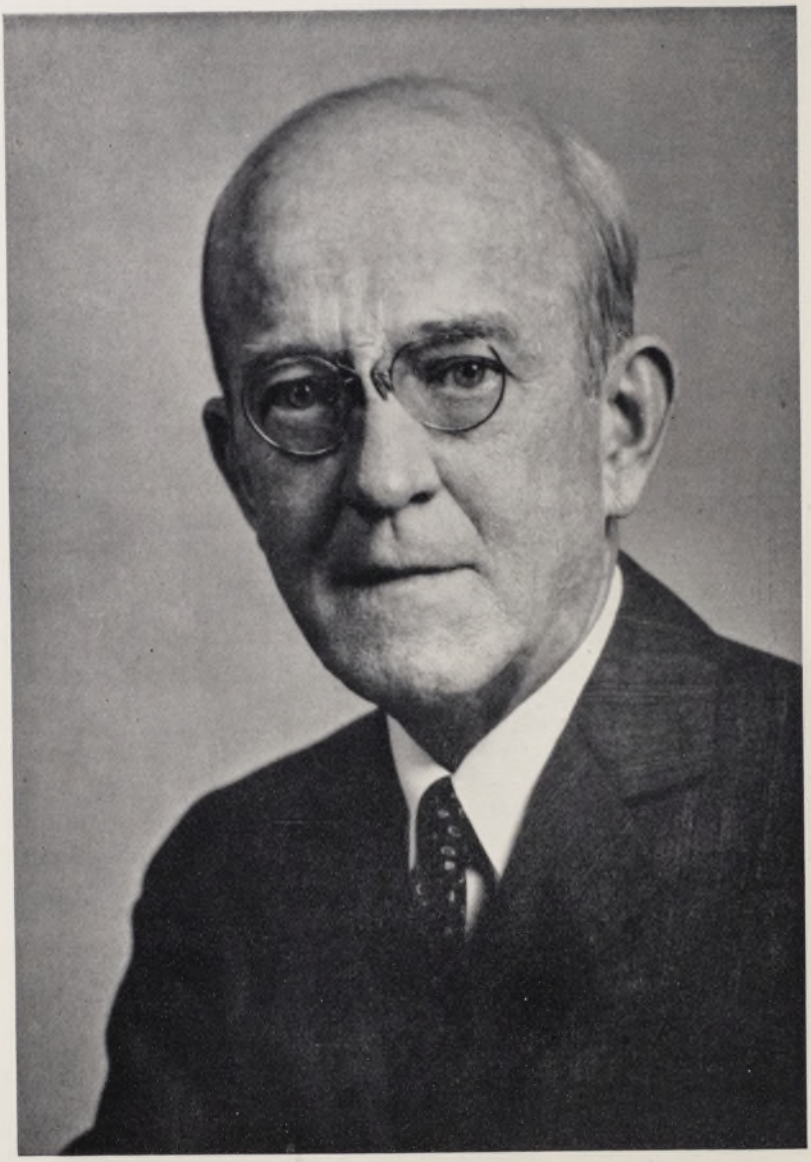

OSWALD THEODORE AVERY

1877-1955

Oswald Theodore Avery, Emeritus Member of the Rockefeller Institute for Medical Research, died in Nashville, Tennessee, on 20 February 1955 at the age of 78. His name calls to mind a slender, affable, neatly dressed man with large brilliant eyes and a smile of welcome. Very early in his career Avery came to be known as 'The Professor'—or more familiarly 'Fess'—and he retained this nickname throughout his life even though he eventually gave up lecturing almost entirely. He was indeed 'The Professor' by virtue of his gentle wisdom in counsel and of his art as an expositor of science—always spicing his performance with mimicry, pithy remarks, picturesque analogies and verbal pyrotechnics.

The appellation 'The Professor' symbolizes the extroverted, engaging aspect of Avery's personality, which made any contact with him such an enjoyable and rewarding experience. To a few of us who saw him in everyday life, however, there was often revealed another aspect of his personality, less obviously pleasurable but with a more haunting quality. We remember a brooding forehead that appeared too heavy for the frail body, a gaze focused inwardly as if unconcerned with the surrounding world, a melancholy figure whistling gently to himself the lonely tune of the shepherd song in 'Tristan and Isolde'. Avery's response to the demands of society was made up of these two conflicting attitudes. The telephone would ring announcing a visitor, or bringing an invitation to some social gathering. The reaction was immediately one of joyful acceptance, or of profuse regrets couched in the most flattering language in case of refusal. Then, as the conversation ended, the smiling mask was suddenly dropped. From behind it appeared a tired and almost tortured expression. The telephone was pushed away on the desk as a symbol of lassitude and of protest against the encroaching world.

An acute need for privacy, even if it had to be bought at the cost of loneliness, conditioned much of Avery's behaviour. He hardly ever spoke of his private life, or of his past, unless the events had some bearing on his scientific activities. His conviction that scholarly achievements should be evaluated on their own merit, without concern for the personal affairs of the scholar, was reflected in the obituary notice that he published in 1944 on the occasion of K. Landsteiner's death. The editor of the journal in which the notice was to be published requested that the account be supplemented with details of Landsteiner's personal and family life, but Avery firmly refused with the statement that these details would not contribute to the understanding of

either the achievements or the mental processes of the scientist. The same view had once been expressed by Claude Bernard 'A great man is not great when he goes to bed, gets up, sneezes, etc, but only when he writes, thinks . . . It is in these moments that . . . we can reach him through his works. We had better ignore the rest; it does not add anything to the man.' I shall respect this attitude and present only the barest outline of Avery's private life.

Avery was born on 21 October 1877 in Halifax, Nova Scotia. His father, a clergyman, moved in 1887 to New York City where he undertook missionary work in the Bowery. Although Avery did not become a U.S. citizen until 1917, his entire life from the age of 10 to 70 was spent in New York. He attended Colgate University from which he received an A.B. degree in 1900. He concluded his formal medical education at the College of Physicians and Surgeons of Columbia University in 1904. After early work in bacteriology, at the Hoagland Laboratory in Brooklyn, he joined the Rockefeller Institute in 1913, and was appointed to full membership of this Institute in 1923. After becoming Member Emeritus in 1943, he continued his research at the Rockefeller Institute for five years, then retired from active work to Nashville where he joined his only brother, Roy Avery, Professor of Bacteriology at Vanderbilt University Medical School.

Avery was richly endowed with many intellectual gifts. In his early youth he had been much interested in music and had become proficient with the trumpet. Indeed he once played in a concert given by the National Conservatory of Music of New York under the direction of Antonin Dvorak. He had also talent as a draughtsman. Several ink caricatures that he made—especially those of himself—had pictorial beauty in their simple but strong design, and revealed much psychological insight. He turned his skill later to landscape painting in water colour.

Throughout his life Avery displayed an extraordinary ability to express himself with words. While in college at Colgate he had been selected as the runner-up for the valedictorian address—his competitor was Harry E. Fosdick who eventually became one of America's most eloquent preachers. When in a playful mood in later years, Avery was wont to declaim with obvious pleasure some of the sonorous sentences on Chinese history that he had prepared for the college oration. It was a few years later during the Hoagland laboratory days that his success as a lecturer won him the appellation 'The Professor'. However, he lectured but rarely after he joined the Rockefeller Institute, but each address was a matchless performance, prepared with infinite care and delivered with much force. Each emphasis, each nuance was indicated in the manuscript of the lecture and all inflexions of voice were tried repeatedly beforehand, using the laboratory staff as a sounding board. Although reluctant to speak in public—almost coquettishly so—he was always willing and even eager to engage in conversations with either friend, collaborator or stranger. More often than not, the conversation

evolved into a monologue in which each statement, each word, indeed each hesitation, was carefully weighed and staged. The marvellous precision of the performance was not achieved by accident. Endless rehearsals assured the perfection of conversation pieces that most of us came to know by heart and referred to as 'the Red Seal Records'.

Avery was even more of a purist in the writing of his scientific publications. Each statement was the subject of much thought and discussion—as to content, form and implications. The style became rather impersonal because so laboured and polished, but it achieved by that very token a classical character of austere objectivity.

With all these gifts, it is clear that Avery could have achieved success in many different types of intellectual activity, but he made an early choice. With extraordinary singleness of purpose he devoted all his energy and talents to the problems of medical microbiology and of the pathogenesis of infectious disease.

Upon graduating from medical school Avery served for a few months as a substitute in a Park Avenue medical office. From all accounts—including his own—he was very successful in his dealings with patients but found nevertheless little pleasure in the practice of medicine. Fortunately, medical America was then becoming research conscious. Sir Almroth Wright had just been lecturing in the U.S.A. and had stimulated interest in the relation between phagocytic index and susceptibility to infection. As a result of his visit, a small research fund was established for the study of the phagocytic index in respiratory disease and this provided Avery with an opportunity to enter research in this field.

A more permanent position was offered to him a year later at the Hoagland laboratory in Brooklyn—the first institute privately endowed in the U.S.A. for bacteriological research. The director of the laboratory was Benjamin White who on his retirement was to write a lengthy monograph *The biology of the pneumococcus*, which constitutes a monument to Avery's own investigations. Alone or in association with Ben White, Avery published from the Hoagland laboratory a number of papers on several problems of bacteriology and immunity. These studies were scholarly in approach, thorough in execution, but they exhibited little originality and can be regarded as merely the products of a self-training period. One of them, however, deserves some mention as belonging to a type of systematic clinical testing, very different from the more imaginative studies that were soon to follow. Ben White, having developed tuberculosis, went to take the cure at the Trudeau Sanatorium. Avery accompanied him on the initial trip and later spent several periods of vacation at the sanatorium. This experience naturally stimulated in him an interest in tuberculosis; several of his notebooks of the time are full of extensive and carefully written analyses of the current publications on the experimental and clinical aspects of the disease. While vacationing at the Trudeau sanatorium, Avery carried out 100 consecutive

blood cultures of patients in the active phase of the disease without ever recovering tubercle bacilli or observing evidence of secondary infection. This experience demonstrated his ability to carry out a systematic clinical study. But routine work was not his bent and circumstances fortunately soon gave him the occasion to display his imaginative talents.

In 1913, Avery was appointed as bacteriologist to the Rockefeller Institute Hospital. Since lobar pneumonia was then one of the most active fields of investigation at the hospital, he joined with A. Dochez who had undertaken an investigation of the types of pneumococci present in pneumonic patients and in carriers. An important outcome of this co-operative program was the discovery of specific soluble substances of pneumococcus origin in the blood and urine during lobar pneumonia. Thus began a collaboration which persisted in an informal but highly creative form even after Dochez left the Rockefeller Institute. The two men shared a bachelor's apartment thereafter and apparently never tired of discussing night after night problems of etiology and pathogenesis. It would demand much psychological perspicacity to delineate the respective contributions of each participant in these midnight dialogues which had so much influence on the evolution of medical microbiology.

The volume and range of Avery's scientific activities increased rapidly during the following years and it would be confusing to describe them chronologically. Instead I shall outline his contributions under several categories, even though they were closely related in his mind, and were often made almost simultaneously. In this presentation, I shall omit the names of the many distinguished scientists who collaborated in the different projects. For, whatever the importance of their individual contributions, it was Avery who provided for a period of 30 years the guiding hand and the driving force of his department.

First to be considered of course are the studies on the role played by capsular polysaccharides in determining the immunological specificity and virulence of pneumococci. In brief, the findings of his department can be summarized as follows:

There exists a definite correlation between the virulence of pneumococci and their possession of a capsule detectable by microscopic and immunochemical techniques.

The non-capsulated variants are more rapidly killed than the capsulated forms, both *in vivo* in the normal animal, and *in vitro* in mixtures of normal serum and leucocytes. The capsule participates in virulence by increasing the resistance of the bacteria to phagocytosis.

Encapsulated pneumococci can be separated into several different serological types by virtue of chemical differences in their capsular substances. All these are polysaccharidic in nature.

Specific antibodies directed against the capsular polysaccharides protect against infection by neutralizing the ability of the capsules to interfere with phagocytosis.

Although the reactive groupings responsible for immunological specificity of the capsular polysaccharides can survive many types of chemical and enzymatic treatment, the antigenic effectiveness of the complex polysaccharide antigen is far less stable. In other words, the ability of capsulated pneumococci to elicit the production of antibodies protective against infection is optimum only when the bacteria used for immunization are prepared by techniques which maintain the antigenic integrity of the capsular material.

Immunization with pneumococci elicits the production of many antibodies directed against components of the bacterial cell other than the capsular substance (other polysaccharides, proteins, etc.). These non-capsular antibodies, however, have little if any ability to protect against infection although they may play a part in certain pathological processes, for example in those caused by allergic reactions to bacterial products.

Parallel studies carried out under Avery's influence at the Rockefeller Institute Hospital demonstrated that a similar pattern of relation of capsular polysaccharide to immunological specificity and virulence obtains also in the case of *Klebsiella pneumoniae* and *Hemophilus influenzae*. Further evidence of the relationship—if any was needed—was furnished by the demonstration that an enzyme extracted from a soil micro-organism which hydrolyzed *in vitro* the capsular polysaccharide of type III pneumococci was also capable of destroying *in vivo* the capsule of these organisms and could thereby protect mice, rabbits and monkeys against experimental infection.

The results of the studies on capsular polysaccharides soon yielded practical applications. They permitted the development of exquisitely sensitive and specific diagnostic procedures *in vitro* (serological typing) and *in vivo* (skin test for the demonstration of circulating antibody). They also guided the preparation of immunizing antigens, and of therapeutic sera, which proved their worth in practice.

Needless to say, these discoveries focused attention on the hitherto unrecognized immunological activity of polysaccharides. Fortunately, Karl Landsteiner was at that time carrying out his classical immunochemical studies at the Rockefeller Institute. His techniques were applied in Avery's laboratory to the synthesis of antigens in which polysaccharides or simple sugars were the determinant antigenic groups. A spectacular outcome of these studies was the production of a synthetic antigen which conferred to experimental animals a definite degree of protective immunity against certain pneumococcus infections.

The significance of all these discoveries can be discussed from several different points of view. For many workers, the most original contribution made by Avery was the demonstration that the role played by complex carbohydrates in various immunological processes is at least as important as that classically attributed to proteins. Of less obvious, but perhaps greater interest was the recognition that virulence and immunity can be analyzed apart from the parasite cell as a whole, in terms of some highly specialized cellular component. In the pneumococci, the important structure was found

to be the capsule, made up of polysaccharide; in other microbial species it might be some other cellular structure, with a different chemical nature. It is of interest to mention in this regard the immunochemical studies on streptococci carried out at the Rockefeller Institute Hospital. Although Avery's name appears only in the first two of these studies, his continued guidance played no small part in the recognition that a protein, the M stubstance, plays in the virulence of the group A streptococci a role analogous to that played by capsular polysaccharides in pneumococci. The constant theme throughout all these interests was the possibility of analyzing infection not only as an ecological phenomenon, but also in terms of the cellular components of the parasite which affect the host and against which the host reacts.

Despite these successes, Avery was acutely aware of the fact that immunological phenomena do not account for all the aspects of the pathogenesis of infection. For this reason, he was eager to investigate the metabolic characteristics of the infective agent, and the physiological-biochemical disturbances produced in the host by infection. To the former area of interest belong a number of valuable studies of the oxidative and autolytic enzymes of pneumococci, and of the growth requirements of influenza bacilli. Worthy of particular mention was the discovery that certain strains of *B. influenzae* require for growth two different vitamin-like factors (then designated as X and Vi and later identified by other workers as haem and cozymase). Commonplace as this discovery appears today, it was then (in 1921) a pioneering step in the new field of bacterial nutrition.

Avery's concern with what he was wont to call 'host chemistry' led to the recognition in the serum of pneumonic patients of a peculiar protein which appears during the acute phase of the disease and which was first detected by its ability to react with the C polysaccharide of pneumococci. It was shown that the 'C reactive protein' is not an antibody but rather a product of cellular damage released in a number of pathological processes of unrelated etiology.

In 1932 a bombshell exploded in the field of pneumococcus immunology. It was the report by F. Griffith that pneumococci could be made to change immunological specificity by certain laboratory manipulations. For many months, Avery refused to accept the validity of this claim and was inclined to regard the finding as due to inadequate experimental controls. This scepticism was understandable in one who had devoted so much effort and skill to the doctrine of immunological specificity. Avery was at that time suffering from Graves's disease and soon was compelled to leave the laboratory for some six months. When he returned in the fall of 1932 new evidence had come to light in favour of Griffith's claims; the results had been duplicated by Neufeld in Germany and at the Rockefeller Institute Hospital by M. H. Dawson. It was with reluctance that Avery eventually accepted that pneumococci could be made at will to undergo transmissible hereditary changes in immunological specificity. But once he had accepted the new phenomenon

he immediately visualized its far reaching implications not only for bacteriology and genetics, but also for general biology and medicine. He was then approaching 60 years of age and many felt that he had shot his bolt. Yet it was during this last phase of his life, and in part after his official retirement, that he made the discovery that may well prove to be his most important achievement—indeed one of the milestones of experimental biology.

He first proceeded to separate from capsulated pneumococci a soluble fraction capable of bringing about the change of type *in vitro*. Enlisting as he had so often done in the past the enthusiastic interest of younger collaborators, he soon obtained a highly purified fraction that could transfer to non-capsulated variants and to their progeny the hereditary property to produce the capsular polysaccharide of the strain used for the preparation of the extract. The climax of this study, and of his scientific career, was the demonstration that the substance responsible for the hereditary alteration of the cell was a desoxyribonucleic acid.

In summary it can be said that the investigations carried out by Avery and his school between 1913 and 1940 have provided the pattern, the master plan, used by our generation for the immunochemical study of infectious processes. His later publications, on the other hand, threw a brilliant light on problems which bid fair to constitute some of the dominant preoccupations of the workers of tomorrow; namely, the nature of those modifications of host chemistry which result from infection, and the mechanism by which hereditary characters are transmitted in micro-organisms. It was largely due to his work that microbial parasitism evolved from an ecological concept into a body of facts and doctrines which define in physicochemical terms the mechanism of host parasite relationships.

It is not surprising, therefore, that his scientific achievements as well as his wisdom soon gained him a large following in the world of science. He was truly worshipped by a host of admirers and friends. He was made president of several scientific societies even though he remained completely aloof from their social and political activities. He was recipient of the John Phillips Memorial award of the American College of Physicians in 1932, the Paul Ehrlich Gold Medal in 1932, the Copley Medal from the Royal Society of London in 1945, the Kober Medal of the Association of American Physicians in 1947 and the Passano Foundation Award in 1949. He was also the recipient of several honorary degrees: Sc.D., Colgate University, 1921; LL.D., McGill University, 1935; Sc.D., New York University, 1947; and Sc.D., Rutgers University, 1953. He was elected to the National Academy of Sciences in 1933. He was made a foreign member of the Royal Society of London in 1944. He was also an honorary member of the Société Philomathique de Paris and the Académie Royale de Médecine de Belgique. That he was not made a Nobel Laureate remains to this day a matter of painful surprise in many scientific circles, since all his discoveries had an obvious quality of perfection and finality, immediate useful application, and great influence in moulding the activities of other investigators. One might hope that the Nobel Academy

will some day acknowledge this oversight, and publicly recognize as once the Académie Francaise did for Molière

'Rien ne manquait à sa gloire
Il manquait à la nôtre.'

The mere statement of Avery's discoveries would be sufficient to secure for him an important place in the history of science. Other aspects of his scientific life are also of great interest—namely his method of work, his manner of collaborating with other scientists, the unity of spirit that he instilled among his associates despite the absolute lack of formal organization of his department. These are difficult problems to discuss in a few lines, because they involve so many judgments of values and attitudes. I shall nevertheless make bold to present a few personal views on these matters—knowing well that they will not be accepted as a true picture by others who were closely associated with Avery for many years and enjoyed his friendship.

To be blunt, it is my opinion that Avery was not as broadly informed a scholar as one could assume from his achievements and fame. He had received an excellent training in school and had read a good deal during his early days. In later years, however, he made little effort to follow modern trends in science or in other intellectual fields, but instead focused his attention on subjects directly related to the precise problem that he had under study. In the laboratory, he was limited to a rather narrow range of techniques, which he rarely changed and to which he added little. But he had a form of genius which went far beyond the pedestrian attributes of the tradesman of science. First and foremost, he had an uncanny sense of what was truly important. Among the innumerable things that could be done, he knew how to select those that were worth doing. Once he had decided on the goal, he spent countless hours—alone or in conversation—formulating and reformulating the essence of the problem in as precise terms as possible. He consulted with any one that was likely to contribute some fact relevant to the understanding of the question or some technique that might help the experimental approach. When work was under way, he was not satisfied with any but the most exacting criteria of evidence. He wanted the last experiment to be a perfect 'protocol experiment'—one in which all the significant variables and controls had been introduced and which yielded without fail the desired result—a demonstration so obvious that it never required statistical analysis. His ideal was an experiment in which the conclusion was inescapable from the observation of a few cages of mice or a few test tubes in a single small rack. Indeed these protocol experiments were so decisive, so demonstrative, that they always had dramatic quality. This was showmanship, perhaps, but of such a high quality that it constituted an artistic performance in which all the demands of scientific integrity were satisfied.

Most experiments were carried out in close association with younger scholars, many of whom have since gained envied laurels in other fields of

research. In fact, one of the most intriguing aspects of Avery's department is the fact that such a large percentage of his former collaborators now occupy important positions in medical schools and research institutes all over the world. Few laboratories—if any—can boast of such a large percentage of highly successful alumni. It is not easy to account for the continued distinction of scientific performance by most of those once associated with Avery. This success was hardly the result of care in the selection of collaborators, for Avery never took the trouble to investigate carefully the qualifications of candidates or Fellows that joined his laboratory. Most of them came as a consequence of usual hospital appointments, or because they had been sent by some Fellowship program. There was no organized teaching or training in the department; in fact, there was no formal organization. Avery never asked or urged anyone to do anything, or to participate in any of his problems, or to initiate a new program. However, consciously or unconsciously, he had developed a subtle and effective technique to create unity of purpose among staff and visitors alike. His office was always open and he was ready at all hours of the day to welcome in his usual gracious manner the questions or statements of any one of us. But whatever the scientific problem in the mind of the intruder, Avery would soon find a way to emphasize one aspect of it that had a bearing on some problem of his own concern—as likely as not some phase of pneumococcus lore. And the conversation would thus naturally evolve into a performance of one of the 'Red Seal Records' which stated with art and precision the questions of interest to the department as a whole. Although all of us appreciated the perfection of the 'Red Seal Records', there were times when we became somewhat tired of hearing them. And yet, there is no doubt that they maintained in the department a remarkable unity of purpose. Whatever the training of the listener—clinician, bacteriologist, immunologist, chemist—his attention was soon focused upon some aspect of the departmental problems to which his particular skill was well suited. And without ever being given a task, or even being asked to participate in the work, the newcomer thus became a part of the team. More important, he himself selected the area of work best suited to his own taste and gifts.

This subtle manner of fostering co-operative action contributed greatly of course to the effectiveness and variety of the research program. Its indirect consequences were even more important, for it gave each one of us the opportunity to discover our individual attributes and to gain confidence in their exploitation. Avery did not select or train his collaborators. He created an atmosphere in which their potentialities had a chance to emerge from their unknown selves. His department was a nursery in which any form of genius could unfold.

The two views of The Professor that I attempted to convey in the opening paragraphs of this memoir were complementary aspects of a rich personality. His engaging smile, and skill in identifying himself for a moment with the

visitor, corresponded to that part of his nature which made him so perceptive and responsive with regard to the outer world. His lonely mood symbolized the phase when the phenomena and impressions that he had perceived became part of his own substance, were organized by selection and alterations into a pattern peculiar to his own personality. He was a scientist in his respect for facts and in his exacting requirements for evidence, but his scientific creation was conditioned by a highly developed artistic sense and classical taste. He despised confusion and uncertainty in facts and in language. Although his temperament was not large and robust enough to encompass the world in its discouraging if glorious complexity, he had the creative vigour to select from the confused mass of events and phenomena the few that were clearly relevant to his problems. He had the aesthetic sense to transform the apparent chaos of nature into the orderly and meaningful pattern that we call Art.

R. J. Dubos

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