NATIONAL ACADEMY OF SCIENCES

WALTHER FREDERICK GOEBEL
1899–1993

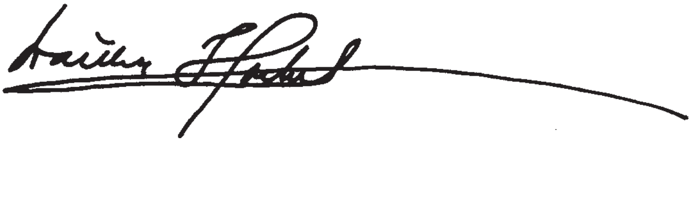
A Biographical Memoir by

MACLYN MCCARTY

Biographical Memoirs, VOLUME 77

PUBLISHED 1999 BY
THE NATIONAL ACADEMY PRESS
WASHINGTON, D.C.

Photo by R. Carter



WALTHER FREDERICK GOEBEL

December 24, 1899–November 1, 1993

BY MACLYN MCCARTY

IN 1924, SOON after he completed his training as an organic chemist, Walther Goebel joined Oswald T. Avery and Michael Heidelberger at the Rockefeller Institute for Medical Research in their seminal work on the nature of the soluble specific substances of the pneumococcus. Their studies had recently established that these constituents of the capsule of the organism were polysaccharides and provided the first evidence that polysaccharides were capable of inducing the formation of specific antibodies. Over the next 20 years, Goebel made major contributions to the understanding of the basis for serological specificity of polysaccharides and their role in eliciting antibodies that protected against pneumococcal infection.

In the course of World War II, Goebel turned to work on the complex antigens of the dysentery bacilli, with the aim of providing more effective antigens for vaccination against infection with these organisms in the military. His work in this area continued during the postwar period and extended to studies on the bacterial viruses and colicines of these organisms before his retirement in 1970.

Walther Goebel was born in Palo Alto, California, on December 24, 1899, at a time when his father Julius Goebel was teaching in the Germanic language department at Stanford University. In this setting he experienced the great San Francisco earthquake of 1906, which destroyed the family home in Palo Alto. There were seven children in the family with an age range of 15 years, and under the influence of their parents, they had strong musical interests, with each child playing a musical instrument. In a pattern rather unusual even early in this century, Walther was tutored at home and did not attend school until he started high school in 1912 in Urbana, Illinois, where his father had moved to a professorship at the University of Illinois.

After completing high school, where an inspiring teacher, L. B. Howell, had stimulated his interest in chemistry, the remainder of Walther's formal education was at the University of Illinois. He received a B.A. in 1920, and then went on to an M.A. (1921) and a Ph.D. (1923) in the Department of Chemistry under the supervision of Professor W. A. Noyes. He added a year of postdoctoral work in Germany (1923-1924) with Professor Richard Willstätter at the University of Munich. This period coincided with the rise of Hitler, and he witnessed the infamous storm trooper attack on students on the Odeons Platz, during which he had the narrow escape of having his hat shot off.

On his return from Germany, Goebel found a position as an assistant in the hospital of the Rockefeller Institute for Medical Research, joining the immunochemical studies of Avery and Heidelberger. He remained at Rockefeller for the rest of his active research career, with promotion to associate member in 1934 and member in 1944. The title "member" was replaced by "professor" in 1957, after the institute initiated a predoctoral program and was renamed Rockefeller University. He became professor emeritus in 1970 on reaching the age of seventy.

Goebel married Cornelia van Renssalaer Robb in 1940.

They had two daughters, Cornelia van Renssalaer Bronson and Anne Kathryn Barkman. Cornelia Goebel died in 1974 after a long battle with rheumatic heart disease. Walther married Alice Lawrence Behn in 1976 and spent his remaining life in retirement in Greenwich, Connecticut. He died at age ninety-four on November 1, 1993.

I got to know Walther Goebel well soon after my arrival in the Avery laboratory in 1941, and we became good friends over the years. He was helpful to me in my early orientation in the laboratory and in general displayed a friendly demeanor. On occasion, however, he assumed a gruff and aggressive exterior that upset some people, but I found this had no depth whatever and could be turned off with a quip. The interest in the arts he had acquired in his early years was maintained, but I do not believe he continued to play a musical instrument. He was, however, responsible for organizing and recruiting the instructor for an evening art course at Rockefeller, which was appreciated by faculty and staff over a period of years.

He was elected to the National Academy of Sciences in 1958. His research contributions were also recognized by an honorary Sc.D. degree from Middlebury College, Vermont, in 1959. In May 1973 he sent me a copy of a letter he had just received and included a handwritten note that read:

> Dear Mac: I thought this would interest you. It was given me the other evening by hand by Westphal. He is here for only three days. Needless to say, I was thrilled, though not certain of my deserving it. We plan to go. There's great wine in Alsace!

The letter was from the German Gesellschaft für Immunologie announcing the creation of the Avery-Landsteiner Prize for pioneering research in immunology and Goebel's selection as the first recipient. Otto Westphal was a distinguished German immunologist, president of the society, and a signatory of the letter. The prize was, of course, named after Goebel's mentor Oswald Avery and Karl Landsteiner, a Nobel laureate, who had also played a major role in laying the foundations of modern chemical immunology and had come to Rockefeller from Vienna in 1922, so that he was well known by Goebel during his early years with Avery. The prize was presented at the first European Congress of Immunology held in Strasburg in September 1973.

In 1978, at the annual convocation for the awarding of degrees at Rockefeller University, I had the privilege of presenting Goebel for the honorary doctor of science degree, another honor he treasured.

The research activity that Goebel joined on his arrival at the Rockefeller Institute provided new insights in both bacteriology and immunology. The pathogenic bacterium involved, called the pneumococcus (and today classified as *Streptococcus pneumoniae*), was the principal cause of lobar pneumonia, one of the leading causes of death at that time. Earlier work on this organism, much of it from the Avery laboratory at Rockefeller, had established that many serologically different types of pneumococci existed, and that immunity to infection was type-specific (i.e., immunization with one type provided protection against only that type). Avery and his coworkers had found that this type-specific immunity was referable to a "soluble specific substance" present in the capsule surrounding the pneumococcal cells. Since it seemed important to know more about this soluble substance, Avery had sought the aid of a biochemist in the hospital, Michael Heidelberger, in determining the nature of this capsular material. At the time of Goebel's arrival, they had recently reported that this material responsible for type specificity of pneumococci was composed of polysaccharides.

Polysaccharides are large molecules formed by the joining together of many molecules of simple sugars. Common table sugar, sucrose, is a disaccharide composed of only two sugars: glucose and fructose. Starch, on the other hand, is a polysaccharide made up of numerous glucose molecules. There are a large number of different simple sugars, thus providing for a wide variety of diverse polysaccharides, some of which have four or more different simple sugar components. When the nature of the soluble specific substances was discovered by Avery and Heidelberger, polysaccharides were not believed to be antigenic to induce the formation of specific antibodies. Only proteins were considered to have these properties. The findings of Avery and Heidelberger were thus revolutionary and not immediately accepted, so that it was important to undertake studies to further verify them and to establish the basis for the antigenic specificity of the polysaccharides. Goebel was quickly immersed in this work, which he pursued for the next 20 years.

He joined the ongoing research of Heidelberger and Avery and participated in the studies that led to the third paper on the polysaccharide nature of the specific soluble substance of the pneumococcus. With Heidelberger he turned to more detailed analysis of the composition and structure of the type III polysaccharide. They showed that this was an acidic molecule made up of two sugars, glucose and glucuronic acid. Additional work revealed that the total molecule was composed of repeating units of a disaccharide of the two sugars, combined in a specific linkage referred to as aldobionic acid. Thus, the principal antigen of one of the most virulent of the known pneumococcal types was shown to have relatively simple, repetitive composition.

During this period, the group also showed that their findings were not limited to the pneumococci. They found that the specific soluble substances of another bacterium associated with pneumonia, termed "Friedländer's bacillus" for its discoverer, were also polysaccharide in nature. This was another organism that occurred in different specific types determined by the nature of the polysaccharides involved. In later years, other examples of the importance of the capsular polysaccharides in pathogenic bacteria were described elsewhere.

Goebel began his own studies directed at determining the relationship between the chemical composition of monosaccharides and disaccharides and their ability to induce the formation of specific antibodies. To accomplish this it was necessary to devise a way of obtaining specific antibodies to the simple sugars. This he accomplished by synthesizing p-aminophenyl derivatives of several common sugars and disaccharides, so that they could be coupled to proteins for use as antigens. Distinct differences were found in the antibodies formed by even closely related sugars. The most dramatic of these experiments was the demonstration that the anomeric forms of glucose could be distinguished from one another by the antibody response. These anomers (termed alpha and beta) are determined solely by the relative position of the -H and -OH substituents on the first carbon of the molecule. Thus, Goebel established that a minor change in the configuration of a sugar molecule could alter its antigenic specificity.

Using these procedures, Goebel returned to a study of the type III pneumococcal polysaccharide. He synthesized the glucose-glucuronic acid disaccharide and linked it with p-aminophenol, so that it could be coupled with proteins. Antigens formed in this manner with several different proteins were each able to induce the formation of antibodies that precipitated with the type III polysaccharide. In addition, these antibodies protected animals against infection with type III pneumococci but not types I or II. This established with a synthetic antigen that the disaccharide was the determinant of antigenic specificity and sufficient for eliciting neutralizing antibodies against the intact polysaccharide as expressed on living pneumococci.

In the latter phases of his work on pneumococci, Goebel and his colleagues turned up other findings of interest. Examples are studies on the type XIV pneumococcal polysaccharide and its relationship to the blood group A specific substance, and work on the nature of the group-specific or somatic polysaccharide of the pneumococcus, which is common to all types of the organism.

At the onset of World War II Goebel changed the subject of his research in order to participate in the war effort, selecting studies of the principal organisms involved in dysentery. He and his colleagues focused on the specific antigens of *Shigella dysenteriae* and the development of these substances as more effective immunogens for use as vaccines against the disease. His work with the various Shigellae and their dominant surface antigens, which were shown to be composed of a lipo-carbohydrate protein complex, continued in the postwar years. These studies were extended to the bacterial viruses, or bacteriophages, of these organisms, showing that the antigenic complex included the receptors required for infection with these agents. Subsequently, studies were carried out on the nature and properties of substances known as colicines, which were produced by the bacteria and also found to be associated with the surface antigenic complex.

These were productive and useful studies, but they lacked the flavor of novelty and originality associated with the earlier work on polysaccharides. Interestingly, in a brief assessment of his "discoveries" found in the biographical material on file at the National Academy of Sciences' membership office, Goebel cites only the studies on the polysaccharides and does not mention the later work. His summary of his discoveries was as follows:

> These investigations indicated beyond question that it is the precise chemical structure of the carbohydrate, be it simple or complex, that determines its immunological specificity, a fact hitherto unknown.

This personal statement of his contributions provides a concise and objective summary of his most important work.

Although he maintained some contact with laboratory work after leaving Rockefeller, this part-time effort was finally replaced by full retirement in Greenwich.

THE BIOGRAPHICAL MATERIAL from the files of the National Academy of Sciences, including the personal observations Goebel had supplied, provided a range of the most useful sources. A copy of the complete list of Goebel's collected papers was obtained from the Rockefeller Archives. In addition, my own personal files (e.g., those related to the presentation for the honorary Sc.D. in 1978) also proved useful.

SELECTED BIBLIOGRAPHY

1923

With W. A. Noyes. Derivatives of camphoronic acid. *J. Am. Chem. Soc.* 45:3064-70.

1925

With M. Heidelberger and O. T. Avery. The soluble specific substance of pneumococcus. Third paper. *J. Exp. Med.* 42:727-45.

1926

With M. Heidelberger. The soluble specific substance of pneumococcus. IV. On the nature of the specific polysaccharide of type III pneumococcus. *J. Biol. Chem.* 70:613-24.

1927

With O. T. Avery. The soluble specific substance of Friedländer's bacillus. III. On the isolation and properties of the specific carbohydrates from types A and C Friedländer's bacillus. *J. Exp. Med.* 46:601-607.

1930

With W. S. Tillett and O. T. Avery. Chemical and immunological properties of a species-specific carbohydrate of pneumococci. *J. Exp. Med.* 52:895-900.

1931

With O. T. Avery. Chemo-immunological studies on conjugated carbohydrate proteins. IV. The synthesis of the p-aminobenzyl ether of the soluble specific substance of type III pneumococcus and its coupling with protein. *J. Exp. Med.* 54:431-36.

1933

With O. T. Avery. Chemo-immunological studies on the soluble specific substance of pneumococcus. I. The isolation and properties of the acetyl polysaccharide of pneumococcus type I. *J. Exp. Med.* 58:731-55.

1934

With F. H. Babers. The synthesis of the p-aminophenol β-glycosides of maltose, lactose, cellobiose and gentiobiose. *J. Biol. Chem.* 105:473-80.

With F. H. Babers and O. T. Avery. Chemo-immunological studies on conjugated carbohydrate-proteins. VIII. The influence of the acetyl group on the specificity of hexoside-protein antigens. *J. Exp. Med.* 60:85-94.

1935

Chemo-immunological studies on the soluble specific substance of pneumococcus. II. The chemical basis for the immunological relationship between the capsular polysaccharides of types III and VIII pneumococcus. *J. Biol. Chem.* 110:391-98.

1936

With R. D. Hotchkiss. Derivatives of glucuronic acid. VII. The synthesis of aldobionic acids. *J. Biol. Chem.* 115:285-92.

Chemo-immunological studies on conjugated carbohydrate-proteins. X. The immunological properties of an artificial antigen containing glucuronic acid. *J. Exp. Med.* 64:29-38.

1937

With R. D. Hotchkiss. Chemo-immunological studies on soluble specific substance of pneumococcus. III. The structure of the aldobionic acid from the type III polysaccharide. *J. Biol. Chem.* 121:195-203.

1938

Chemo-immunological studies on conjugated carbohydrate-proteins. XII. The immunological properties of an artificial antigen containing cellobiuronic acid. *J. Exp. Med.* 68:469-84.

1939

With P. B. Beeson. The immunological relationship of the capsular polysaccharide of type XIV pneumococcus to the blood group A specific substance. *J. Exp. Med.* 70:239-47.

Immunity to experimental pneumococcus infection with an artificial antigen. *Nature* 143:77.

Studies on antibacterial immunity induced by artificial antigens. I.

Immunity to experimental pneumococcal infection with an antigen containing cellobiuronic acid. *J. Exp. Med.* 69:353-64.

1940

Studies on antibacterial immunity induced by artificial antigens. II. Immunity to experimental pneumococcal infection with saccharides of synthetic origin. *J. Exp. Med.* 72:33-48.

1941

With R. E. Reeves. Chemo-immunological studies on the soluble specific substance of pneumococcus. V. The structure of the type III polysaccharide. *J. Biol. Chem.* 139:511-19.

1945

With F. Binkley and E. Perlman. Studies on the Flexner group of dysentery bacilli. I. The specific antigens of Shigella paradysenteriae (Flexner). *J. Exp. Med.* 81:315-30.

With E. Perlman and F. Binkley. Studies on the Flexner group of dysentery bacilli. III. Antibody response in man following the administration of the specific antigen of type 5 Shigella paradysenteriae (Flexner). *J. Exp. Med.* 81:349-58.

1958

With G. T. Barry. Colicine K. II. The preparation and properties of a substance having colicine K activity. *J. Exp. Med.* 107:185-209.

1975

The golden era of immunology at the Rockefeller Institute. *Perspect. Biol. Med.* 18:419-26.

Photo by R. Carter