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COLIN MUNRO MACLEOD

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AS A BEGINNER in science, Colin Munro MacLeod was granted the most wonderful of gifts, a key role in a major discovery that greatly changed the course of biology. Great as this gift was, it came not as unalloyed treasure. On the contrary, for reasons that are not wholly clear even today, the demonstration by Avery, MacLeod, and McCarty that deoxyribonucleic acid is the stuff that genes are made of was slow to receive general acceptance and has never really been saluted in appropriately formal fashion. The event was originally recorded in the now famous paper of 1944 in the *Journal of Experimental Medicine*,[1] entitled: "Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types. Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III."

The title tells the story; clearly this was an historic watershed. Sir MacFarland Burnett states that "the discovery that DNA could transfer genetic information from one pneumococcus to another heralded the opening of the field of molecular biology."[2] Writing in *Nature* in the month before MacLeod died, H. V. Wyatt[3] reports it as "generally accepted" that the field of molecular biology began with the

appearance of this paper. Lederberg terms the work "the most seminal discovery of twentieth-century biology."

To make an important individual contribution to one of history's great scientific achievements was an act of creation of a special sort. It took place in the decade between MacLeod's twenty-fourth and thirty-fourth years. He could have rested on this achievement; he could have continued with it, thus emphasizing his role; or he could have gone on to something else. As things worked out, he followed the last-named road, influenced to an undeterminable extent by World War II.

But there are other forms of creation in science, and, in some of these, MacLeod also excelled. Before looking at these aspects of his life, it is worthwhile to pause a moment over the question of how he had been prepared so that he might make such great contributions. (Dr. Robert Austrian, in a sensitive and perceptive piece, has described MacLeod's early years.[4])

One of eight children of the union of a schoolteacher and a Scottish Presbyterian minister, the young MacLeod skipped so many grades in school that after being accepted at McGill University he had to be "kept out" a year because he was too young. His birth on January 28, 1909 took place in Port Hastings, Nova Scotia. In his early childhood, he moved with his family back and forth across Canada from Nova Scotia to Saskatchewan to Quebec. He obviously was a splendid student, for, as related by his sister, Miss Margaret MacLeod, he skipped the third, fifth, and seventh grades and graduated from secondary school (St. Francis College, Richmond, Quebec) when only fifteen years of age. His career as an educator started almost immediately. While being "kept out" of school to become old enough for McGill, he was induced to leave an office job to serve at the age of sixteen as a substitute teacher of the sixth grade in a Richmond school. He held this job wholly on his own for the entire year. These

early signs of superior intellectual capacity were not a part of the stereotype "infant prodigy." Indeed a clear sign to the contrary was the fact that within only a few years he was on the McGill varsity hockey team—then, as now, a most impressive athletic achievement.

After two years of premedical education at McGill, he entered the Medical School and received his degree in medicine in 1932. In 1934, at the age of twenty-four, after two years of residency training at the Montreal General Hospital, he came to New York. Less than ten years later, he would make his own highly important individual contribution to the Avery–MacLeod–McCarty study.

The nature of the reception of this work was to test the remaining thirty years of his life, for its significance did not receive the early attention it might be thought to have merited. Shortly before MacLeod died, this aspect of the story formed the basis of several articles in scientific and popular periodicals.[5] He had the chance to see these, but sadly enough, he did not live to see the most extensive and authoritative account, published in 1976 by R. J. Dubos in his book, *The Professor, the Institute and DNA*.[6]

There is no intent here to attempt to add to this literature. The chance of painting a distorted picture is too great for one who was not close to the situation at the time. Moreover, the endpoint of "acceptance" is hard to measure, for in science it does not occur all at once like a directed plebiscite in a totalitarian state. Some highly knowledgeable scientists perceive the full significance of a particular discovery right away; others require longer. It is necessary, however, to cite the major events in the research itself in order to describe MacLeod's clearly definable and individual contribution. And, given that contribution, some mention of what happened to the recognition of the work is inescapable in telling the story of MacLeod's career in science. For it is the way the

whole story seemed to him that could have had a telling influence on his subsequent career.

When he first arrived at the Rockefeller Institute, MacLeod fell under the influence—or spell—of O. T. Avery, or "Fess" as he was called, who was the inspiring teacher of so many others, including Rene Dubos, Maclyn McCarty, and the late Frank Horsfall and Martin Henry Dawson.

Some years before, as related by Dubos, an old school friend of MacLeod's, Henry Dawson, had been asked by Avery to investigate the variations in pneumococcal colonial morphology from "rough" to "smooth" (R/S) then being studied by Griffith in England. Several years later, when Griffith[7] demonstrated that one pneumococcus type could be transformed *in vivo* into another, in effect a directed and heritable alteration, Dawson was captivated by the feat. Working with R. H. P. Sia, he was able to repeat the experiment and to produce the change.[8] Dawson had to abandon the project, which was taken up by J. S. Alloway,[9] who was able to show that the substance responsible resided in a thick, syrupy preparation.

The techniques used by Dawson, Sia, and Alloway were not at all reliable. Neither the phenomenon of transformation nor the harvesting of transforming principle could be reproduced with a high degree of predictability. A phenomenon of potentially great biologic significance had been clearly identified. Yet without methods to produce it with predictability and to extract its active principle in ways permitting precise characterization, any attempts to study the matter further were bound to be marked by frustration. Nevertheless, because of the potential significance of the phenomenon, Avery decided that the work must go on. He continued to see the first essential task to be the chemical characteriza-

tion of the active material, but the available techniques were obviously not sufficiently reliable to permit such chemical studies. It was at this point that MacLeod entered the picture in 1935. By improving the medium and isolating a consistently reproducible rough strain of pneumococci, MacLeod made it possible (with Avery's encouragement and counsel) to move the project from what was the study of a fascinating phenomenon, but one of irregular occurrence and not possible to assay, to a predictable one. The critical substance could then be fully characterized in chemical terms. The subsequent phase of the study, the actual conduct of these chemical studies, became the responsibility of McCarty.

Each of the six investigators who worked with Avery thus made a contribution to the solution of Griffith's mystery, but it is now fully conceded that the critical contributions were those made by MacLeod and McCarty under the continuing, brilliant intellectual stimulation, advice, and counsel of Avery himself. Oddly enough, as Dubos has described, although MacLeod and McCarty worked closely together on the project, they were not officially at the Institute at the same time, for in 1941, at age thirty-two, MacLeod became chairman of the Department of Microbiology at the New York University School of Medicine. He left the Institute as McCarty arrived. As the Medical School of NYU and the Rockefeller laboratories are both in the mid–East Side of Manhattan, it was easy for MacLeod to travel back and forth, and he maintained a continued and wholly recognized association with the project. In large measure, however, whether it was realized or not at the time, he had made his contribution. He had taken an almost formless, erratic phenomenon and made it into something predictable and measurable. This had to be done, and he did it. Thus, the problem had been brought to the very stage at which McCarty's own considerable biochemical ex-

pertise was exactly what the situation called for. Two years later (November 1943), the paper was submitted to the *Journal of Experimental Medicine.*[10]

In subsequent years, MacLeod continued to work on this problem in his laboratory at New York University, first with M. R. Krauss[11] and R. Austrian,[12] and at a later period with E. Ottolenghi.[13] It is appropriate to postpone discussion of these subsequent phases of his scientific career in universities and government and to dwell for a moment on the story of how the finding presented by Avery and his two younger colleagues in the 1944 paper was received.

A revolutionary concept, as pointed out by Kuhn,[14] does not usually increase knowledge by adding on to it; it is more apt to replace it. A problem in 1944, and a far greater one today, is how one can evaluate new research with implied revolutionary findings when, as a practical matter, one cannot employ the techniques necessary to repeat it.

The scientists who read the 1944 paper by Avery, MacLeod, and McCarty had, in theory, two choices: they could accept or deny the validity of the demonstration on the basis of comprehension, or they could repeat the experiments. To do the former requires an intimate knowledge of the reliability of the techniques. At first glance that is a statement of the obvious—something that occurs on the reading of any scientific paper. But such is really not the case. Most of the time, in biomedicine at least, published experiments represent logical sequences in a series of experiments on the same subject. The degree of reliability of the key methods is known to be understood by those intimately engaged in the field, and the rest take it on faith. When this is not the case—when the results depend on a new method—if the field is reasonably in the scientific fashion of the day, it contains other workers. These other workers soon define the limits of the technique. Obviously, this system depends on the judg-

mental decisions of presumed experts, but the scientific community and the public are protected against prolonged error by the competitive nature of the studies in a particular field. It is one part of the familiar "marketplace of ideas."

The trouble with the Avery–MacLeod–McCarty studies was that the approaches they used did not happen to be fashionable. They were not part of a race to glory, such as that described by Watson in the *Double Helix*.[15] Or, more accurately, the successful approaches that were used by the Rockefeller group were far out of the ken of most of those who were working actively to solve the question. Moreover, the nucleic acids were not believed to have any biologic activity nor was their structure well defined. There really was no community of competing investigators fully armed with the requisite techniques ready to jump in and repeat the experiments. Indeed, to do this would require assembling a team with the talents, experience, and expertise of Avery, MacLeod, and McCarty. What is more, it would have to be assembled from a markedly constricted biomedical research community, for by this time the U.S. involvement in World War II had begun.

Acceptance of the chemical basis of transformation might seem to have been slow, although clearly there was no set period within which it should have occurred. There is now a small body of published material on this question of acceptance by some of the people who were close to the field at the time. Some of these comments were recorded during the period in question or a little later; others are present-day recollections of what was thought at the time. As might be expected, these reports ranged from outright acceptance of the role of DNA to a definite interest short of conviction, to, at the other extreme, a belief that the phenomenon was not mediated by nucleic acid at all, but by minute amounts of contaminating protein. Stent believed the work had little im-

pact on genetics.[16] Lederberg strongly dissents from this point of view and presents important contemporary citations in support of that position.[17] Indeed, in the year following the original report, J. Howard Mueller[18] appears to have correctly perceived the whole story, as may be seen in his article in the *Annual Review of Biochemistry.* Dubos,[19] in his 1976 analysis of the entire record, suggests that one of the factors in the slow acceptance was the starkly noncommittal way the results were presented, which was notable even in a scientific report. In those days at the Rockefeller Institute, there was a philosophy concerning the style in which experimental results should be presented. This style was largely initiated by Avery but was also adhered to with conviction by most of his younger associates, especially MacLeod. In this style, the key words were carefully chosen to convey only that which had been clearly proved and nothing more; any suggested implications were rigorously excluded. Lederberg also credits this attribute, which he terms "Avery's own a-theoreticism," with helping to postpone "the conceptual synthesis that now identifies 'gene' with DNA fragment."[20]

Whether or not acceptance was slow, it evolved steadily. For Lederberg also mentions: "In 1946, at the Cold Spring Harbor Symposium, where Tatum and I first reported on recombination in *Escherichia coli,* we were incessantly challenged with the possibility that this was another example of transformation, a la Griffith and Avery."[21]

Dubos cites a summary by Andre Lwoff of a 1948 conference in Paris in which the genetic role of the nucleic acids is obviously accepted. But as Dubos also states:

> It took an experiment, outside of the Institute, with a biological system completely different from that used by Avery to win universal acceptance for the genetic role of DNA. Using coliphage marked with 32P (restricted to the DNA component of the virus) and with 35S (restricted to the protein component), Hershey and Chase at the Cold Spring Harbor Laboratory

showed in 1952 that most of the viral DNA penetrates the infected bacterium, whereas most of the protein remains outside. This finding suggested that DNA, and not protein, was responsible for the directed specific synthesis of bacteriophage in infected bacteria. In reality, the interpretation of this wonderful experiment was just as questionable on technical grounds as was the chemical interpretation of pneumococcal transformation, but those obtained by Avery 10 years before, that the few remaining skeptics were convinced. The case for the view that DNA is the essential and sufficient substance capable of inducing genetic transformations in bacteria was not won by a single, absolute demonstration, but by two independent lines of evidence.[22]

In his Nobel Prize lecture,[23] Lederberg puts it in essentially the same way. He attributes to Avery and his colleagues the demonstration that the interpneumococcus transference of an inherited trait was through DNA, the broadening of the evidence to Hotchkiss,[24] and the reinforcement of this conclusion to Hershey and Chase,[25] with their proof that the genetic element of a virus is also DNA. Eventually such situations right themselves. Today if one looks in elementary texts on human genetics, the Avery–MacLeod–McCarty 1944 paper is cited, in effect, as the historic watershed.[26]

Little imagination is required for anyone who has ever been engaged in science to envision what a deep-seated disappointment the relative lack of formal recognition of his key contribution to the DNA work could be to a scientist, especially to one who was just starting out in his career. A sense of having in some way suffered an injustice would not be at all unusual. This could well lead to bitterness, particularly as the years went on and others reaped wide professional and public recognition for studies on DNA. But MacLeod would have none of this. Not for him would be the stereotype of the unhappy investigator living off scientific "might have beens." Indeed, as far as I have been able to ascertain, at no time did he ever publicly express, even by indirection, the thought that, in the DNA story, he had been slighted in any way.

MacLeod's seven years in Avery's "department" at the Institute were not all occupied by the work on the pneumococcal transforming factor. On the contrary, he was engaged in a number of other studies, as may be seen from his sixteen publications of this period, eleven of which list him as senior author. Two things are striking in looking over this list today. First, although a number of different topics appear to be involved, they almost all deal with host-parasite relations at the very time antimicrobial therapy was coming on stage, so that the influence of this intervention in the disease mechanism could also be embraced by the studies. Second, virtually all were concerned with pneumonia, notably pneumococcal pneumonia; there was one study on the so-called primary atypical pneumonia[27] just then coming into medical recognition. Given Avery's preoccupation with pneumococcus, the fact that MacLeod, working in his laboratory, published a number of studies on pneumonia may not seem too surprising. What is important, however, is that this interest led MacLeod to highly productive studies in his subsequent career.

MacLeod's start as a university professor coincided roughly with the entrance of the United States into World War II. Viewed in retrospect, the impact of so pervasive a force as World War II was bound to have deep and enduring effects on a young man just emerging as a leader in science. From this time on, three characteristics were prominent. He was forever conscious that the university department he headed was in a school for the training and education of physicians, he was deeply convinced of the social value of unfettered basic scientific research, and he felt a responsibility to contribute what he could to the shaping of public policy in that interface of government and the universities that developed so rapidly in importance dating from that time. To a considerable extent, all three characteristics tended toward