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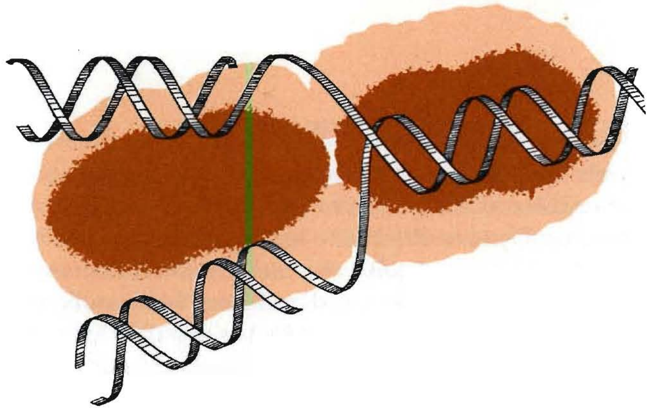


THE ROCKEFELLER UNIVERSITY

RESEARCH PROFILES

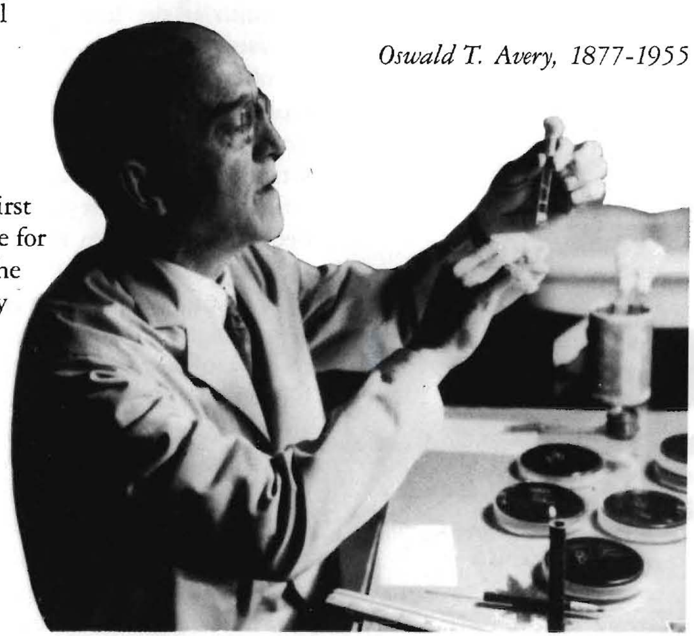
SPRING 1988

Oswald Avery and the Sugar-coated Microbe

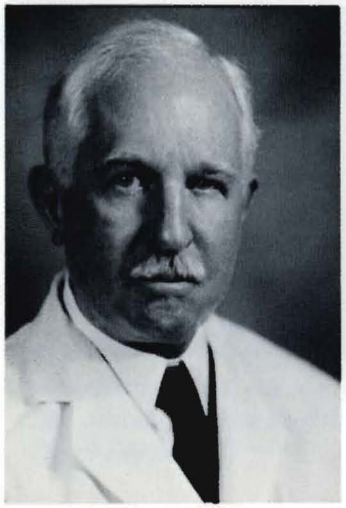
When, in 1910, Director Rufus Cole and his small staff of scientists at the newly opened hospital of The Rockefeller Institute for Medical Research picked their first targets for study, the list included poliomyelitis, syphilis, heart disease, and lobar pneumonia. Dr. Cole chose lobar pneumonia, the greatest killer of all, as his special problem. At the time, medicine had no specific weapon with which to fight this "captain of the men of death," as it was called. Its bacterial agent, pneumococcus, inflamed the lungs, blocking respiration, and released toxins damaging to the heart. About all physicians could do was provide supportive care for their patients until the inevitable life or death "crisis" (melodramatically portrayed in early movies). More than twenty percent of those patients—fifty thousand a year in the United States—succumbed to the invading organism.

Cole's objective was to develop a therapeutic "serum" against the pneumococcus by inoculating horses with increasing quantities of the microbes to stimulate production of antibodies capable of arresting the disease when injected in human patients. Such a method had been used by Emil von Behring in Germany in his successful search for a protective serum against diphtheria. Simon Flexner, at The Rockefeller Institute, had, in the same way, scored a partial victory over epidemic cerebrospinal meningitis.

It was a time when infectious diseases commanded major medical attention, and microbiology grew in glamour as it promised to track down and control the germs that caused them. The Rockefeller Institute was established in 1901, and its hospital nine years later, to be the standard bearers of medical science in America. This, in the minds of the founders, meant primarily the investigation of infectious diseases. But Simon Flexner, the Institute's first director, anticipated a broader scope for the fledgling research center when he stressed the crucial role of chemistry in biology and medicine. Oswald Avery, soon to join Rufus Cole's group, would amply prove Flexner's point. Cole and his co-workers shared the hope that the pneumococcus could be mastered in the same way that a number of other virulent bacteria already had been. But they soon ran into



Oswald T. Avery, 1877-1955



Rufus Cole, first director of The Rockefeller Institute Hospital.

problems, the main one being the variety of pneumococcal strains. As scientists abroad had discovered, these strains differed in their deadliness. The Rockefeller team also found that the strains were different enough chemically to elicit somewhat different antibodies in their victims. Each of the three most common types of pneumococcus would require a different serum. By the end of 1912, the Cole group had developed a serum for use against type I, and they also had developed a procedure, using laboratory mice, for determining what type of pneumonia microbe was infecting a patient. But Cole realized that further progress depended on an analysis of the slight chemical differences between the pneumococcal strains. The researcher for such a project would need a broad knowledge of bacteriology and immunology and a talent for chemical studies.

Cole took a drive to the Hoagland Laboratory, in Brooklyn, to see Oswald Avery, a bacteriologist then working with cultures of pneumococcus. A paper by Avery on secondary infection in tuberculosis patients had caught his attention because it demonstrated the ability to carry out a systematic clinical investigation. Cole came away from the meeting convinced that he had found his man. A few days later, Avery was invited to lunch at the Institute with Dr. Flexner and, shortly after, received a letter from Cole offering him a position as bacteriologist to The Rockefeller Institute Hospital. There was no reply. Cole wrote a second letter and, when it, too, went unanswered, drove again to Brooklyn to make Avery a more attractive offer. He learned that Avery had ignored the initial offer not because it was financially inadequate, but simply because he had been too busy to respond.

Today Avery might be described as a late bloomer in science. He came to the Institute at the age of thirty-six with a record of thorough and diversified research and a competency sufficient to gain the respect of men like Cole and Flexner. But as Avery's biographer and colleague René Dubos* points out, he was almost forty before he hit his stride as a creative scientist who, in the quarter century that followed, was to quietly and persistently make a unique series of major contributions to biomedical science. This career was capped, when Avery was sixty-seven, by the identification of DNA as the substance of the genes, a discovery that opened up a new epoch in biology and turned an ulgy duckling of a molecule into a swan.

"BABE" BECOMES "FESS"

Friends and family of the young Avery probably would not have predicted a life in science for him. Born in Halifax, Nova Scotia, on October 21, 1877, he was ten years old when his father, Joseph F. Avery, a Baptist minister, received an invitation to be pastor of a mission church at Henry Street on New York's lower East Side, a neighborhood Dubos describes as "a melting pot of sin" with, as Avery's mother, Elizabeth, put it, "people, people everywhere." In the midst of the poverty and squalor of the Bowery, the family was buoyed by the support of the city's closely knit Baptist community and made the Mariners' Temple a busy center of religious and social activities.

John D. Rockefeller, whose philanthropy was to create The Rockefeller Institute, was deeply involved in the programs of the Baptist church and frequently contributed to the Mariners' Temple. A more personal note is struck in a letter of December 30, 1890 from Mr. Rockefeller to the Reverend Avery enclosing a Christmas check for fifty dollars and inviting the Averys to join the Rockefellers at their house on 54th Street for ice skating in the backyard. "You will find an entrance on either side to the house," wrote the richest man in the country. "Put your hand through the gate and pull the bolt."

Oswald and his older brother, Ernest, were to be seen on Sunday afternoons playing their cornets on the steps of the Mariners' Temple to attract worshipers. Their proficiency eventually won them scholarships to the National Conservatory of Music, but the duo was sundered by Ernest's death in 1892, the same year in which their father died. Mrs. Avery went to work for the Baptist City Mission Society. Oswald continued alone as church musician with two new responsibilities: man of the family and surrogate father to his younger brother, Roy.

In 1893, Oswald left the sidewalks of New York for the upstate village of Hamilton to enter Colgate Academy. Three years later he enrolled in Colgate University. "Babe," as his classmates dubbed him, became leader of the band, distinguished himself in oratorical contests, and made excellent grades. He was graduated with a major in the humanities. In science, he had taken only the few basic courses that were compulsory.

**The Professor, The Institute, and DNA,* The Rockefeller University Press, 1976.

What moved him to choose medicine as a profession is not clear. Dubos suggests one reason may have been that "medicine provided him with an outlet compatible with his familial missionary background." Noting also that the Reverend Frederick Gates had recently advised Mr. Rockefeller to put some of his fortune behind medical research, Dubos concludes: "Medicine apparently fitted well into the mood of the Baptist community at that time."

Avery was admitted to Columbia University's College of Physicians and Surgeons— the science entrance requirements were minimal—and got his degree in 1904. His career as a practicing physician lasted only about three years and reflects the state of medicine at the time. Although he got on well with his patients, he was frustrated at being able to do so little for people suffering from serious diseases. He made a complete break with clinical practice when he was appointed associate director of the Hoagland Laboratory, where he learned scientific techniques and the chemical approach to research.

Student nurses whom Avery taught at the laboratory nicknamed him "The Professor." At Rockefeller, "The Professor" became "Fess" to close associates. His practice of teaching by conversation reached its peak in the "Red Seal Records," so called by his colleagues because of his beautifully planned and delivered explanations of his research.

THE CAPSULE WAS THE CULPRIT

The problem of Avery's lifetime was, in the words of colleague Rollin Hotchkiss, "that little gram-positive coccus, which he felt presented in small compass most of the basic questions of biology." The source of the pneumococcus's virulence was unknown when Avery, installed by Cole in a laboratory made over from a disused ward kitchen, joined forces with pathologist Alphonse Dochez, with whom he would also share an apartment for many years. Their "midnight dialogues," as Dubos calls them, turned many evenings at home into spirited and creative exchanges of scientific ideas.

One of their most significant discoveries was the role played in disease by the coating or capsule of clear gelatinous material that encloses virulent pneumococci. Scientists had suspected some association but it had not been investigated. Dochez and Avery made their first step in this direction in 1917 when they found a substance in culture fluids of pneumococcus, filtered to remove bacteria, that reacted to pneumococcal antisera in a type-specific manner. That is to say, culture fluids in which type I pneumococci had grown would react only with type I antisera, type II cultures with type II antisera, and so on.

Further research showed that this substance, which they called "specific soluble substance," or SSS for short, was present in the urine of pneumonia patients. Knowing this, it was possible to diagnose the pneumococcus involved by a urine test when a patient entered the hospital. Meanwhile, as evidence accumulated that the pneumococcal capsule was essential for virulence—bacteria that had lost their coats in culture could not infect—Avery had discovered that SSS was present in the capsules.

In the midst of the laboratory's other studies, including the development of a serum therapy for pneumonia which remained the only therapy available until the advent of antibiotics, Avery continued his quest for the chemical nature of SSS. Frustrated, he sought help from Michael Heidelberger, a young chemist in another laboratory. Busy with a project for his own lab leader, Heidelberger kept Avery waiting. Meeting Heidelberger in the corridor, Avery would hold up a small vial of brownish powder and ask, "When can you work on this, Michael? The whole secret of specificity is in the vial."

By 1922, Heidelberger was ready and the two went to work extracting the chemical ingredients of the capsule and testing them for their immunological reactions. They found that chemical differences in the capsular substances of the types of pneumococcus were responsible for differences in the microbes' virulence and the specific antibodies they induced in the patient. The capsule was the culprit, but what was it made of?

The answer was a surprise. When Avery and Heidelberger analyzed the specific substances of the capsules they turned out to be polysaccharides, complex structures of linked sugar molecules. Hence, Avery's nickname for the virulent pneumococcus—"the sugar-coated microbe." Because up to that time it was generally assumed that only proteins could incite an immune response in a host, the discovery met with considerable skepticism. Then the finding was carried a step further by Walther F. Goebel, who joined the Avery group in

Avery family with Oswald, front left, at around nine years old.

"Babe," front center, with the Colgate University band.

"Fess" and his laboratory group, circa 1932, with Walther Goebel, seated far right, and René Dubos, standing third from left.

Colin MacLeod, left, and Maclyn McCarty at the dedication of the Avery gate in 1965.

1925. Goebel split the immense polysaccharides—literally "many sugars"—into the simple sugars of which they were composed, and showed that the specificity of a given pneumococcal strain depended upon whatever set of sugars formed its capsule.

The volume and range of Avery's scientific output increased rapidly. Only vacations at Deer Island, in Maine, where he became an ardent sailor, interrupted his laboratory routine. When alone, associates recall, he moved about slowly whistling the plaintive shepherd's song from Tristan and Isolde. Although immensely popular, he rarely accepted any of the social invitations he received. He hardly ever traveled, even to accept the many awards that marked his achievements.

DNA—THE LONG SHOT

The research that led to Avery's greatest discovery had its roots in work reported in 1928 by Frederick Griffith, a medical officer in the Ministry of Health in London, who claimed that pneumococci might lose their polysaccharides and then be induced to switch types under special circumstances. Griffith had observed that when mice were injected with a mixture of live bacteria that had lost their capsules, and were therefore harmless, together with heat-killed virulent pneumococci of a different type, the animals died of the infection. The pneumococci recovered from the mice's blood were now the same type as the heat-killed organisms.

Griffith was a well-established investigator with a reputation for care in experimentation. Nonetheless his description of pneumococcal "transformation," the term applied to this switch in immune specificity, strained the belief of other investigators, including Avery. The accepted view was that descendants from one type of pneumococcus always remained true to type. Avery changed his mind when Griffith's findings were later duplicated by other scientists, including members of his own laboratory. What followed was a decade of research aimed at identifying the transforming substance responsible for transmissible changes in the immunological specificity of pneumococci.

The work got off to a slow start. Avery was sidelined for months by thyroid surgery, and throughout a good deal of the period there was the press of other projects. Above all, there were enormous technical difficulties. Several colleagues recall Avery's backward-looking observation: "Many are the times we were ready to throw the whole thing out the window." Indispensible to the ultimate success of the research were the contributions of two brilliant young collaborators, Colin M. MacLeod and Maclyn McCarty.

Finally, in 1944, Avery, MacLeod, and McCarty published in the *Journal of Experimental Medicine* what is now considered one of the landmark papers in the history of biological science, "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III." The meaning? The agent of transformation in pneumococcal types is what is now called deoxyribonucleic acid: DNA. The inference, which Avery and his team clearly understood and which subsequent research (most importantly by Rollin Hotchkiss) confirmed, was that the agent of transformation was the genetic material. In other words, the genes of pneumococcus were made of DNA.

Today, when DNA has become a household word, it is difficult to imagine the impact of the paper. DNA was a very long shot as a candidate for genetic honors. Proteins, more complex and more intricately folded molecules, were the favorites. Avery and his colleagues faced considerable challenge. Like Griffith's, their experimental methods and chemical analyses were suspected of flaws. Dr. McCarty has told the story in fascinating detail in his book, *The Transforming Principle,* written in part in his Rockefeller office where the laboratory notebooks from the climactic years of the DNA research are lined up on a shelf behind his desk. The memoir is dedicated to "Oswald Theodore Avery, who was not inclined to write such a book, and Colin Munro MacLeod, who ran out of time before he could do it."

Avery retired in 1943 and later went to Nashville, Tennessee, to live near his brother Roy, who taught bacteriology at Vanderbilt University, and his family. He died of cancer on February 20, 1955.

At the northwest corner of the Rockefeller campus a granite gateway had been erected in his name—a somewhat massive memorial for someone who never weighed much more than a hundred pounds, but a fitting one for the scientist who opened the way to a new biology. □

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