

## ORIGINAL CONTRIBUTION

# One Hundred Years of Presidents of SAB/ASM: The Rockefeller Connection

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## INTRODUCTION

This article on "The Rockefeller Connection" will focus on three Presidents who served terms that occurred during a period of eleven years in the middle third of the century: Oswald T. Avery in 1941, Rebecca C. Lancefield in 1943, and Rene J. Dubos in 1952. Each of them was, thus, president while the institution was still officially known as The Rockefeller Institute for Medical Research. There is also a close connection between the three, since both Lancefield and Dubos began their Rockefeller experience in the Avery laboratory and remained devoted admirers of "The Professor," or "Fess" for short, as he was known, for the rest of their lives. I was well acquainted with all three.

## OSWALD THEODORE AVERY

Avery had been brought to Rockefeller by Rufus Cole, the director of the Hospital, in 1913, and he quickly became involved in studies on the pneumococcus, the principal bacterial agent causing lobar

pneumonia. Nearly all of his research until he retired from the laboratory 35 years later was devoted to some aspect of this organism. Early work in collaboration with Alphonse Dochez identified a soluble specific substance that occurred in culture supernates, as well as in the blood and urine of patients with pneumonia. This substance was detected with antisera and was specific for the different serological types of pneumococci. Their work revealed the origin of the substance in the capsule surrounding the organism, and established its central role in virulence and disease production [1].

Avery became obsessed with the idea that it was of first importance to determine the chemical nature of this capsular substance, and after some frustrating attempts to obtain information on this point, he managed to enlist the aid of the biochemist Michael Heidelberger in an all-out attack on the problem in the early 1930s. Out of this came the surprising finding that they were composed of polysaccharides and that pure complex sugars of this type were

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<sup>b</sup> Abbreviations: SAB, Society of American Bacteriologists.

Submitted July 26, 1999; accepted November 30, 1999.

able to induce the formation of specific antibodies. This was a revolutionary finding and was greeted at the outset with considerable skepticism. As a result, they conducted studies, in which they were joined by another young biochemist, Walther Goebel, to determine the chemical basis for the specificity of saccharides. Acceptance of the polysaccharide story gradually became general, but the early resistance, based on the notion that a contaminating protein in the polysaccharide preparations was responsible for the antigenicity, caused Avery to try another approach to the problem that I will return to later.

A new problem was introduced into the Avery laboratory in 1928 with the publication of Fred Griffith's paper on the transformation of pneumococcal types [2]. This seemed contrary to the observed stability of serological type in pneumococci and was thus hard to believe. However, Griffith's results were soon confirmed by Neufeld in Berlin [3] and then by Martin Dawson in the Avery laboratory [4]. Griffith's experiments were carried out in the mouse, but Dawson succeeded in obtaining transformation in the test tube [5]. Another Avery associate, J. Lionel Alloway, added the important step of showing that a soluble extract of an encapsulated pneumococcus was capable of inducing transformation of an unencapsulated strain derived from a different type [6].

Thus, by 1934, the possibility of determining the chemical nature of the transforming substance clearly existed, and Avery certainly considered this the real goal of future work, just as he had in the case of the soluble specific substance. However, it proved a much more difficult task than it appeared to be, and resisted all efforts for a considerable period of time. Colin MacLeod joined the laboratory in 1934 and made several advances in the research, but was so short of the goal after three years that it was necessary to turn to

other studies. In the fall of 1940, Avery and MacLeod together returned to a renewed attack on the problem, and again new information was added during the year that still left unresolved questions. Then in the summer of 1941, MacLeod left to become head of microbiology at the New York University School of Medicine. It was my good fortune to arrive at Rockefeller as a new post-doctoral fellow in the Avery lab in September 1941 and to join him in a continuation of these studies that culminated in 1944 in the report that the transforming substance was DNA [7].

Sometime during the fall of 1941, I became aware that I had arrived in the year that Avery was President of the Society of American Bacteriologists (SAB)<sup>b</sup>. This was because he frequently remained in his office working on his presidential address. I attended the SAB meeting, which was held in Baltimore in the week between Christmas and New Years, and heard the address and its warm reception. It was never published because Avery had developed a strong distaste for publishing his general talks of this kind, and the typescript would have been lost because he had all of his files destroyed when he left Rockefeller in 1948. However, Rene Dubos had in some way managed to rescue it from a wastebasket, and he reproduced one page in his 1976 book on Avery, *The Professor, the Institute, and DNA* [8], in order to illustrate his use of penciled notations to indicate the manner in which the talk was presented (e.g., the emphases and inflections), a practice that dated back to Avery's interest in oratory during his college days at Colgate.

The title of his address was "The Commonwealth of Science" and began with the development of the thesis that, as he put it, "microbiology from its very beginning became intimately linked with chemistry, physiology, and medicine." He proceeded with a variety of examples and quotations and arrived at the conclusion

that "Complete freedom of scientific thought, and the free interchange of knowledge are prerequisites for the survival of the spirit of inquiry. They are to the Commonwealth of Science what the Bill of Rights is to the life of Democracy." At the close he added quotes from a "Declaration of Scientific Principles" that had recently been presented by Sir Richard Gregory at the conference in war-torn London and from Pasteur's address at the founding of the Pasteur Institute in 1888. The focus of the Avery talk is perhaps a little blurred, but it was well-received by his audience three weeks after Pearl Harbor.

### REBECCA CRAIGHILL LANCEFIELD

One of the rare deviations from Avery's concentration on pneumococcal research had occurred some 23 years earlier during World War I. In February 1918, he and Dochez had been sent to Fort Sam Houston in San Antonio, Texas on contract from the U.S. Army to consult on an epidemic of streptococcal infections associated with measles among recruits. They returned to New York in late March with a large collection of cultures of streptococci and began attempts to further characterize them. At a conference on *Streptococcus hemolyticus* held on June 1, 1918, they reported that they had not yet been able to determine whether they were all alike or whether they constituted one or several types. They had not obtained immune serum that could protect against infection of mice with the organisms. Shortly thereafter a young woman who had just received her master's degree at Columbia University, Rebecca C. Lancefield, was brought in as a technical assistant to work with them on this problem.

There was no way one could have known at this time that this project would be her cup of tea, but it became clear that this was a case of bringing the right person to the right place at the right time. Within

less than a year, they had identified four distinct serological types, as determined both by agglutination and mouse protection, that served to classify 70 percent of the 125 strains under study. An extensive paper describing these results was submitted for publication in the *Journal of Experimental Medicine* on June 1, 1919 [9]. That Lancefield had contributed more than simply technical help was acknowledged by her inclusion as an author of the paper, a type of recognition seldom accorded to technical assistants in those days.

Lancefield returned to Columbia University at this point but came back to Rockefeller in 1922 to join the recently established laboratory devoted to the study of streptococcal infections and rheumatic fever under the direction of Homer F. Swift. This new laboratory shared the sixth floor of the Hospital with that of Avery, so that she had an opportunity to resume frequent contact with him. Initially, her research was concerned with the viridans streptococci, which had erroneously been suspected of having something to do with rheumatic fever, and these studies formed the basis for her thesis for her Ph.D. from Columbia University. By 1925, however, she was able to resume her work on hemolytic streptococci, thus initiating the remarkably productive attack on the nature of these organisms that continued for over 50 years. The fruits of this sustained effort were widely recognized, and today both the national and international societies concerned with streptococci and streptococcal infections are named The Lancefield Society.

I will not attempt to summarize here her research that led to major advances in our understanding of these organisms. It is important to realize that the relationship of hemolytic streptococci to human disease was not well characterized in the early 1920s. They tended to be considered as secondary invaders, and the prevalence of primary streptococcal sore throat and even

their key role in scarlet fever was not generally recognized. There was even less of a clue with regard to their implication in the pathogenesis of rheumatic fever and glomerulonephritis. The systematic classification that emerged from her serological grouping and typing of streptococci provided a basis for a better understanding of streptococcal pathogenesis. Her discovery that the type-specific antigen of group A streptococci, the principal human pathogen, was a protein came as a surprise. She was able to show that the M-protein had the same relation to the virulence of the organism as the capsular polysaccharide in pneumococci. The group-specific antigens, on other hand, were carbohydrate in nature, and were later shown to be major components of the bacterial cell wall. In the case of group B streptococci, initially identified as bovine in origin but found to be important in human puerperal and neonatal infections, the type-specific antigens were found to be capsular polysaccharides as in pneumococci.

Work on the various antigens and their pathogenic significance continued through the 1930s, and in 1941 Lancefield summarized her findings in her Harvey Lecture, entitled "Specific Relationship of Cell Composition to Biological Activity of Hemolytic Streptococci" [10]. This was the first Harvey Lecture that I had attended, and I had already become acquainted with Lancefield as result of the proximity of our laboratories. I was not aware, however, of her activities as president of the SAB in 1943. I knew that she was extremely busy providing antisera and other materials for streptococcal identification in military laboratories. Because of the war, there was no meeting of the SAB that year, and she did not prepare a presidential address. I suspect she was relieved not to be required to find time to prepare a general talk of this kind under the circumstances. Just after the end of the war in 1946, Homer Swift became emeritus, and

I was offered the position to replace him as head of the rheumatic fever service. I accepted the appointment, and Becca Lancefield and I were colleagues and co-workers for the next 35 years until her death in 1981. Her devotion to streptococcal research never flagged, and she continued to provide invaluable help and sage advice to a host of workers in the field.

## RENE JULES DUBOS

We will turn back now to the mid-1920s, at the time that Avery was concerned with the doubts that had been expressed about the polysaccharide nature of the soluble specific substance. He conceived the idea of finding an enzyme that would specifically break down the polysaccharide with loss of antigenicity, and he had tried of variety of possible sources of such an enzyme without success. He was still thinking of this in 1927 when a young French soil microbiologist, Rene J. Dubos, who had just received his Ph.D. with Selman Waksman at Rutgers came to Rockefeller to visit his countryman, Alexis Carrel. Avery met Dubos in the famous lunchroom of that period, and they began discussions that were continued after lunch and covered both Dubos's work on the products of soil bacteria and Avery's pneumococcal studies. In the course of these interchanges, Dubos indicated that he considered it possible to find enzymes produced by soil bacteria that would degrade pneumococcal polysaccharides. Avery was impressed and soon thereafter took the steps necessary for Dubos to be offered a place in his laboratory. As a result, in the fall of 1927 Dubos arrived at Rockefeller, where he spent most of the rest of his active life in science.

He began by becoming familiar with the pneumococcus and at the same time tackling the problem of finding soil organisms that would produce enzymes active on the polysaccharides. He used the type

III pneumococcal polysaccharide as his model, trying soil samples from a variety of sources. The task proved somewhat difficult, but in the end he found an organism in soil from a cranberry bog that when grown with the polysaccharide as the principle source of carbohydrate was induced to produce an enzyme that degraded it. The enzyme digested the type III polysaccharide to its disaccharide repeating units with total loss of ability to precipitate with type-specific antisera. In addition, the enzyme was as effective as specific antibody in protecting mice against lethal infection with the organism [11]. There was no longer room for doubt about the role of the capsular polysaccharides.

The continued work of Dubos on soil organisms with special properties led to the discovery in the 1930s of the antibiotics, gramicidin and tyrothricine, a notable contribution to the dawn of the antibiotic age. The range of his interests and work continued to expand with time, changing dramatically to a study of tuberculosis on his return to Rockefeller after a two year stint at Harvard as head of the Department of Comparative Pathology and Tropical Medicine. He also became a prolific writer, beginning with his book *The Bacterial Cell* in 1945 [12] that was followed over the years with twenty-odd other volumes on a variety of subjects, including three on Pasteur and one on Avery. In his latter years, he became an environmentalist, reflected in his later books and in the establishment of the Rene Dubos Center for Human Environments.

In 1948, Dubos delivered the Oswald T. Avery Lecture at the meeting of the SAB, and it was published in *Bacteriological Reviews* in expanded form and under the title "Cellular Structures and Functions concerned in Parasitism" [13]. This was clearly a tribute to Avery and designed, as he put it, "to strive for a better understanding of the manner in which Dr. Avery's work has altered the course of our science

and is now affecting many of our efforts and viewpoints." To achieve this he provided a review of the developments from the Avery laboratory and other groups, as well as his own recent studies on tuberculosis. It provides an interesting treatment of the subject, and I had totally forgotten it and the fact that there was an O.T. Avery Lecture until I recently encountered a reprint of the paper in Dr. Lancefield's collection.

It would appear that Dubos took a more active role in the affairs of the SAB during his presidency in 1952 than had either Avery or Lancefield. At least, I have more evidence for it. For example, in the Society's News Letter in April, 1952 the lead item is "A Message from President Dubos," which he presents as a progress report on his education regarding the complexity of the problems facing the membership. He proceeds to discuss some of these problems and his current views on them, and concludes by inviting criticism, advice and help from the membership. Although he dated this message February, 1952, it appeared only shortly before the annual meeting of the Society in Boston, April 27-May 1, where he was scheduled to present his presidential address at the annual banquet.

The address, which appeared in a modified form in the September, 1952 issue of *Bacteriological Reviews* [14], strikes me as a rather curious piece for Dubos. It was titled "Microbiology in Fable and Art," and begins with the premise that "Alone of the biological sciences, microbiology at first sight appears to be without a remote and fanciful past." He then proposes to show that "the lore of primitive civilizations, the poems, novels, drama and arts of all times yield much material that microbiology can legitimately claim as belonging to its past." He proceeds to provide a number of examples of this from various stages of past history. He then moves to the impact of epidemics,

such as plague and the Black Death, now known to be of microbial origin, on the literature and arts of the period. Naturally, he also touched upon his current interest in tuberculosis, noting its responsibility for the death of large numbers of young people during the 19th century, including talented writers like the Brontë sisters.

At the end he turns to his soil microbiology roots by noting the crucial role that microorganisms play in the "cycle of life" by degrading complex organic molecules to the inorganic state, thus preparing them to again become available to plants. It was clearly a somewhat diverse message. Unfortunately, this is one of the many SAB meetings that I did not attend, and so I cannot report on the reception by the audience, as I did in the case of Avery's address.

### THOMAS MILTON RIVERS

I have selected this trio of Avery, Lancefield and Dubos for presentation as the Rockefeller Connection because of their close inter-relationships. This is not quite the complete story on SAB presidents from Rockefeller, however, since there was an earlier one in 1936, Thomas M. Rivers. Rivers had been brought from Johns Hopkins to the Rockefeller Hospital by Rufus Cole to initiate studies on viral disease. He progressed rapidly and was invited to organize a symposium on viruses at the 1926 meeting of the SAB. His talk at this time included the following famous defining statement that influenced the future of virus research: "Viruses appear to be obligate parasites in the sense that their reproduction is dependent on living cells." This had not been clearly understood up to that time [15].

Rivers succeeded Cole as director of the hospital in 1937 and was thus in charge during the period of the presidencies of the three that I have discussed. There is ample evidence that he had a high regard for their

research abilities, and I will close with one example of this. Rivers had had the foresight to organize a Naval Reserve Medical Research Center in the hospital as the clouds of World War II began to gather. It was called to active duty in March 1942, with the hospital devoted to clinical problems of naval recruits and Rivers in charge with the rank of Commander. Much of the rest of the staff were included as junior officers. Thus, in the spring of 1942 in the midst of the exciting developments in the work on pneumococcal transformation with Avery, I found myself in uniform as a Naval Lieutenant, junior grade. I had no desire to give up my research activity, but my conscience plagued me about not being involved in studies more directly related to the war effort. When I went to Rivers with this problem, suggesting that maybe I should join one of the other units, his response was immediate: "No, you keep on working with Fess. That study is too important to drop. You don't have to worry about it." He was well aware of what was going on. In the end, I was to spend four more years as a naval officer working on pneumococcal transformation and was kept from "worrying about it" by the excitement generated by the accumulating evidence that the transforming substance was DNA [16].

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