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COLIN MUNRO MACLEOD

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A Biographical Memoir by
WALSH MCDERMOTT

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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 characterization 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 expertise 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 judgmental 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 impact 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 self-effacement, and each one influenced the expression of the others.

Some contradiction exists between the fairly sharp sense of mission of a medical school and unfettered basic research as a major goal of one of its departments. MacLeod believed this contradiction could be resolved. He accomplished this not only by developing a highly organized and constantly renovated program of medical education but also by a quiet display to his associates of his own attitude concerning the choice of subjects for research. He constantly maintained the position that any question to be studied should be studied with the most penetrating and "basic" techniques and that the investigator was obligated to go where the study led him. There should be no emphasis or pressure to come up with new knowledge for practical application. By the same token, it was to be hoped that, in a medical school, the initial choice of a broad question for study would bear a clear relationship to disease in man.

At the beginning it was not possible to start building on this concept; in a nation at war, the research needs of the military came first. To a surprising extent, however, without in any way overlooking the military need, it was possible to carry on a certain amount of free inquiry. In part this was because a great deal of MacLeod's and the department's considerable contribution to the war effort came not from quick ad hoc laboratory experiments but from their ability to use a deep background in microbiology to advise and to help solve the disease problems of the military, which could arise virtually overnight.

With these concepts in mind, starting with the nucleus of microbiologists in the department when he arrived in wartime, and more rapidly thereafter, there assembled at NYU a group that brought the department recognition as one in a rapid growth phase characteristic of a basic discipline. Not only was the DNA story unfolding, with its many ramifications, but there were also the development of antimicrobial drugs and the rapidly widening capability to deal with viruses in the laboratory. The high national and international reputation of the NYU department was not founded only on research but, as has been mentioned, a great deal of departmental time and thought went into creating a teaching program. Indeed, it was the NYU group that was among the first, if not *the* first, to introduce the actual handling of viruses to the regular laboratory exercises in the medical student's course. This was done at a time when, in many of the academic medical centers throughout the country, any manipulation with viruses was considered something only for the research laboratory. Ironically, the desire to provide a research environment free from the pressure to seek results for immediate practical application yielded certain studies that ultimately led to important practical applications.

A look at the list of departmental publications for the fifteen-year period beginning in 1941 shows an unusual degree of diversity. It must be recalled that when the United States entered World War II, microbial disease represented a far greater portion of the total health threat to young adults than is the case in peacetime today. This portion was enlarged still further by the actual process of military mobilization. As young adults from all over the country were introduced to communal and often crowded living conditions, outbreaks of microbial disease of a sort not usually seen in civilian life became not infrequent. Pneumonia in its commonly recognized forms was a major threat. MacLeod had long been a student of this disease complex, and the departmental publications list shows a 1943 paper[28] by him on the newly recognized primary atypical pneumonia, a disease of considerable importance to the military. (He published the results of a field study of this condition with Hodges in 1945.)

Of greater ultimate importance was a series of studies on antipneumococcal vaccine. This work, done in the last years of the war, was a development of public health importance that is only now coming into its own. MacLeod was a senior author of the 1945 paper "Prevention of Pneumococcal Pneumonia by Immunization with Specific Capsular Polysaccharides."[29] Mothballed at war's end, largely because of the development of penicillin, this work formed the base three decades later for the antipneumococcal vaccine developed and clinically validated by R. Austrian,[30] who had been a research fellow with MacLeod and his lifelong close friend.

The early days of World War II were a period in which the limits of effectiveness of the sulfonamides introduced some five years previously were being defined; at the same time the extraordinary characteristics of penicillin were being discovered. Among the publications from the department are two by MacLeod: one on the sulfonamides alone,[31] the other on the differences in the nature of the antibacterial action of the two substances and the relations of these differences to therapy. Viewed today, such a presentation would seem far too elementary for serious consideration in a department with a strong orientation toward basic science. Yet in the early 1940s, it dealt with important and largely unanswered questions.

During the fifteen years in which MacLeod headed the department, in addition to his own work, there were five main lines of inquiry pursued by its members. These were: the studies of hemolysins and the studies of other streptococcal products that led ultimately to streptokinase and streptodornase; the studies of diptheria toxin and toxoid, including clinical observations; and studies of metabolic effects on mouse brain produced by viruses. Any one of these programs would have been considered a great feather in the cap of a department of microbiology. Taken together, they represented an extraordinary contribution to our understanding of the pathogenesis of microbial disease and hence in some instances formed the base for preventives or therapy.

MacLeod took an immense interest in all of these activities and followed their progress in considerable detail. With some, for example, the studies that eventually led to enzymatic debridement, he participated sufficiently to coauthor one of the key papers (Christensen, 1945).

There were two lines of research activity, however, in which MacLeod's participation was complete. These were the further studies on various aspects of the transforming factor and a series of studies including field trials of the development of an antipneumococcal vaccine.

In the studies on transforming factor, having first shown a relation between the quantity of capsular polysaccharides formed *in vitro* and the virulence of pneumococcal strains for mice, MacLeod and Krauss[32] showed that the transformation of a pneumococcus from R to S was genetically controlled quantitatively as well as qualitatively. In other studies with Austrian,[33] he was able to show the presence of an M protein that could be transferred from one pneumococcal type to another through the transformation process. (In a subsequent study, Austrian with Colowick demonstrated that it was possible to modify the fermentative activities of pneumococcus by means of the transformation reactions.)

The studies of immunity to pneumococci mentioned previously were extraordinarily complete and were published in a series of eleven papers[34] from 1945 through 1947. The specific capsular polysaccharides could be obtained by the methods first developed by Heidelberger. In collaboration with him, MacLeod and the group were able to demonstrate and to define the antibody response in man. A vaccine consisting of the specific capsular polysaccharides of four pneumococcus types was made and proved effective in the prevention of pneumonia by these types in a military school during 1944–45.

In the brief period between the experimental production of small amounts of this quadrivalent vaccine and the end of the war, the vaccine was not tested again and the increasing use of penicillin immediately thereafter dampened further interest in the vaccine. It remained for Austrian, almost thirty years later, to successfully convince the bureaucracy and industry that it would be worthwhile to develop a 14-serotype vaccine and then, in clinical trials headed by himself, demonstrate its effectiveness.[35] This is an example of the length of the shadow that can be cast by one man, for Austrian[36] received his early education in research in MacLeod's laboratory at NYU.

In 1956 MacLeod gave up the responsibility of being chairman of a teaching department but continued his university career—first as John Herr Musser Professor of Research Medicine at the University of Pennsylvania and then in 1960 back at New York University as professor of medicine. He carried on research at both places—the most important being further studies on the transforming factor (E. Ottolenghi and C. M. MacLeod) and genetic transformation and so forth, with Ottolenghi.

These years in microbiology in the university, particularly the first decade starting in 1941 at NYU, represented a form of scientific creativity different from that at Rockefeller. He was creating a science department in a medical school. It was an achievement widely scrutinized and praised on the national scene; it was also one that inevitably caused a change in the nature of his own work in science.

There was the usual temptation to be selfish and husband time for his own research at the expense of engagement in the problems of the other departmental members. This he successfully resisted, but at the quite considerable sacrifice of himself, for to the usual departmental demands were added his wartime work, very little of which could be accomplished in his own laboratory. Instead, he had to spend substantial periods either in Washington or on trips (usually by train) to military installations scattered across the country. With considerable effort, he continued to keep abreast of the research going on in the department, and he did not fail to make his own contributions to the teaching program. But he had to obtain his intellectual satisfaction in science vicariously, as a student and adviser with engagement in the work of others. As seen above, this was not the case right from the beginning, but it developed on an increasing scale throughout the war years.

Thus, in the same way that the change from Rockefeller to NYU ushered him into a different form of scientific creativity, the end of World War II marked the beginnings of the third and final form, that of a highly respected science adviser to government. From this time on he was able to do relatively little in the laboratory, although he worked hard at his other departmental duties. Indeed, one of the major attractions of the offer of the Pennsylvania chair was the prospect, erroneous as events proved, that he would have much more free time for research. It is worth noting that in each of these three phases of MacLeod's life in science he was highly successful; in retrospect, each phase was a splendid preparation for its successor.

He was now starting to perform a function of a sort not hitherto performed in our society or, more precisely, not performed on anywhere near so large a scale. To be sure, some precedents existed. President Theodore Roosevelt obtained advice from medical leaders in New York City on whether to support Walter Reed when he became engaged in controversy during the construction of the Panama Canal. The National Academy of Sciences itself had, in its 1863 charter, the responsibility for advising our government on scientific (and certain other) matters "when asked." It was during World War II, however, that the interfaces of government, university, and industrial science became such an important sphere of activity, for the exigencies of the war happened to coincide with the early years of the great burst of biomedical scientific creativity. Only in part in response to the war, biomedical research and development increased thereafter because of the expanding productivity and intellectual liveliness of the field. Among other things, they had attained a high social value. New institutional forms involving government and the universities had to be created for their proper management and support. MacLeod's wartime work thrust him into this field, and his obvious skill in it made his deep involvement almost inevitable.

Today it is easy to forget how primitive was the institutional framework (including that in the Academy) available for managing affairs in this arena of society and government. In a very real sense, MacLeod was a pioneer in an activity now dignified in increasing numbers by a formal place in the university structure as a department or program entitled Science and Society or Science and Public Policy. With his terrific energy, he was not an occasional contributor to this scene—he worked at it virtually every day.

To serve productively in this field of science policy requires a whole set of characteristics that must be possessed, in addition to the ability to do scientific work itself. For, although the findings and the future picture of the various sciences are conceived in objective terms, it is also necessary to explain things in a convincing manner to a spectrum of people with little or no background in science. It is appropriate, therefore, in discussing MacLeod's contributions to science policy and as an institution-builder, to consider him as a person reacting to others.

Continued grace under what seemed to him as nonrecognition of a major role in an important scientific or biomedical contribution tells us one part of his character, but what kind of a person was he all-in-all? As one who interacted with others, MacLeod was a full-formed individual by the time he went to New York University, although the occurrence of considerable inner growth thereafter could be sensed by his associates. It was at about that time, in late 1941, that I first met him. Then and thereafter, he showed a number of wonderful qualities, a few of which were paradoxical in a way that is hard to describe. He would give the impression at one and the same time of approaching problems with a light touch, yet of taking them with all appropriate seriousness. He radiated competence. He also gave the impression of a great depth of knowledge of his chosen sector of science, microbiology, yet he managed to do this without the slightest hint of intellectual arrogance. The "light touch" was physical as well as behavioral; he would enter a room quickly, get off some bit of quick wit as a salutation, and be ready to go. He gave the impression of being in command of himself physically as well as emotionally and intellectually.

For all of these reasons, he was the perfect chairman and usually ended up in that spot. This job requires patience, something not too difficult to employ when a group is discussing things one wishes to learn more about. Almost invariably, however, he would know much more about the question than the group over which he was presiding, and yet he would not betray that fact. If the situation called for it, MacLeod *would* suffer fools gladly—he would not cause people to lose face. Like a skilled symphony conductor, he always seemed to know just what it was his committee members *did* know; he would extract it and weave it into the fabric of a group contribution. He was absolutely unflappable and he operated in a world—particularly in the last decade of his career—in which one crisis followed another daily as a part of the regular business of life. In a very real sense, these attributes were a carry-over into adult life of that remarkable performance when he was a highly precocious child, yet had no trace of being an infant prodigy. This patience was not only a kind tolerance for the shortfalls of others; it had a "Robert Bruce and the Spider" quality about it when applied to himself. This characteristic was presumably of great value also in the laboratory when he took on the until-then hopeless task of attempting to bring orderliness into the on-and-off phenomenon of transformation.

He was known to be readily approachable by young people who were considering careers in science, and he would have long sessions with them. In addition, he had that great gift of seeming to the young as if he were taking their ideas with seriousness, and most of the time he did. Understandably, he had great influence as a teacher of medical students and research fellows. This patience and tolerance for the shortfalls of others were not those of someone too good-natured or popularity-seeking to be a good teacher. On the contrary, he could clearly communicate his disapproval to the young people in the laboratory when their approach and work habits were not of high quality, but it was done with kindness. With his sharp intelligence, his high standards for the quality of research, and his rich background in microbiology, he was a keen critic of newly appearing work in the field. He was not, however, an instinctively negative critic. When he heard or read about some new observation, he would talk about it with a sort of wonderment—almost that sense of innocent wonderment we fantasize in the young child walking for the first time through a daisy-studded field. He would hold forth eloquently on such new developments as a member of an informal monthly dinner club formed soon after World War II.[37]

Above all there was one characteristic he had and maintained throughout that was important in developing as a role model, if you will, in his field. Despite the frequent temptation, he never gave an inch on his values in science in order to be perhaps more persuasive to prospective donors or government officials in the hope of attaining acceptance of a particular program of the moment. In a figurative sense, he refused to "sell out," despite almost innumerable opportunities to do so.

In his career in science policy, he worked through four main institutions; three were in government, the other an institution with a special relationship thereto. They were: the War Department, later the Department of Defense; the National Institutes of Health; the President's Science Advisory Committee; and the National Academy of Sciences, to which he was elected in 1955.

In the early days of the war, a major part of his work had to do with the Army Epidemiological Board, which was attached to the Office of the Surgeon General of the War Department. At the end of the war, MacLeod became president of the Board. A few years thereafter, the Board was enlarged to embrace all the armed forces, and MacLeod was made president of the combined Boards. He continued to fill this position until 1955. It should be emphasized that his position as president, although part time, was nevertheless quite demanding; indeed, it necessitated that several days each week be spent in Washington. In short, it was at least a half-time job, even in the pattern of the long hours customary in the life of a research scientist. In addition to the time required, there was a considerable intellectual challenge because the Armed Forces Epidemiological Board included some ten or twelve individual commissions on various aspects of diseases or conditions important to the army. These comprised such subjects as streptococcal disease, influenza, military wounds, peacetime trauma, pneumonia, and staphylococcal disease. It was necessary for the president of the Board to steep himself in all that was known and was being developed in each of these fields. MacLeod appeared to do this effortlessly, yet at no time did he give the impression of superficiality. He seemed deeply interested in each development in each field and would talk about them with the infectious enthusiasm he had for all feats of human imagination in the works of science. When his term as president was completed, he continued in an active role as a Board member, including membership on two of its commissions, and served also as chairman of the Scientific Advisory Board of the Walter Reed Army Institute of Research.

The medical research of World War II was largely conducted in the civilian laboratories and in a few centers set up by the military. Field studies were done mostly in the military cantonments. The total effort was financed in part by the army and the navy—the only U.S. military departments then in existence. The major portion of the wartime program, however, was supported and directed by a tight partnership between the Office of Scientific Research and Development, an arm of government, and the National Research Council, an arm of the Academy. Although formally separate, the two operated as one, even to the point of having an identical membership and chairmen for their committees. Despite his heavy commitments to the Army Epidemiological Board, MacLeod also worked hard in the OSRD–NRC programs, where he was chief of the Preventive Medicine Section of the Committee on Medical Research of the OSRD. Among the activities of this unit were large-scale studies of sulfonamide prophylaxis of streptococcal disease.

At the conclusion of the war in 1945, there was a sudden need to do something about finding continued support for certain of the research activities in the university laboratories that had been supported in the National Research Council program. The National Science Foundation was just being proposed at that time, but its actual creation encountered delays. These were caused, in part at least, because the mechanisms proposed by the scientists for the appointment and removal of its director were so unrealistic as to lead President Truman to veto the authorizing legislation. Meanwhile, the U.S. Public Health Service expanded a grant-making authority it had long had and created the extramural grant program of the National Institutes of Health.[38] A number of the wartime grants were immediately taken over and approved by the newly formed study sections of NIH. MacLeod was a member of the first one, the Antibiotics Study Section (1946), and continued as a member until the Section was merged with two others three years later.

This appointment marked the beginning of his long period of association with the National Institutes of Health. By service on various committees, commissions, task forces, and training grant committees, and as a frequent informal personal consultant to successive directors, he exerted a considerable influence in helping to shape the direction and quality of what became the quite extraordinary development, the whole extramural complex of programs conducted largely in the universities.

These NIH experiences in helping to build institutions linking the government and the universities and his work for the military occurred largely at the same time; both continued throughout his lifetime. In many instances the scientific substance of what was under scrutiny was similar under both auspices, but the range of biomedical subjects in the NIH world was understandably greater. Moreover, the issues of public policy involved tended to be different in the two programs. The work for the army and for the newly formed Department of Defense, and that for the NIH and the subsequently formed Department of Health, Education, and Welfare, gave MacLeod a considerable insight into how the two largest departments of the federal government operated from the time of their formal beginnings.

With this knowledge and the opportunity to help shape the developing relationships between government and science, MacLeod entered a new role in 1961 as chairman of the Life Sciences Panel of the President's Science Advisory Committee and a year later as a member of PSAC itself. This activity was followed in 1963 with his appointment by President Kennedy as the deputy director, Office of Science and Technology (OST), Executive Office of the President.

Stemming from the nature of its location in government, PSAC tended to operate in a crisis-like atmosphere, for it had to be responsible for authoritative advice over an extremely broad range of science and technology. MacLeod was the first to hold the position of deputy director. The thought was that whoever held the post should have a background in science that would complement that of the director, who, at that time, was Jerome Wiesner. Thus it was visualized that MacLeod's principal concerns would have to do with biology and medicine. This responsibility he did fulfill, but the demands on the PSAC operation were such that he also had to cover a considerably wider range of scientific subjects than those purely biomedical. Nevertheless, he was able to make a number of achievements in the biomedical field. Among these were: the in-depth report on the status and suggested future of the life sciences; the Task Force report on medical manpower; a report on the use of pesticides; and the U.S./Japan Cooperative Program in the Medical Sciences. The last named is a case in point. The OST then (as its successor, the OSTP today) was not an operating agency; hence, its visible accomplishments frequently took the form of a program lodged in some other part of government. This is not to say the program was necessarily implanted there full grown. More often the idea was initiated or passed through OST, whose staff then shared in greater or lesser degree in the actual creation of the program. Thus much of the work in OST, although not secret, was by its nature unheralded, or at least the role of OST was not emphasized.

For example, the U.S./Japan program was worked out through the Department of State, but MacLeod had been chosen by President Johnson to organize and direct it and was chairman of the U.S. delegation from the start until his death. This program or institution is another instance of the creation of mechanisms whereby two governments and their respective scientific communities can engage in productive scientific work. Almost fourteen years old now, the program appears to be thriving.

An appreciable portion of MacLeod's work in OST, as with the U.S./Japan Program, involved international activities. This work abroad did not begin for him at OST, for he had long been active in the international field. Indeed, early in 1956, he was one of a group of four scientists to visit the U.S.S.R. These individuals probably represented the first official biomedical group to visit the Soviet Union since the end of World War II; indeed, there had not been many unofficial visits in the entire Stalin era. Two years later, MacLeod was appointed as the U.S. representative to an international group of distinguished scientists who formed the "charter members" of the Committee on Research for the World Health Organization. A year later he became chairman of the NIH Advisory Committee responsible for some five or six International Centers for Medical Research and Training located in Asia and South America.

In the following year (1960), he became deeply engaged in the problem of Asiatic cholera. The South East Asia Treaty Organization (SEATO) wished to focus some of its effort on health matters and made a formal request to the United States for scientific advice and counsel. Dr. James Shannon, the Director of the NIH, and the late Dr. Joseph Smadel, a former associate of MacLeod's at Rockefeller, appointed a small group to examine the health situation in the SEATO region and to suggest ways in which its problems might be productively attacked.

The group recommended the creation of a facility for intensive laboratory and field research on cholera. The facility was established initially with SEATO funds. It has been funded since from a variety of sources, notably the U.S. National Institutes of Health and the Agency for International Development. Throughout its existence, MacLeod served as a leader and wise counselor for this laboratory in which much has been accomplished by an international roster of distinguished investigators. Starting in 1963, MacLeod was chairman of the Technical Committee to the Laboratory. Indeed, he was en route to the Dacca laboratory when he died in his sleep at the London Airport Hotel. The wisdom of the initial choice of cholera for the major research effort was borne out, not only by the successful development of oral hydration as a treatment for cholera but also by its potentially great usefulness in the treatment of other diarrheal diseases.[39] The laboratory has now become the International Center for the Study of Diarrheal Diseases. Today it is recognized that diarrhea, particularly of infants, it probably the world's greatest killer, and the World Health Organization has recently launched a major program for its management.

In his years as a member of the National Academy of Sciences, MacLeod served in a number of roles, of which only two will be mentioned. He was elected a member of the Academy Council in 1964 and he was appointed to the NAS Board on Medicine. The latter was a group set up in 1966 to advise the Academy on the question of what kind of an institutional framework might be created by the Academy to meet the needs of society with respect to biomedicine. The Board led to the creation of the Institute of Medicine, and MacLeod was a member of its first Council.

MacLeod left the Office of Science and Technology in 1966 to become vice president for medical affairs of the Commonwealth Fund in New York City. Leaving a full-time position in government did not mean, however, that he had given up all governmental work. On the contrary, he continued as a very active adviser. He resumed his place on the President's Science Advisory Committee and continued his chairmanship of the U.S./Japan Program. From this time until his death roughly five years later, he spent his time in foundation and university work and as president of the Oklahoma Medical Research Foundation. Although he had gone to Oklahoma less than two years before his death, he had made an impact there with his great ability to help young people facing the problems of scientific research.

His major achievements in this final period had to do with his foundation work, which was largely concerned with helping to strengthen the teaching and research capability of biomedical institutions. He was able to expand his activity in this field by virtue of his membership (and frequent chairmanship) of the Health Research Council of the City of New York. This organization was a municipal fund-granting agency that he had helped to found in 1959. For more than a decade, it had been able to award some eight million dollars yearly to the support of the science base of New York City's biomedical institutions.

His interest in medical education was constant, irrespective of the extent of his university activities of the moment. When primarily engaged in work for the government, his efforts necessarily had to do principally with education and training in science and in biomedical science. His interest, however, was in medical education in its totality; in his few years as an executive of the Commonwealth Fund, he was able to concentrate largely on this field. Among his major accomplishments was the successful effort to convince the Fund to make a substantial investment in support of the medical education of black students. Moreover, by no means opposed to the "Centers of Excellence" concept, he was nevertheless among the first to encourage the university-based medical centers to concern themselves also with the broad societal issues of medical care. Probably the most carefully written of his analytic essays on the social choices before us regarding the support of medical education and its sciences is "The Government and the University," given as the dinner address in 1966 before the Association of American Physicians.[40]

These three different phases of MacLeod's scientific and professional life were largely sequential. There was his fine work in the laboratory culminating in the sharply focused scientific effort with Avery and McCarty that led to the identification of DNA as the material of heredity. In the second phase, there was the creativity involved in building a model basic-science department in a university. He led in the creation of an exciting teaching program. He assembled a group of splendid scientists, junior and senior, and provided the leadership and the environment in which they could attain their maximal potential. There was the third and longest phase in which he pioneered in an area essential to the proper life of science: science and public policy or the interface between science in the university and in government.

The writer had the opportunity to observe him on many occasions at work in each of the institutional frameworks in which he labored for so long a period. It was easy to see why he was so much in demand. He was responsible, knowledgeable, always even-tempered, and quick to sense a group tension that could be allayed by his quick wit.

He had attributes somewhat unusual for a young person in science—at least in biological science in those days. He had a considerable interest in intellectual affairs outside of science as well as those of science, and he usually appeared willing, one might almost say eager, to stay up all or half the night in discussions about them. To these he brought a quick wit and great gifts as a raconteur—particularly as a teller of stories in Scot's dialect. Perhaps he possessed these behavior patterns, while others of his cohort in science did not, simply because he had the physical strength others lacked. As Robert Austrian has put it:

> One of Colin's remarkable attributes was his boundless energy. Despite the multiplicity of his responsibilities, his endless travels here and abroad, he never seemed to tire. He required less sleep than most men; and, after an animated evening of discussion with colleagues lasting into the wee hours, he could attend a meeting the next day without visible evidence of the influence of fatigue on his thinking.[41]

He had strong characteristics that in another person could have been defects. What in someone else might have been unattractive rigidity, in him was an enviable firmness and responsible consistency. While believing deeply in the social responsibility of science and in the need to work out ways to apply its useful products, he was equally deeply convinced of the importance of scientific inquiry of a completely unfettered sort. Even in his manner there were the contradictions—his small size, quick movements, and careful grooming might easily get the label of dapper—but not in him. In puzzling over why these apparent paradoxes formed an immensely effective person, one might say that the contradictions were in balance, but it was something more than that, it was really a matter of a disciplined control.

The greatest paradox of all was in personal relations. Here he gave much of himself; he had a wide circle of extremely devoted friends and was always open to their seeking of help. He gave much of himself, but he gave very little *about* himself. Several people who knew him well have commented that there seemed to be an extraordinarily large group of people, each one of whom considered themselves to have been a close personal friend of MacLeod.

Although he would not talk of himself in a personal factual sense, he would get into quite serious discussions about his philosophical beliefs. His view of life as I heard him express it on more than one occasion was based on the concept of immanence. He was fascinated with this idea. Unfortunately for a precise discussion, the concept of immanence has several rather different meanings. My own understanding from our numerous conversations is that MacLeod's immanence had the "God is everywhere" meaning. Certainly this fitted well with his unpretentious and utterly convincing wonderment about the effective intricacies and orderliness of living systems—a characteristic not so often met with in one who also was extremely interested in disease and the human condition.

Described in this way, he seems like a paragon of virtues —something I suspect he was, but cannot testify to because of the familiar phenomenon of our relative ignorance of the "other sides" of persons we know quite well. I did not know him in his roles as brother, husband, or father. I knew him as an extraordinarily capable member of the scientific community and an equally effective leader in the world of science and public policy. In short, I knew him in a certain environment, and it is the particular environment that is especially concerned in these archives. In the relatively broad confines of that environment, this is the way he was to me.

Tolstoy believed our method of classifying people by attributing to each some particular leading quality was all wrong. He conceded that one could say that someone is more frequently kind, wise, or energetic than the opposite, but to him:

> Men are like rivers. The water is alike in all of them; but every river is narrow in some places and wide in others; here swift and there sluggish, here clear and there turbid; cold in winter and warm in summer. The same may be said of men. Every man bears within himself the germs of every human quality, displaying all in turn; and a man can often seem unlike himself—yet he still remains the same man.[42]

It is on this Tolstoyan scoreboard that the MacLeod career stands so high, for almost without exception, regardless of how wide or how cold the river, he remained the same man.

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