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with

best greetings

Al. Coburn

OSWALD T. AVERY

1877-1955

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Ernest M. ...

OSWALD T. AVERY

1877–1955

AMONG the achievements of O. T. AVERY, who considered himself a microbiologist, are two developments that were turning points in biochemistry. He is responsible for the first demonstrations that complex polysaccharides on the one hand and deoxyribonucleic acids on the other are responsible for biologically specific actions—actions which contemporary and expert opinion strongly and even hotly maintained could only be attributed to proteins. The polysaccharides of pneumococcus were analyzed to become a classic example of one family of type-specific cellular antigens, and the deoxyribonucleic acids (DNA) of the same organism were later shown to be the foundation of the genetic determinants for this species.

Both of these great developments were first explicitly conjectured, demonstrated, consolidated and broadened in AVERY's laboratory, some part in investigation by associates who warmly and frequently expressed their indebtedness to his advice and example. The academic world these days does not often pause for sufficient perspective to see how such major advances come about, and a step-wise grand philosophical development is often not as greatly or as promptly honored by accolade as the easily grasped concrete discovery about which we may learn in an academic quarter hour. One must needs pay continual and watchful attention to the innovator who espouses controversial issues, if only for the reason that he may never succeed in removing the controversy from the situation. How ironic that, when the great teachers, be it of laboratory, writing desk or lecture table, construct a rational and logical view of some broad area, they usually labor until the matter seems utterly "obvious" to those who come after. Consequently their harvest is gathered up and enjoyed, without long pause to consider their labors, methods or originality. Be that as it may, anyone who has witnessed at close hand this kind of excellence has small taste remaining for teaching which is stimulatory mainly by its assertiveness. AVERY's scientific accomplishments demonstrate that, when men and ideas rub against each other, the ideas receive maximal polishing if the man is gentle and his principles hard.

OSWALD THEODORE AVERY was born in Halifax, Nova Scotia, in 1877, the son of a clergyman. After the age of 10 years, he lived in New York City until retirement. His education at Colgate University (A.B. 1900) and medical school in Columbia University (M.D. 1904) prepared him for a career in which he practiced medicine only a short time but always remained close to medical problems, patients and people, contributing personally indeed to the atmosphere and newly arising tradition of the research hospital at the Rockefeller Institute. Although other positions and responsibilities were opened to him, he remained there from 1913 until 1947, taking his diversion in the trends of his work and the flow of a goodly line of microbiological and medical coworkers, numerous by American

standards, through his workshop. At a later time, more than twenty of his former associates occupied significant positions in academic microbiology and immunology. This group was virtually the only feature of his career of which he would allow himself to speak almost pridefully, although they were generally referred to as people who "have been in this laboratory", or simply as his friends, "the boys".

Honors and learned society appointments came his way, including the Ehrlich Medal in 1932, the Kober and the Copley Medals in 1945, but they did not come in autocatalytic profusion, for this scholar admired the facts and logic behind nature's ways more than he did his own unique talents, and customarily avoided opportunities for public attention. A number of these honors were for the microbiological researches made before his fundamental contribution to genetics at age 67.

Any attempt to discuss AVERY's contributions and philosophy will be limited here to the purpose of illuminating how a major and fundamental identification of genetically active substance came to be made. A selection of articles representative of his total major research interests is appended, and it illustrates how insistently throughout his career he sought the explanation of different biological relationships in chemical terms. The decades from 1930-50 may have been rich in biochemical achievement, but no one was quicker than AVERY to ask "what is the substance responsible?" when a new biological phenomenon was encountered, in laboratory or literature. And the question was viewed in a modern manner, too—the specificity (now "information") was assumed to reside in individual molecular structures ("messages") capable of influencing (being "translated") or interacting with (complex forming, repressing, etc.), cellular enzymes responsible for growth (biosynthetic systems). The confidence that a substance and an interaction underlie every manifestation was expressed continually and with contagious optimism. This was the pattern of a whole biochemical era, but the places were still few where the interest spanned the whole distance from biology to chemistry. In AVERY's laboratory, the joy came from understanding, through irresistably marshalled logic, some feature of the behavior of that marvel of organization, the living cell.

The philosophy and approach are unmistakably among those now ranked under the banner of "molecular biology." This latter discipline, if that is what it is, partakes of much of the same optimism and contagious confidence and has brought forth brilliant achievements. But it may be more common today to find joy in the cleverness of bypassing logical steps to reach quick hypotheses, in the artful disposing of alternative hypotheses; satisfaction may now be taken in the early and prominent public display of hypothesis and in the anticipated delights of the conclusions. By moving impulsively and impatiently, we now move swiftly indeed, but we tend to emphasize the cleverness and authority of the individual and of his techniques rather than that of the integrated living cell which knows all of the secrets.

AVERY enjoyed all of these intellectual pleasures but saw them as only early steps and, therefore, disciplined himself to indulge them only in private discourse

and in the laboratory. He saw little value for the nonspecialist to be exposed to all of the uncertain stages in a development, and perhaps for that day and age the stimulation of a broad public with vignettes and vistas would have been to no good purpose. Correspondingly, he felt that science had little need for such personal detail and reminiscence as we are indulging in here. He was acutely aware of human fallibility and always ready to assume his own; therefore, his doubts were not turned outward toward criticism and he quietly ignored that which he could not believe. He, instead, approached others with generous and charitable acceptance of their good faith and seriousness. But countless coworkers and individuals were fortunate enough to obtain a private first-rate appraisal of their own work and had to be amazed at the way this modest little man could open out for them its ramifications or the weaknesses in its strategy or logic.

To bring a manuscript, whether joint or personal, to DR. AVERY was to impose on him a task in which he worked as hard as the author. One's eyes were likely to be opened to undreamed of ambiguities and pitfalls that nest in the everyday language. A device he often used was to read aloud the prepared text, in the most gracious tones, but slyly emphasizing the wrong words, or pausing at the wrong places, so that new linkages were created, hanging participles were absurdly exposed, independent thoughts became comically interdependent, and the writer learned from a subtle master actor how weak the connection between thought and words can be. The elegance of AVERY's own speech and writing, of course, was created by the habitual application of the same process of polishing and tasting.

The joy of intellectual search was most characteristically expressed in a series of discourses reenacted by AVERY (in these roles he was called "Fess", for Professor) for the benefit of visitor or colleague in the quiet of his little office. These were well rounded coherent presentations of a segment of pneumococcus lore or a related topic, and were called within the family "Red Seal records" after the then top grade of musical recording. In them, he successively played the parts of narrator, expositor, loyal opposition and finally attorney-in-summation. Even at the second or third hearing of one of these presentations, one could emerge, eyes glowing, surprised to find that dusk had fallen outside while the new inner light was dawning.

These gems of perfection were continually revised and repolished. The highly organized presentation was a kind of debate with himself, punctuated with rhetorical questions like, "now, why should that be?" or "what does that all mean?" The auditor who was moved to try to respond, however, quickly found himself overwhelmed—and indeed suppressed—by the ongoing flow of well-rehearsed logic, that even in the voice of the man who seemed merely its spokesman, would brook no interference. These dissertations probably played a great part in concentrating the attention of his younger collaborators on basic problems, especially those involving "that little gram-positive coccus" which, he felt, presented in small compass most of the basic questions of biology. Many who were never coauthors with him in publication were among his research students in this relationship. For example, I had always felt so deeply that I was an associate of

AVERY, that when preparing this article it was with great astonishment that I realized for perhaps the first time that we had never published a joint paper. The same association must have been felt by Drs. FRANK L. HORSFALL and GEORGE K. HIRST, to mention two virologists among many microbiologists who learned from him. Does the historian of science who leans heavily upon the printed word always learn of these vital but undocumented family pedigrees?

The AVERY laboratory in its last two decades was housed in former hospital ward and auxiliary rooms. The high ceilinged glass paneled rooms seemed deep and quiet, but in almost every corner was a bacteriologist or medical associate transferring or examining cultures at a wooden office desk. The apparatus consisted mainly of quiet incubators or water vacuum pumps occasionally squalling at the single porcelain sink each room possessed. The staff tended to be self-selected into quiet and busy groups—the latter being the young physicians. With these latter, some problem from the hospital service was always obtruding into the picture and requiring some experimental bacteriological detective work, so that this group and the closely associated group of Drs. LANCEFIELD and SWIFT were in close microbial control over most of the hospital patients. During the day, these physicians were often to be found leaning against the tables respectfully listening to Drs. AVERY or DUBOS, MACLEOD or GOEBEL discuss laboratory features of bacterial growth and chemistry.

By 1928 it had been well established by particular work of AVERY's laboratory that pneumococci fall into true-breeding immunologically specific types and their routes of infection can be traced by means of their polysaccharide capsules. Small wonder that the work of GRIFFITH in that year seemed doubtful and contrary to all that had been carefully established; for this young English microbiologist described transformations that seemed to be conversions of one true-breeding type into another.

GRIFFITH had already applied the mild selective effect of a specific antiserum to elicit "rough" nonencapsulated pneumococcal variants from normal "smooth" encapsulated strains. Trying to modify host response to rough strains by material from encapsulated cells he reported in 1928 combining living rough-type organisms with heat killed smooth cultures in another selective environment, the subcutaneous tissue of the susceptible laboratory mouse. His now well-known discovery showed that the "capsule remnants" could bring about conversion of rough-type cells into heterologous smooth types, which would be selected somewhat preferentially in the mouse. The heat killing was thoroughly demonstrated and systematically intensified until first the heterologous and then the homologous capsular transformations disappeared.

AVERY, and MARTIN H. DAWSON in his laboratory, had already considerable experience in GRIFFITH's antiserum selection, but could hardly believe the transformation until later in the same year NEUFELD, the original discoverer of these serotypes, confirmed it. By 1930, DAWSON was writing of the importance of GRIFFITH's finding and attempting to extend it, which he soon did, with STA, into a test tube transformation, effected by from one to six passages of rough cultures in media containing antiserum and killed smooth-type cells. Surviving

witnesses do not describe exactly what AVERY was doing at this time, but it is certain that he closely followed and formatively influenced DAWSON's work. By 1935, I was myself being excited by his discourses on transformation, and they included vivid descriptions of the frustrations and difficulties at this stage of the *in vitro* multiple passage transformations. They described in detail too the important contributions made by the young physician ALLOWAY also in AVERY's laboratory, who succeeded in recovering an extractable, alcohol precipitable transforming agent of considerably stabilized activity from the killed smooth cultures. ALLOWAY was probably the first person to see fibers of precipitated biologically active crude DNA, but AVERY working in the same room must have been initiating, spurring, and aiding in many of the experiments. It is characteristic that having perhaps inspired the work with his scientific discourses and having followed, influenced or guided it, he would usually not accept co-authorship unless his manual participation was also very considerable. In this way, both logic, which belonged to everyone, and actual experimental work, which was personal, became emphasized as the twin foundations of scientific work. "Ideas", which can be actual or illusory, original or automatic, fundamental or merely verbal, almost disappeared from consideration as such.

One can be certain that AVERY was frequently prodding these collaborators as he did his others by asking, "what is the substance responsible?" DAWSON and SIA speculated that it might be the capsular substance; ALLOWAY could nearly exclude this and was inclined to consider it a protein, the type-specific antigen. These evolving answers themselves were in terms of entities recognized through AVERY's investigations and insight. But my personal notes of 1936 record that in one of his discourses on transformation, AVERY outlined to me that the transforming agent could hardly be carbohydrate, did not match very well with protein, and wistfully suggested that it might be a nucleic acid! His judgment had already seen that protein was not likely, and the reasons were probably sound, if preliminary. In 1938, returning to his laboratory from a year in Denmark, I begged for an opportunity to work on transformation, but he was anxious to further the work on blood proteins in acute infection, and asked me to wait, saying "we will get to that later." Shortly after, we were all drawn into various responsibilities by the second great war. But luckily, he and MACLEOD did get back to the problem, and a new young pediatrician, MACLYN McCARTY, with superb biochemical skill helped them to convert ALLOWAY's extract into a highly pure DNA, reported in 1944. The coincident virtual discovery and development of the enzyme deoxyribonuclease gave strong biochemical confirmation of the elementary analysis presented in the now classic paper.

Subsequent history is probably well enough known. Some of us were still concerned over the chemical data. MIRSKY pointed out the deficiencies of elementary analyses in distinguishing between nucleic acid and protein, and proposed a study of nucleoprotein fractions. AVERY continually asked me, as soon as I was able to help, how protein or nucleic acid could be more explicitly recognized, and I entered on a study (reported only in a symposium paper) showing that the purine and pyrimidine groupings as well as the elementary composition,

were those of DNA, but occurred in different proportions than in thymus DNA. Furthermore, the other candidate groupings, amino acid residues, did not seem to be present in significant amounts. Later on, physical studies contributed other correlations with DNA. And HERSHEY and CHASE in 1952 added the elegance of isotopic differentiation to distinguish the elementary analyses of protein and DNA in the effective genetic elements of bacteriophage.

With purification of the specific pancreatic deoxyribonuclease by McCARTY, acceptance of the DNA nature of pneumococcal transforming agent became general and widespread. The subsequent chemical analyses of DNA's, and the extension to other transformable bacteria of course brought other kinds of confidence. The development of other transformable traits in pneumococcus added general significance. All of those advances AVERY followed with enthusiasm and deep understanding.

The absorption of these chemical findings into the body of genetic thinking required the remaining step of accepting bacteria as genetically functioning organisms. Fortunately, LURIA and DELBRÜCK's, and DEMEREC's, studies of mutations, and the several new modes of genetic transfer in haploid organisms first seen in the GRIFFITH-AVERY transformations, have made this step a logical and highly productive one.

Although AVERY's transformation papers include only the barest mention of genes and viruses, I can testify that he was well aware of the implications of DNA transforming agents for genetics and infection. In fact, he collected, read, and commented on, with great interest and some amusement, the conjectures of many leading geneticists and biologists about transformation, from 1930 to 1948. But, since at that time the operational unit—the sperm nucleus or viral particle—could not be broken down experimentally into injectable nucleic acids, then for AVERY it seemed merely clever for him to do so only conceptually, and a rather vainglorious and irresponsible thing to do, before an impressionable public.

In his last two years at The Rockefeller Institute, DR. AVERY began his self-disciplined withdrawal from participation. At first he would disappear only when we (by that time only HARRIETT EPHRUSSI-TAYLOR and the writer) were planning experiments. I believe that he was determined not to be observed in any of the stages of ageing when he might be losing some of his mental faculties, as he had seen others do. This precaution was unjustified, for his remarkable acuity and ability to focus never diminished. But the delight of performing experiments and observing the results he could not forego, and he would appear at the moment we commenced the work, asking "what are we doing today?" and start to help. We still enjoyed his influence at the time of discussing and interpreting the outcome. But this participation too he began to surrender, especially in the last year, when I was attempting new chemical analyses, although all of his friends tried to make him welcome in the laboratories.

In this deliberate withdrawal, the still-bachelor professor, somewhat lonely though widely loved, left New York in 1947 and went to live in Nashville with his brother ROY S. AVERY, a bacteriologist, in company with an old family friend. In this relaxed atmosphere he came into contact with workers at the Vanderbilt

Medical School and until his death he followed some bacteriological-medical researches going on there with his usual fundamentally directed and stimulating enthusiasm.

ROLLIN D. HOTCHKISS

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