the rejection of tissue grafts was somehow mediated by immunologic mechanisms. Then, Ray Owen (1945) described the paradoxical situation in which dizygotic twin cattle might share one another's red cells without being able to mount an immune response to these foreign antigens. Macfarlane Burnet, biologist *par excellence*, called attention to all of these inexplicable phenomena and hypothesized the existence of a fundamental biologic mechanism to explain Owen's finding—an embryonic interaction that would suppress the ability of an individual to respond to his/her own native antigens (Burnet and Fenner, 1949). This was soon confirmed by Medawar's group (Billingham et al., 1953), and would be termed *immunologic tolerance*. Yet another observation to emphasize the awakening biomedical movement in immunology was the description of a group of immune deficiency diseases.

Taken together, these new questions and phenomena foretold a radical change of direction—termed elsewhere the “immunobiologic revolution” (Silverstein, 1991). Not only did these questions challenge the accepted dogma but they also served to stimulate the entry of a new group of investigators into the field. These were basic scientists from such fields as genetics and physiology, and clinicians from a variety of medical disciplines. They were unfettered by any allegiance to earlier ideas and techniques, and thus could entertain iconoclastic ideas and design novel experiments.

Perhaps the best illustration of the long period during which immunologists showed little interest in disease is provided in Table 1.1. Here, for each organ or disease entity, the interval is given between the last significant study during the “classical” period and the first significant contribution of the “modern” era. The average hiatus, where both end and restart dates can be identified, is about 44 years. This is an extremely long interlude for a field that was only some 70 years old in 1950.

Thus, in the context of a growing interest in the more biomedical aspects of the immune response, work on autoimmunity became respectable. This was due also to the increasing use of Freund adjuvant, which made animal models of the various autoimmune diseases more readily available and more reproducible. Advances came rapidly.

TABLE 1.1 Dark ages of autoimmunity*

Disease/system	Last “classical” contribution	First “modern” contribution
Hemolytic disease	1909	1945 (Coombs et al.)
Sperm and testicular	1900	1951 (Voisin et al.)
Encephalomyelitis	1905	1947 (Kabat et al.)
Sympathetic ophthalmia	1912	1949 (Collins)
Phacoanaphylaxis	1911	1957 (Halbert et al.)
Thyroid	1910	1956 (Rose and Witebsky; Roitt et al.)
Wassermann antibody	1909	—
Platelet disease	—	1949 (Acroйд)

*Modified from Silverstein (1989).

Coombs et al. (1945), using the antiglobulin test, showed that many cases of acquired hemolytic anemia were due to the “incomplete” (nonagglutinating) antibodies, Kabat et al. (1947) refocused attention on the immunopathogenesis of “allergic” encephalomyelitis. Collins (1949) introduced a reproducible animal model of sympathetic ophthalmia. Voisin et al. (1951) showed how to produce an experimental allergic orchitis. Finally, Rose and Witebsky (1956) demonstrated in experimental animals and Roitt et al. (1956) in human Hashimoto's disease that some forms of thyroid disease might be based on autoimmune processes. In addition, an understanding of the pathogenesis of some of these diseases was made easier by the increasing appreciation of the fact that not all these diseases were mediated by circulating antibodies; some involved the action of subclasses of lymphocytes that originate in the thymus.

These new findings not only opened wide the floodgates of autoimmunity studies, but stimulated further interest in the more general field of immunopathology as well. This new movement was provided with a theoretical base with Talmage's (1957) suggestion and Burnet's (1959) clonal selection theory, emphasizing for the first time the biologically important role of cell dynamics in the antibody response. It is no accident that the late 1950s saw the first international conferences on immunopathology (Miescher and Vorlaender, 1958; Grabar and Miescher, 1959) and on the fundamentals of hypersensitivity (Lawrence, 1959; Shaffer et al., 1959). For the first time, in 1963, there appeared a textbook aimed at medical students (Humphrey and White, 1963), and then two comprehensive descriptions of immunologic diseases aimed at clinicians (Gell and Coombs, 1963; Samter et al., 1965). It was in the spirit of the new immunology that Mackay and Burnet (1963) could summarize contemporary knowledge in the increasingly active field of the autoimmune diseases.

CONCLUDING REMARKS

This, then, is the story of the early stirrings of interest in the possibility that disease might result from an immune response to an individual's own autochthonous antigens. Perhaps the initial reports were too premature to be incorporated into the received wisdom of the young field of immunology, just as the discovery of several allergic diseases could not at first be integrated. Certainly Paul Ehrlich's dictum of *horror autotoxicus* contributed to an unwillingness to recognize the full significance of the initial findings of a response to spermatozoa, erythrocytes, and retina. But the mounting challenges to the dogma would eventually prove irresistible and the field of autoimmunity would finally flourish, as the following chapters in this volume attest.

References

- Ackroyd, J. F. (1949). The pathogenesis of thrombocytopenic purpura due to hypersensitivity to sedormid. *Clin. Sci.* 8, 269–287.
- Behring, E. and Kitasato, S. (1890). Über das Zustandekommen der Diphtherie-immunität und der Tetanus-immunität bei Tieren. *Dtsch. Med. Wochenschr.* 16, 1113–1114.
- Billingham, R. E., Brent, L., and Medawar, P. B. (1953). Actively acquired tolerance of foreign cells. *Nature (London)* 172, 603–606.
- Bordet, J. (1899). Sur l'agglutination et la dissolution des globules rouges par le sérum d'animaux injectés de sang défibriné. *Ann. Inst. Pasteur* 12, 688–695.
- Bordet, J. and Gengou, O. (1901). Sur l'existence des substances sensibilisatrices dans la plupart des sérums anti-microbiens. *Ann. Inst. Pasteur* 15, 289–302.
- Breinl, F. and Haurowitz, F. (1930). Chemische Untersuchung des Präzipitates aus Hämoglobin und Anti-Hämoglobin und Bemerkungen über die Natur des Antikörpers. *Z. Physiol. Chem.* 192, 45–57.
- Burnet, F. M. (1959). *The Clonal Selection Theory of Acquired Immunity*. Cambridge: Cambridge University Press.
- Burnet, F. M. and Fenner, F. (1949). *The Production of Antibodies*, 2nd ed. New York: Macmillan.
- Collins, R. C. (1949). Experimental studies on sympathetic ophthalmia. *Am. J. Ophthalmol.* 32, 1687–1699.
- Coombs, R. R. A., Mourant, A. E., and Race, R. R. (1945). A new test for the detection of weak and "incomplete" Rh agglutinins. *Br. J. Exp. Pathol.* 26, 255–266.
- Detré, L. (1906). Über den Nachweis von spezifischen syphilis und der Antigenen bei Luetikern. *Wien. Klin. Wochenschr.* 19, 619–689.
- Donath, J. and Landsteiner, K. (1904). Über paroxysmale Hämoglobinurie. *Münch. Med. Wochenschr.* 51, 1590–1593.
- Donath, J. and Landsteiner, K. (1906). Über paroxysmale Hämoglobinurie. *Z. Klin. Med.* 58, 173–189.
- Ehrlich, P. (1897). Die Wertbemessung des Diphtherieheilserums und deren Theoretischen Grundlagen. *Klinische Jahrb.* 6, 299–326.
- Ehrlich, P. (1900). On immunity with special reference to cell life: Croonian Lecture. *Proc. R. Soc. London* 66, 424–448.
- Ehrlich, P. (1902). Die Schutzstoffe des Blutes. *Verh. Ges. Dtsch. Naturforsch. Aerzte* 1, 250–275.
- Ehrlich, P. and Morgenroth, J. (1900). Über Hämolysine. Dritte Mitteilung. *Berlin Klin. Wochenschr.* 37, 453–458.
- Ehrlich, P. and Morgenroth, J. (1901). Über Hämolysine. Fünfte Mitteilung. *Berlin Klin. Wochenschr.* 38, 251–255.
- Elschnig, A. (1910a). Studien zur sympathischen Ophthalmie. *von Graefes Arch. Ophthalmol.* 75, 459–474.
- Elschnig, A. (1910b). Studien zur sympathischen Ophthalmie: Die Antigene Wirkung des Augenpigmentes. *von Graefes Arch. Ophthalmol.* 76, 509–546.
- Fleck, L. (1979). *Genesis and Development of a Scientific Fact*. Chicago: University of Chicago Press.
- Friedenwald, J. S. (1934). Notes on the allergy theory of sympathetic ophthalmia. *JAMA* 17, 1008–1018.
- Gell, P. G. H. and Coombs, R. R. A. (1963). *Clinical Aspects of Immunology*. Oxford: Blackwell Scientific.
- Goltz, D. (1980). *Horror Autotoxicus: Ein Beitrag zur Geschichte und Theorie der Autoimmunpathologie im Spiegel eines vielzitierten Begriffes*. Thesis, University of Münster.
- Grabar, P. and Miescher, P. (1959). *Immunopathologie-Immunopathologie*. Basel: Benno Schwabe.
- Halbert, S. P., Locatcher-Khorazdor, D., Sonn-Kazar, C., and Swick, L. (1957). Homologous immunological studies of ocular lens II. Biological aspects. *J. Exp. Med.* 105, 453–462.
- Heidelberger, M. and Avery, O. T. (1923). The soluble specific substance of pneumococcus. *J. Exp. Med.* 38, 73–79.
- Humphrey, J. H. and White, R. G. (1963). *Immunology for Students of Medicine*. Oxford: Blackwell Scientific.
- Jerne, N. K. (1974). Towards a network theory of the immune system. *Ann. Immunol. (Paris)* 125C, 373–389.
- Kabat, E. A. and Mayer, M. M. (1949). *Quantitative Immunochemistry*. Springfield, IL: Charles C. Thomas.
- Kabat, E. A., Wolfe, A., and Bezer, A. E. (1949). The rapid production of acute encephalomyelitis in Rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants. *J. Exp. Med.* 85, 117–130.
- Krusius, F. F. (1910). Über Empfindlichkeitsversuche vom Auge aus. *Arch. Augenheilk.* 67, 6–35.
- Kuhn, T. (1970). *The Structure of Scientific Revolutions*, 2nd ed. Chicago: University of Chicago Press.
- Landsteiner, K. (1900). Zur Kenntnis der antifermentativen, lytischen und agglutinierenden Wirkung des Bluteserums und der Lymphe. *Centralbl. Bakteriol.* 27, 357–362.
- Landsteiner, K. (1962). *The Specificity of Serological Reactions*, Reprint of 2nd ed., 1945. New York: Dover.
- Lawrence, H. S. (1959). *Cellular and Humoral Aspects of Hypersensitivity States*. New York: Hoeber-Harper.
- Mackay, I. R. and Burnet, F. M. (1963). *Autoimmune Diseases*. Springfield, IL: Charles C. Thomas.
- Medawar, P. B. (1945). The behavior and fate of skin autografts and skin homografts in rabbits. *J. Anat.* 78, 176–199.
- Metalnikoff, S. (1900). Études sur la spermotoxine. *Ann. Inst. Pasteur* 14, 577–589.
- Metchnikoff, I. I. (1884). Über eine Sprosspilzkrankheit der Daphnien: Beitrag zur Lehre über den Kampf des Phagozyten gegen Krankheitserreger. *Arch. Pathol. Anat.* 86, 177–195.
- Metchnikoff, E. (1900). Sur les cytotoxines. *Ann. Inst. Pasteur* 14, 369–377.
- Miescher, P. and Vorlaender, K. O. (1958). *Immunopathologie in Klinik und Forschung*. Stuttgart: Georg Thieme.
- Owen, R. D. (1945). Immunogenetic consequences of vascular anastomoses between bovine twins. *Science* 102, 400–401.
- Pasteur, L. (1880). Sur les maladies virulentes et en particulier sur la maladie appelée vulgairement choléra des poules. *Compt. Rend. Acad. Sci.* 90, 239–248.
- Pauling, L. (1940). A theory of the structure and process of formation of antibodies. *J. Am. Chem. Soc.* 62, 2643–2657.
- Pfeiffer, R. (1894). Weitere Untersuchungen über das Wesen der Choleraimmunität und über spezifische baktericide Prozesse. *Z. Hygiene* 18, 1–16.

- Rivers, T. M. and Schwentker, F. F. (1935). Encephalomyelitis accompanied by myelin destruction produced in monkeys. *J. Exp. Med.* 61, 689–702.
- Rivers, T. M., Sprunt, D. H., and Berry, G. P. (1933). Observations on attempts to produce acute disseminated encephalomyelitis in monkeys. *J. Exp. Med.* 58, 39–54.
- Roitt, I. M., Doniach, D., Campbell, P. N., and Vaughan-Hudson, R. (1956). Auto-antibodies in Hashimoto's disease (lymphadenoid goiter). *Lancet* 2, 820–821.
- Römer, P. (1905). Die Pathogenese der *Cataracta senilis* vom Standpunkt der Serumforschung. *von Graefes Arch. Ophthalmol.* 60, 175–186.
- Römer, P. and Gebb, H. (1912). Beitrag zur Frage der Anaphylaxie durch Linseneiweiss und Eiweiss aus andern Geweben des Auges. *von Graefes Arch. Ophthalmol.* 81, 367–402.
- Rose, N. R. and Mackay, I. R. (1985). Introduction. In N. R. Rose and I. R. Mackay (eds), *The Autoimmune Diseases* (p. xxxiv). New York: Academic Press.
- Rose, N. R. and Witebsky, E. (1956). Studies on organ specificity V. Changes in the thyroid gland of rabbits following active immunization with rabbit thyroid extracts. *J. Immunol.* 76, 417–427.
- Sachs, H. (1909). Hämolysine und Cytotoxine des Blutserums. In Handbuch der Technik und Methodik der Immunitätsforschung, vol. 2. (pp. 896–897). Jena: Fisher.
- Samter, M. et al. (1965). *Immunological Diseases*. Boston: Little Brown.
- Santucci, S. (1906). Citossine. *Riv. Ital. Ottal. Roma* 2, 213.
- Shaffer, J. H., LoGrippe, G. A., and Chase, M. W. (1959). *Mechanisms of Hypersensitivity*. Boston: Little, Brown.
- Silverstein, A. M. (1989). Allergy and immunity: The price of immunity. In *A History of Immunology* (pp. 214–251). New York: Academic Press.
- Silverstein, A. M. (1991). The dynamics of conceptual change in twentieth century immunology. *Cell. Immunol.* 132, 515–531.
- Silverstein, A. M. (1994). The heuristic value of experimental systems: The case of immune hemolysis. *J. Hist. Biol.* 27, 437–447.
- Silverstein, A. M. (2002). *Paul Ehrlich's Receptor Immunology* (pp. 95–122). New York: Academic Press.
- Talmage, D. W. (1957). Allergy and immunology. *Annu. Rev. Med.* 8, 239–256
- Uhlenhuth, P. (1903). Zur Lehre von der Unterscheidung verschiedener Eiweissarten mit Hilfe spezifischer Sera. In *Festschrift zum 60 Geburtstag von Robert Koch* (p. 49). Jena: Fisher.
- Verhoeff, F. H. and Lemoine, A. N. (1922). Endophthalmitis phacoanaphylactica. *Am. J. Ophthalmol.* 5, 737–745.
- Voisin, G., Delaunay, A., and Barber, M. (1951). Sur des lésions testiculaires provoquées chez le cobaye par iso- et auto-sensibilisation. *Ann. Inst. Pasteur* 81, 48–63.
- von Pirquet, C. (1910). *Allergie*. Berlin: Springer. [English transl., *Allergy*. American Medical Association, Chicago, 1911.]
- von Wassermann, A., Neisser, A., and Bruck, C. (1906). Eine serodiagnostische Reaktion bei Syphilis. *Dtsch. Med. Wochenschr.* 32, 745–746.
- Weil, E. and Braun, H. (1909). Über das Wesen derluetischen Erkrankung auf Grund der neueren Forschungen. *Wien. Klin. Wochenschr.* 22, 372–374.
- Witebsky, E. (1954). Ehrlich's side-chain theory in light of present immunology. *Ann. N.Y. Acad. Sci.* 59, 168–181.
- Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R., and Egan, R. W. (1957). Chronic thyroiditis and autoimmunization. *JAMA* 164, 1439–1447.
- Woods, A. C. (1921). Immune reactions following injuries to the uveal tract. *JAMA* 77, 1217–1222.
- Woods, A. C. (1925). Sympathetic ophthalmia: the use of uveal pigment in diagnosis and treatment. *Trans. Ophthalmol. Soc. UK* 45, 208–249.
- Woods, A. C. (1933). *Allergy and Immunity in Ophthalmology*. Baltimore: Johns Hopkins University Press.

