
Obituary Notice

OSWALD THEODORE AVERY, 1877–1955

Oswald Theodore Avery was born in Halifax, Nova Scotia, on 21 October 1877, and lived there until the age of 10, when his father, who was a clergyman, moved to New York City. Except for a period of 4 years at Colgate University in Hamilton, New York, from which he obtained the A.B. degree in 1900, Avery’s life was spent in New York City until the age of 70 when he retired from active investigation to Nashville, Tennessee. He died there on 20 February, 1955.

Avery received the M.D. degree from the College of Physicians and Surgeons of Columbia University in 1904. Following a brief time spent as an assistant in a busy clinical practice, he began his career in bacteriology. He was first employed in a milk control laboratory and at the same time started investigations of respiratory infections as time could be spared from other duties. A year later, in 1906, he accepted a position at the Hoagland Laboratory in Brooklyn, where he began his life-long association with the director, Dr Benjamin White. The Hoagland had the distinction of being the first privately endowed laboratory for bacteriological research in the United States. Avery always spoke with great affection of the time he spent at the Hoagland and of the unique opportunities it was able to provide for him. During his 6 years at the Hoagland Laboratory he published nine papers, mostly in collaboration with White, on a variety of topics including the demonstration of Treponema pallidum in syphilitic lesions; Lactobacillus bulgaricus, then in vogue as ‘the bacillus of long life’; and the immunological reactions of certain vegetable proteins. White developed tuberculosis and was confined to Trudeau Sanatorium where Avery visited him whenever possible, even spending vacations there. An interest in tuberculosis was aroused thereby, and between 1910 and 1913 he and White published three papers on the subject, one of which, concerned with a toxic derivative prepared from tubercle bacillus by extraction in alkaline ethanol, is the first that indicated a pattern he was to follow afterwards with such success, namely, the relationship of chemical composition of bacteria to their biological properties.

Avery’s studies on pneumococcus began after he joined the staff of the Hospital of the Rockefeller Institute in 1918. Rufus Cole, the first director and guiding spirit of the Rockefeller Hospital, was dedicated to the ideal of joining fundamental laboratory investigation and the study of diseases of man. He invited Avery to join the staff of the pneumonia service as bacteriologist. Thereafter most of Avery’s investigations dealt with the biology of a single bacterial species, pneumococcus, and its relation to disease.

He was not concerned directly with day to day clinical problems although keenly aware of the trials of the resident staff in the care of acutely ill patients.
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He rejoiced with them at the spectacular successes that occurred with increasing frequency as specific serum therapy was improved and extended to new pneumococcal types. He also shared their feelings of despair when therapeutic resources failed, as so frequently happened before the advent of sulphonamide compounds and their chemotherapeutic followers.

The elaboration, structure and biological significance of the capsular polysaccharides of pneumococci were the dominant themes of Avery's scientific career from the time he went to the Rockefeller Hospital at the age of 35 until he died 43 years later. In collaboration with a modest number of associates over this long period he published many papers on aspects of pneumococcus that were not related directly to the polysaccharides, but he never varied in his main interest and always returned to it. Except for the period of 1935–40 when his work was seriously interfered with because of Graves's disease, there were only 5 years between 1915 and 1946 when one or more papers dealing with pneumococcal polysaccharides did not appear. In collaboration with A. R. Dochez, he studied the relation of the capsular material, then chemically unidentified, to type differentiation and specific immunity. Their first paper on the specific soluble substances (SSS), later identified as complex carbohydrate polymers, was published in 1917. In 1922 there began a most fruitful collaboration, at first with M. Heidelberger and two years later with W. F. Goebel, on the relationship of chemical constitution to immunological specificity of polysaccharides. This body of work, classic in both concept and execution, is recognized along with the contributions of Landsteiner as forming the main pillars of modern immunochemical theory.

It should be recalled that prior to the observations of Dochez, Avery and Heidelberger on the specific soluble substances of pneumococcus, proteins were generally accepted as the determinants of immunological specificity. Avery commented frequently on the scepticism that greeted the description of the antigenic specificity of polysaccharides and likened it to the doubt that was generally expressed as to the protein nature of enzymes following Sumner's report of the crystallization of bean urease and the crystallization of trypsin by Northrop. He anticipated that even greater scepticism would be manifested on the announcement of the genetic specificity of deoxyribonucleic acids. The memory of the turmoil that attended the description of the immunological specificity of polysaccharides and the protein nature of enzymes haunted him for several years before and after the publication in 1944 of the identification of the principle responsible for type transformation in pneumococci with deoxyribonucleic acids.

Avery's approach to a problem was characterized by a prolonged period of thought and discussion, but the strictest economy of mechanical effort. He was scornful of ill-planned experiments that commonly consisted as he would say, in 'taking something out of one tube and putting it into another'. The approach was thoroughly mulled over with his associates, the goal clearly defined and finally a 'protocol' experiment set up, which, if it failed to yield the expected results, pointed unequivocally to another and often more interesting problem. There would then ensue extensive discussion of the impli-
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cations of the observation, and it was here that another aspect of Avery's
genius became apparent. In contrast to the cautious, economical approach to
a laboratory experiment, his imagination was now fired by a fact. He would
explore the theoretical implications exhaustively in animated discussion,
though usually ending up with the homely reminder that the blowing of
bubbles is all right as long as one remembers to prick them oneself.

The meticulousness that Avery brought to experimental design applied also
to the writing of scientific papers and to his rare public addresses. Indeed, his
concern at such times amounted almost to neurosis. The final products are
models of clarity in organization and expression and perhaps do not reflect the
repeated, careful balancing of one word or sentence against another, and the
discarding of drafts until the final product pleased his critical mind and
aesthetic sense. His disenchantment with the 'raking over of old bones', when
a paper was at last ready for the publisher, was often dismissed with a wry
smile and a remark to the effect that if there were really something to say it
would be easy to say it.

Underlying Avery's studies on the chemical and immunological properties of
the capsular polysaccharides was an even more fundamental interest in their
dominant role in the virulence of pneumococcus. Studies from his laboratory
had demonstrated that the antiphagocytic properties of the capsule were
chiefly responsible for the ability of pneumococcus to survive and grow in the
non-immune host. Means were sought, therefore, to neutralize or destroy the
antiphagocytic activity—to make a specific approach to the prevention and
therapy of the disease in man. There was deep disillusionment on the outlook
for antibacterial chemotherapy with the rejection of ethylhydrocupreine
(optochin) because of its frequent and severe toxicity for the optic nerve and
the rapidity with which pneumococcus acquired resistance to it. At the time
other approaches to chemotherapy seemed barren because the many addi-
tional compounds that had been tested showed toxic indices that were even
more unfavourable. The preparation, refinement and effective use of type-
specific antipneumococcal serum, therefore, occupied much of the early effort
of the laboratory and its associated clinical service. Avery's contributions in
this effort were crucial. The principles were clearly laid down in a monograph
on the prevention and serum treatment of acute lobar pneumonia published
in 1917 in collaboration with Chickering, Cole and Dochez.

During the succeeding 20 years marked improvements were made in serum
therapy for infections caused by many pneumococcal types. Serum for type III
pneumonia, one of the commonest and most lethal varieties, however, had
little or no therapeutic effect, because the capsular polysaccharide is produced
in very large amounts by type III organisms and is weakly antigenic in animals
used for the production of antiserum. In collaboration with R. J. Dubos,
Avery devised what to this day remains a unique approach to rational chemo-
therapy. They announced in 1930 that the capsular polysaccharide of type III
pneumococcus is hydrolysed by a specific enzyme produced adaptively by a
soil bacillus when grown in the presence of type III polysaccharide as energy
source. The following year they reported that the type III enzyme possesses
a remarkable protective effect against type III pneumococcal infections in mice. Subsequently, rabbits and monkeys were shown to be protected or cured. Application of this brilliant concept to the treatment of human disease was not made, because discovery of the therapeutic effectiveness of sulphonamides occurred while the preparation of the type III enzyme was still in a developmental stage.

Although Avery was concerned chiefly with the capsular polysaccharides and the immunological responses of the host to them, he maintained an active interest in more general reactions of the body to infection and toxic damage, or as he termed it, the chemistry of the host. With Tillett and Goebel in 1930 he reported on the properties of the C or somatic carbohydrate common to all pneumococci irrespective of type, and in the same year Tillett and Francis described a precipitation reaction between the newly discovered C carbohydrate and the serum of patients acutely ill with pneumococcal pneumonia as well as certain other acute infections of unrelated aetiology. This finding indicated that the substance in acute phase sera from various diseases that reacted with C carbohydrate represented a general reaction of the tissues to injury. The C-reactive protein, as it came to be called, was finally isolated as a highly purified, immunologically homogeneous protein in 1941 (MacLeod & Avery) and subsequently in crystalline form by McCarty in the same laboratory.

Among studies of general importance that in retrospect may be considered as somewhat apart from the main themes of Avery's contributions are those dealing with nutrition and metabolism of pneumococcus and *Haemophilus influenzae* that appeared between 1918 and 1925. With G. E. Cullen he studied acid production of pneumococcus upon growth in various media as well as the autolytic enzyme system. In collaboration with Thjotta it was shown that strains of the influenza bacillus require two vitamin-like factors for growth, the X and V factors, later identified by others as haem and cozymase. With H. J. Morgan he studied various stimulating and inhibiting factors related to growth of pneumococcus, and with J. M. Neill published a series of papers on its intermediary metabolism.

Avery's bibliography lists only three papers on the subject of haemolytic streptococci. One of these, published in 1917 in collaboration with A. R. Dochez and R. C. Lancefield on antigenic composition, set the pattern for the subsequent brilliant contributions of Lancefield and her associates to this subject. There is little doubt but that the example set by the antigenic analysis of pneumococci, and Avery's close though informal relationship for almost 35 years to the studies carried on by Lancefield, contributed greatly to present understanding of the antigenic components of streptococci and their relation to virulence and immunity.

The remarkable report of F. Griffith in 1928 on type transformation of pneumococci formed the starting point for many of the important studies emanating from Avery's laboratory for the next 18 years. In Griffith's ingenious experiments type transformation was achieved by the subcutaneous injection of mice with unencapsulated R cells derived from a particular pneumococcal type together with heat-killed, encapsulated or S cells of
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homologous or heterologous type. Shortly thereafter, M. H. Dawson and R. H. P. Sia, in Avery’s laboratory, succeeded in demonstrating type transformation in vitro, and Alloway in 1932 made the next step by preparing cell-free extracts that caused type transformation. Although intensive investigation was continued over the succeeding years no further publications appeared until 1944 (Avery, MacLeod & McCarty) when the evidence was reported which demonstrated that the hereditary changes induced by transformation reactions in pneumococci depend upon the presence of highly polymerized deoxyribonucleic acid (DNA), and by inference that deoxyribonucleic acids are bearers of genetic specificity. The biological specificity of DNA, hitherto unsuspected, was established.

It is worthy of note that at the time this very significant contribution was published Avery had already reached the age of 67, and that he continued for several years afterwards to make contributions of importance to this field.

The respect and affection in which Avery was held by his colleagues was unbounded. Throughout most of his career at the Rockefeller Institute he was known to all as the Professor, or more familiarly, Fess. Although Avery had lived in the United States for many years he did not obtain citizenship until 1917 and was inducted into the U.S. Army as a private, while many of his professional associates at the Rockefeller Institute became officers. He was fond of recounting his experiences of that period of World War I when as a private he conducted classes in the bacteriology of acute infections for Army officers. It was they who dubbed him ‘the Professor’. This was his only contact with formal classroom teaching. His influence was exerted rather on individuals who came to work in his laboratory or less directly on those who were members of other departments of the closely knit staff of the Rockefeller Hospital.

His approach to a new assistant was diffident. For a time the recent arrival saw little of the Professor. In some this resulted in a sense of frustration at not being caught up immediately in the scientific life of the active department around them or being made a part of a current problem. Avery did not assign his associates to problems. His approach was indirect and at times seemed excruciatingly slow. After a week or two in the laboratory Avery commonly would invite the new assistant into his tiny personal laboratory that for many years consisted of a former ward kitchen to which the barest bacteriological necessities had been added. A morning or afternoon would be spent in describing the lore of pneumococcus and in tracing the development of knowledge, the problems in which the department was currently concerned and those in which it had an interest. These soliloquies, prose masterpieces of high polish, were widely known as ‘Red Seal Records’, and Avery was prone to repeat them as he sensed the necessity. If the candidate showed interest and began to read and work under his own steam, he was counselled and aided. A minimum of technical assistance was provided and one swam or sank because of one’s own efforts or the lack of them. Avery placed emphasis solely on individual initiative and spurned team projects, or research by squads, as it has been called lately. This method may seem wasteful in the present climate of organized investigation; however, it resulted in a body of work that
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has few modern parallels in scope and originality. In addition it was productive of a group of graduates who have exerted an influence on medical teaching and biological investigation far out of proportion to their number. In 1946 Avery, with characteristic understatement, on the occasion of his acceptance of the Kober Medal of the Association of American Physicians, attributed his inspiration and guidance to Rufus Cole and ascribed the success of his laboratory to the fact that 'Cole picked these men and all I had to do was pick their brains'.

From the beginning of his career at the Rockefeller Hospital in 1918 until his retirement, save for a 2-year period between 1919 and 1921, Avery and A. R. Dochez were intimately associated, at first as active scientific collaborators on the biological activity of the pneumococcal polysaccharides and later as scientific confidants who shared bachelor quarters for many years. What the great scientific contributions of each owe to the other cannot be disentangled, nor should they be, since ideals and practice coincided so closely. Avery, in making the presentation of the Kober Medal to Dochez in 1949 had the following to say, 'Throughout his studies there is unique continuity of thought centering in the dominant problem of acute respiratory diseases. The results of his work are not random products of chance observation. They are the fruits of years of wise reflection, objective thinking and thoughtful experimentation. I have never seen his laboratory desk piled high with Petri dishes and bristling with test tubes like a forest wherein the trail ends and the searcher becomes lost in dense thickets of confused thought. I have never seen him so busy taking something out of one tube and putting it into another there was no time to think of why he was doing it or of what he was actually looking for. I have never known him to engage in purposeless rivalries or competitive research. But often have I seen him sit calmly by, lost in thought, while all around him others with great show of activity were flitting about like particles in Brownian motion; then, I have watched him rouse himself, smilingly saunter to his desk, assemble a few pipettes, borrow a few tubes of media, perhaps a jar of mice, and then do a simple experiment which answered the very question he had been thinking about when others thought he had been idling in aimless leisure.' This paragraph epitomizes also Avery's own approach to investigation and his philosophy of the 'true inwardness of research'.

Colin MacLeod

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Awards

John Phillips Memorial Award, American College of Physicians, 1932.
Paul Ehrlich Medal, 1932.
Passano Foundation Award, 1949.

Honorary Degrees

Colgate University, Sc.D., 1921.
McGill University, LL.D., 1935.
Rutgers University, Sc.D., 1953.

Membership in National Academies

National Academy of Sciences of the United States of America.
Foreign Member, Royal Society of London.
Honorary Member, Société Philomathique de Paris.
Honorary Member, Académie Royale de Médecine de Belgique.