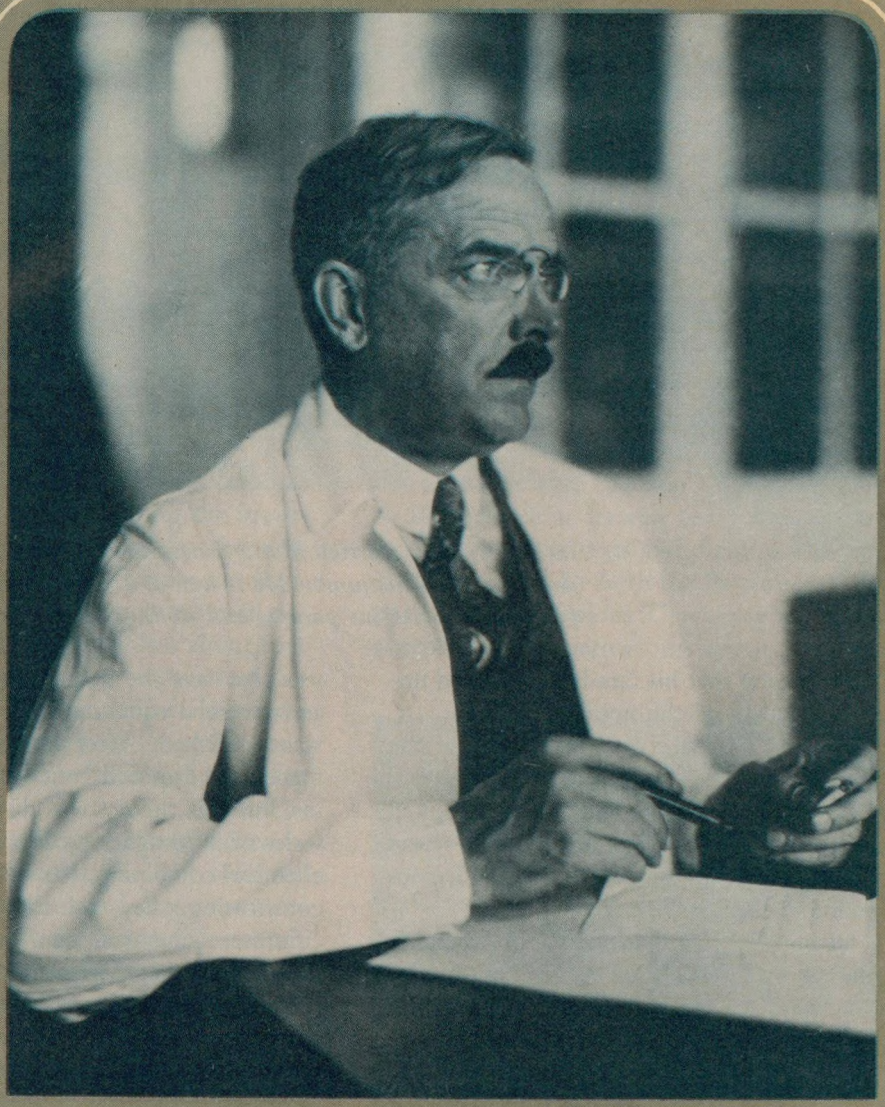
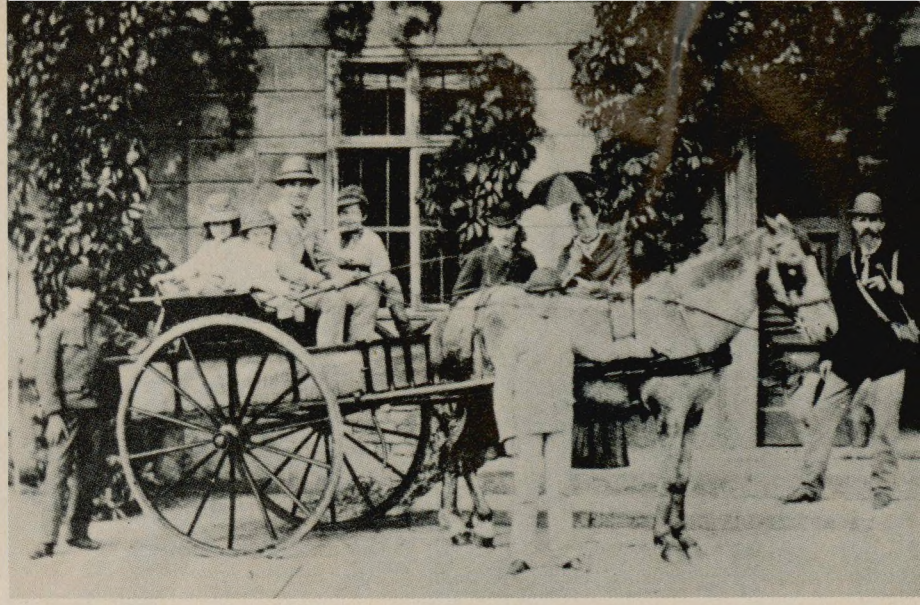


pioneer allergist

Seventy-one years ago an obscure young resident in the Vienna Kinderklinik deposited with the Imperial Academy of Sciences in Vienna a sealed envelope which, when opened five years later, assured Clemens von Pirquet priority as the discoverer of a new concept of the immunologic process from which he elaborated a new branch of medical science. This he named "allergy." ▪ **BACKGROUND.** The sixth child of Peter Zeno and Flora von Pirquet, both of whom were descended from members of the Austrian aristocracy, Clemens von Pirquet was born in Hirschstetten, near Vienna, on May 12, 1874. His father, who served in parliament as a member of the landowners' party, had a strong interest in educational reform. ▪ When their sons were ready to enter secondary school the Pirquets moved to Vienna, where Clemens spent three years at the Schotengymnasium, then known as the "Eton of Austria." He spent the next five years in a Jesuit boarding school in Kalksburg near Vienna and, under the influence of the Jesuits and his mother, prepared for the priesthood. But after obtaining his bachelor's degree at the University of Louvain, he abandoned religion for



In 1904 Pirquet married Maria Christine van Husen, left, of Hanover who was four years his junior. He is seen as a youth, standing above in center foreground, with his parents and siblings at their estate at Hirschstettin.

medicine, a profession that his family considered unsuitable for a member of the nobility.

He spent his first year as a medical student at the University of Vienna, then studied at the University of Königsberg in East Prussia, and finally received his M. D. degree in 1900 as an honor student at the University of Graz, where he had studied pediatrics under Theodor Escherich.

In 1901 he entered the University of Vienna's Kinderklinik as an intern, then as resident under Escherich; within two years he was promoted to clinical assistant. At the invitation of the ranking clinical assistant Paul Moser, who had introduced immune serum for scarlet fever, Pirquet took charge of the scarlet fever pavilion.

Streptococci from scarlet fever patients were agglutinated by a serum prepared by immunizing horses with the bacteria. In studies seeking to elucidate the process of immunization whereby harmful bacteria are neutralized, the eminent immunologist Paul Ehrlich had put forward the "side-chain theory." According to this the harmful invader known as an antigen releases multiple toxins, to which the body responds by producing an antibody, conceived by Ehrlich to be a protein molecule similar to a benzene ring with unstable side chains described by F. A. Kekulé. According to Ehrlich, the side chains, acting as chemoreceptors, combined with the multiple toxins to neutralize them.

The young Pirquet worked with Max Gruber, professor of hygiene at the University of Munich, on a study titled "Toxin and Antitoxin," which Gruber presented to the Society of Morphology and Physiology in Munich in 1903, challenging Ehrlich's side-chain theory. Pirquet provided a graphic analysis that was the foundation of Gruber's research, and received equal credit with him when the paper was published. After its publication Ehrlich reaffirmed his disputed concept of the plurality of toxins, but this theory was displaced as the result of a series of investigations. Ehrlich's concept of specific chemical combining sites on antigens and antibodies, constituting a key-to-lock relationship based on specific stereochemical configuration, has survived as the foundation of present-day immunochemistry.

SERUM SICKNESS. An injection of the Moser antistreptococcal serum (100 to 200 ml.) produced serum sickness, marked by fever and rash, in almost all patients. In what proved to be an historic case, Pirquet injected the serum into a patient who developed serum sickness after an incubation time of seven days. A few weeks later, after the discovery of several cases of diphtheria on the ward, prophylactic injections of 2 ml. were given to prevent further outbreaks. Ten minutes after receiving the injection, the serum patient vomited, developed edema of the face and lips and urticaria.

Since the first treatment of human disease with antitoxic serum from an outside source in 1891 by Shibasaburo Kitasato, there had been a number of reports of serum sickness accompanied by severe shock and in some cases death. Pirquet was the first to note that injected serum caused sudden violent reactions only in previously injected children. He concluded that a pathogenic agent caused signs of illness in the organism only when modified by the presence of antibodies, and that the time required to form antibodies was the incubation time for the illness.

With his friend and coworker Béla Schick, he be-

gan a study of the significance of the changes in incubation time following reinjection. After three years of research they published in 1905 a monograph embodying their theory of the development of serum sickness. They compared the body's destruction of horse serum as a foreign protein to the similar destruction of protein by the digestive juices in the intestinal tract, a process that releases intermediate toxic substances that are detoxified within the intestinal wall and, after absorption, are further detoxified by the liver. They noted that if protein is injected parenterally it must be destroyed by organ cells that are less well prepared than intestinal tract cells. The time needed by the organ cells to mobilize antibodies is the incubation time. During the breakdown of parenterally injected protein by the antibodies, toxic substances are created that are not readily detoxified; symptoms of serum sickness then appear. Antibodies remain in circulation for about four months, and if serum is reinjected within that period symptoms of serum sickness appear almost immediately. Even if antibodies are no longer present, the mobilization of antibodies is faster and results in an accelerated reaction.

Pirquet now began to investigate the broader implications of the altered reactivity he had observed in serum sickness. He demonstrated experimentally the existence of the same phenomenon in smallpox vaccination, but he observed a difference in the effects: in serum sickness altered reactivity was useless and even dangerous, and it did not lead to immunity; in smallpox it increased immunity. He observed that following smallpox vaccination the mobilization of antibodies initiated the disease, then ended it by killing the invading germs. The persistence of the antibodies guaranteed immediate destruction of the invaders in case of reinfection, and even an accelerated reaction minimized the intensity of the infection.

In a paper published in the *Münchener Medizinische Wochenschrift* of July 24, 1906, Pirquet introduced a new term "allergy"* for the concept of altered reactivity in the body resulting from the interaction between foreign proteins, antigens, and proteins mobilized by the body, antibodies, to combat them.

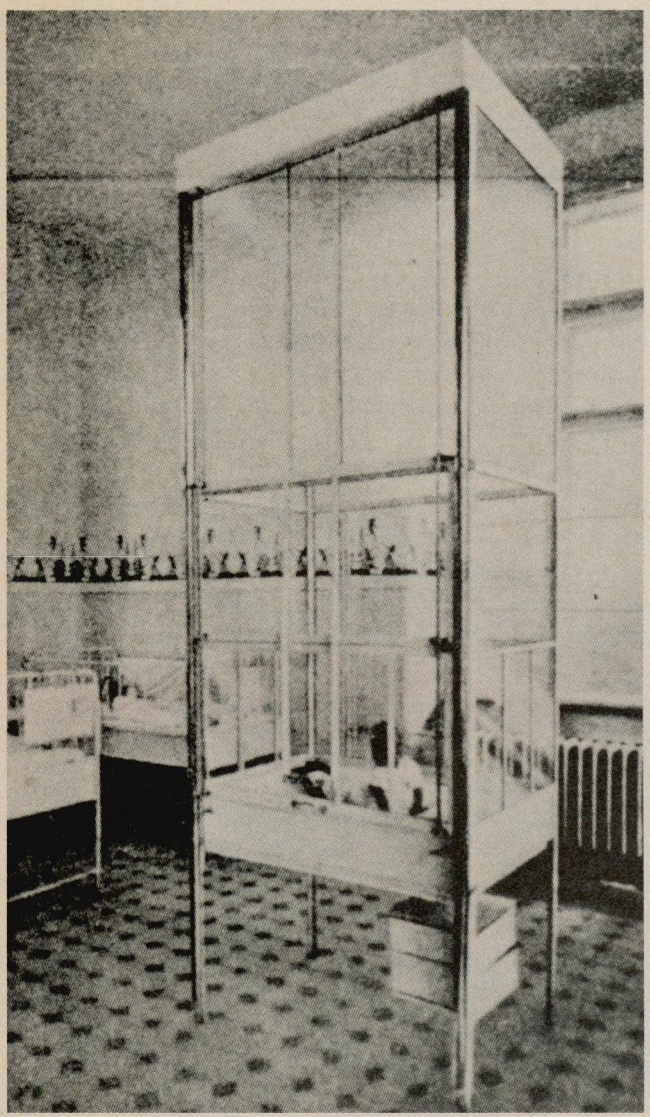
Béla Schick proposed a study to determine whether the tuberculin reaction was also allergic in nature. The reaction consisted of a fever indicating the presence of active tuberculosis following subcutaneous injection of .01 ml. old tuberculin, the famous test developed by Koch in 1895. Pirquet, at first skeptical that tuberculin could be classified as an allergen, sent Schick to Graz to review cases in which a local inflammatory reaction had been observed at the site of a tuberculin injection. After Schick reported that the inflammatory reaction was specific, like the fever reaction, Pirquet decided to use an instrument he had devised for his studies of smallpox vaccination, the borer, for a skin test for tuberculosis.

He announced that the tuberculin scratch test he had developed was a reliable test for discovering the existence of a tuberculous focus in an infant or child, and a large number of papers corroborating his finding soon appeared. He became world famous, and the term "Pirquet reaction" for a positive reaction to the tuberculin scratch test gained acceptance in standard medical texts and dictionaries.

Offered posts by both the Pasteur Institute in Paris and Johns Hopkins University in Baltimore, he accepted the American invitation and became the

Pirquet at a Christmas party at the Kinderklinik in Vienna which was built in 1911 according to the plans of Theodor Escherich, Pirquet's teacher and predecessor in pediatrics at the University there.

*Greek *allos* another, *ergon* work.



Isolation bed devised by Pirquet. He later had six such beds of two different sizes assembled into a spacesaving unit. Observed by the patient's grandmother, right, Pirquet examines an infant in the lecture hall of the Kinderklinik where three times a week he presided at lectures with case presentations.

first professor of pediatrics at Johns Hopkins, a part-time appointment that permitted him to engage in private practice.

He also served as physician-in-chief to the Harriet Lane Johnstone Home for Invalid Children, which made him responsible for planning a new hospital with an amphitheatre. His administrative duties, for which he was temperamentally not equipped (the amphitheatre was built without seats), precluded any new research, but he wrote articles for medical treatises on his previous findings on allergy and on the cutaneous tuberculin reaction. He also read a paper before the Philadelphia Pediatric Society advocating segregation of tuberculous individuals as a means of eradicating the disease.

After a year at Johns Hopkins, he left to accept a professorship at the University of Breslau, Germany, where he continued his studies of allergy, especially in relation to injection against infectious diseases.

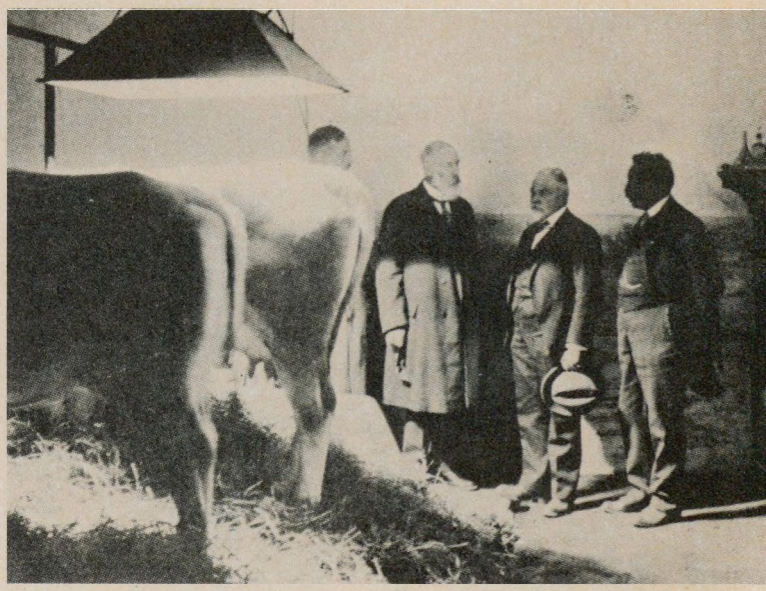
In 1911, following the sudden death of Escherich, the University of Vienna invited Pirquet to succeed him as professor of pediatrics, which he accepted after rejecting a competing offer from Johns Hopkins.

Pirquet took Béla Schick as his principal assistant and gave him the task of supervising the new clinic completed by Escherich just before his death. Six assistant physicians worked in close collaboration with Pirquet and Schick, who treated even the kitchen as a laboratory. They introduced the Nutrition Element Milk (N.E.M.) system devised by Pirquet in which the unit, which Pirquet substituted for the calorie, was the food value of 1 ml. of milk, equiva-

lent to .67 calories. He estimated food requirements by a nutritional index he called the "pelidisi," based on the calculation that the cube of the sitting height in centimeters is equal to ten times the weight in grams in the normal person. By the use of this equation the "pelidisi," or nutritional index, is 100 in a normal person, and the person is overnourished if the index exceeds 100 and undernourished if it falls below. Appointed commissioner general by the Austrian government in 1919 to supervise distribution of food supplies provided by the American Relief Administration directed by Herbert Hoover, Pirquet applied his N.E.M. system to feeding 400,000 children daily.

Another innovation by Pirquet was a glass-walled cubicle for newborn infants who had to be isolated because of precarious health. After building the first experimental unit of a single bed, Pirquet and Schick ordered a unit of six beds, each separated from the others by glass walls, and each accessible to physicians and nurses by raising one wall. Schick later helped to introduce this type of cubicle in Mount Sinai Hospital in New York.

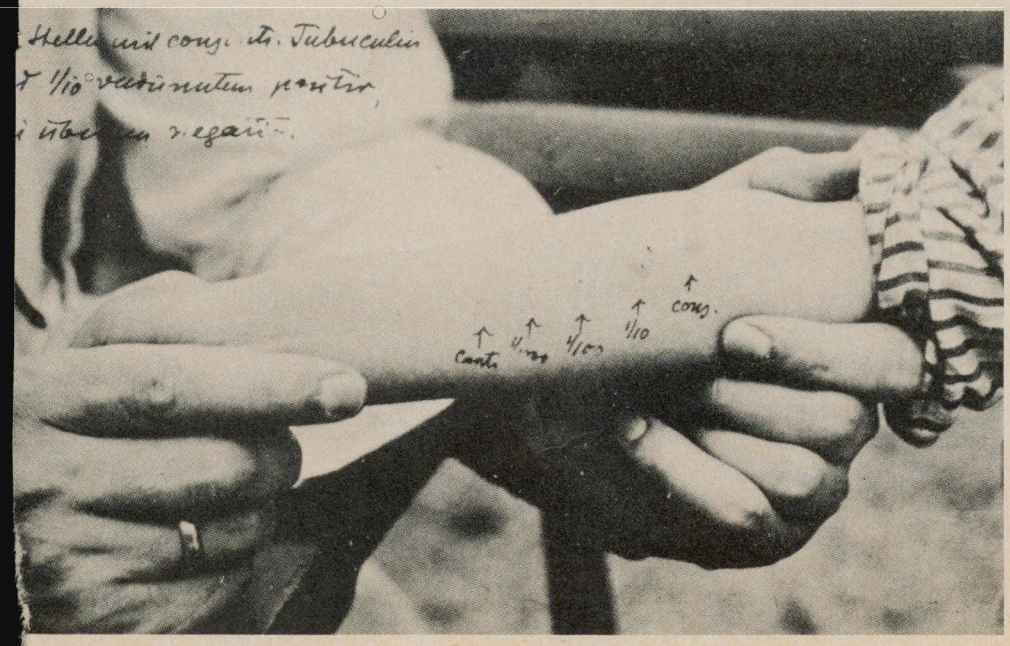
During World War I all the assistant physicians had to serve in the army, which left Pirquet and Schick to run the clinic with the help of an assistant of Russian origin who was ineligible for military duty. In the postwar period the Rockefeller Foundation contributed support for the clinic's chemical laboratory, neglected during the war, and also for a library and an enlarged teaching staff. Pirquet, who conducted the rounds himself three times weekly with a large following, became a trustee of the Rockefeller Foundation.



Pirquet visited the United States in 1921 to lecture at Yale University and at the New York Academy of Medicine. Appointed to a chair in pediatrics at the University of Minnesota in 1924, he found on arrival that he faced the task of organizing a new department with what he regarded as inadequate facilities; after a brief stay he resigned and returned to Austria.

At his suggestion, the hygiene section of the League of Nations established a permanent committee for child health. Appointed chairman of the committee, he directed its comparative studies on child mortality and prepared reports on the health problems of Austrian schoolchildren.

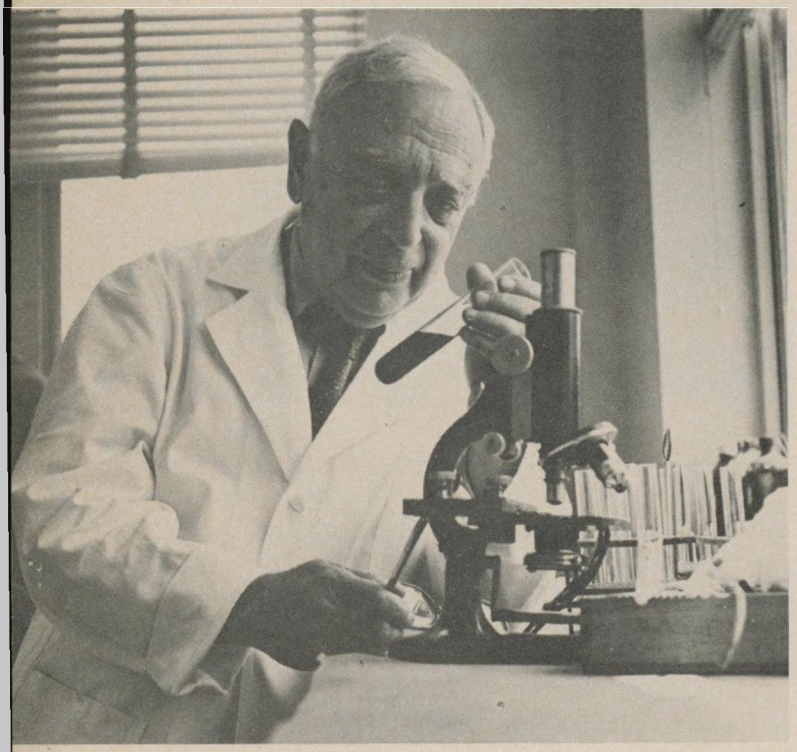
During the 1920s he became less interested in clin-



Pirquet shows visitors, including the Austrian President, his dairy barn at Hirschstetten, above, where he was experimenting to enrich milk with vitamin D. His was the first dairy in Austria to produce pasteurized and certified milk for infants.

Positive reaction in the subcutaneous tuberculin test Pirquet developed indicates the individual has been in contact with the tubercle bacillus.

Dr. Béla Schick, eponym of the diphtheria test, as a young man worked with Pirquet in his studies of allergy and when Pirquet went to Vienna in 1911 he became his principal assistant at the Kinderklinik.



ical pediatrics and devoted himself more to special problems in biostatistics, an interest he had sustained since helping Gruber challenge Ehrlich's side-chain theory. One project was intended to determine what he called "the center of gravity of disease:" using mortality tables for each quarter of the year over a period of eight years, he determined by trigonometry the "center of gravity," or day with the highest frequency of fatalities for each illness.

He published his last work *Die Lebenskerze (The Candle of Life)* in 1929, representing a new development of the concept of altered reactivity, which underlay his theory of allergy. He discussed the problem of how far a reaction toward disease is conditioned by spontaneous changes taking place within the organism during its life course. He summed up the viewpoint underlying this work by declaring that almost every well-defined cause of death has its characteristic age curve.

On February 28, 1929, the bodies of Pirquet and his wife were found in their Vienna home. The inquest verdict was suicide by cyanide poisoning. The suicide shocked friends and associates, but there had been some signs of emotional disturbance in Pirquet in the 1920s, especially during his brief tenure at the University of Minnesota and his abrupt departure in a troubled state.

PERSONALITY. Pirquet was always dressed carefully and conservatively, and he expressed himself in the simplest and most unaffected manner. He enjoyed wine, liked dancing and playing bridge. Mathematics was both a scientific aid and a hobby for him, which he used to design a space saving staircase in his country house and a device to turn an automobile around in one spot. Late in the 1920s he was nominated for the presidency of the Austrian republic; some friends attributed his suicide partly to despondency over his failure to be elected as president.

FORERUNNERS. In the 19th century a number of important discoveries were made about allergic reactions, but their significance was obscured for several decades by the predominant interest in the bacteriologic cause of disease. Charles Harrison Blackley of Manchester, England, found in 1859 the first conclusive evidence that pollen was the cause of hay fever, but Hermann von Helmholtz, the great physicist, himself a sufferer from hay fever, ignored Blackley's findings and attributed the ailment to an organism he had isolated from his nose.

During Charles Richet's research in immunology he observed violent reactions in laboratory animals after a second injection, similar to the hypersensitivity in human beings noted by Pirquet. Richet injected stinging nettle poison into dogs to develop immunity but found that a second injection produced the opposite effect, sudden death. Since immunologists applied the term "prophylaxis" to active immunization, Richet coined the term "anaphylaxis" to define this hypersensitive reaction. In his monograph *Anaphylaxis* published in 1902, he theorized that the injection of a toxin destroyed the body's power of producing an antitoxin, so that it succumbed to a second injection.

When Pirquet and Schick began their work on serum sickness, they regarded it as an anaphylactic reaction in human beings. Working with nontoxic materials, they rejected Richet's concept that foreign toxins first deprived the body of its defenses, then caused death after a second injection.

In 1956, on the fiftieth anniversary of Pirquet's paper on allergy, his old friend Béla Schick paid tribute to the man who "had the satisfaction to live to see that his work was a master stroke. Everyday allergy is discovered to have new applications in medicine. . . . Let us teach the students of medicine the great discoveries of Pirquet, who coined the term allergy and realized its importance for the entire science of medicine."