Maclyn McCarty

1911–2005

BIOGRAPHICAL *Memoirs*

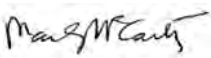
A Biographical Memoir by
Emil C. Gotschlich

NATIONAL ACADEMY OF SCIENCES

MACLYN **McCARTY**

June 9, 1911-January 2, 2005

Elected to the NAS, 1963



By Emil C. Gotschlich

The Journal of Experimental Medicine published on February 1, 1944 the paper by Avery, MacLeod, and McCarty showing that the pneumococcal transforming principle consisted of desoxyribonucleic acid. The importance of this discovery—that DNA, rather than protein, is the chemical basis of heredity— was recognized immediately by some, more slowly by others. Though the discovery eventually led to the creation of the field of molecular biology, it was never honored by a Nobel Prize. A great deal of scholarly fervor has been spent on this apparent lag of acceptance and it is not the intent to revisit this issue. In this writer's opinion, the Biographical Memoir of Colin MacLeod written by Walsh McDermott for the National Academy of Sciences is a very thoughtful summation of the reasons that delayed the prompt general recognition of this contribution.

Early life

Maclyn McCarty was born in South Bend Indiana June 9, 1911. He was the second of four boys born to Earl H. McCarty and Hazel B. Beagle. Mac's father was a branch manager of the Studebaker Corporation Company at the time it transformed itself from a builder of wagons and carriages to an automotive company. Both parents had to go to work following eight years of schooling. Mac's mother was a person with a great love of books and literature, and she instilled this passion for reading in her children.

Mac's early education was punctuated by many moves dictated by the company for which his father worked. His first schooling was in Portland, Oregon in 1917 in a single classroom managed by one teacher serving three grades. In his first six years of schooling Mac attended five schools in three different cities. In 1922 Mac's father left Studebaker and accepted a position with Nash Motors in Kenosha, Wisconsin. After that, except for one year of junior high school at the Culver Military Academy, Mac completed his primary education in Kenosha, graduating from Kenosha high school.

Early research experience

In 1929 he enrolled at Stanford University, and in his second year he decided to major in biochemistry. In his senior year Mac did a laboratory project with Professor James Murray Luck, the founder of the series *Annual Review of Biochemistry*. The project addressed whether the increase of liver size in rats following feeding of a high protein diet was simply storage of proteins, or a hypertrophy of the liver. The outcome of the 10-week study suggested that hypertrophy was occurring.

But to really understand his love of pediatrics was to watch that special light in his eyes when he spoke of it. To him each sick child was a new puzzle that came as a small bundle unable to explain what was amiss, waiting for a physician to draw conclusions based on careful examination, observation and astute analysis of all the clues available.

Already. in his early teens. Mac had decided that he wanted to do medical research and that Johns Hopkins was the medical school he would attend, believing that it was the best school to prepare him for this career. In 1933 his wish came true. In his first year at Johns Hopkins he was excused from participation in the laboratory exercises in physiological chemistry and instead undertook a project with Dr. Leslie Hellerman to carry out the purification of heparin from 20-lb lots of beef liver. This work provided him with the experience of dealing with large lots of biological materials and a lifelong distaste for liver in any form.

Domagk's discovery of Prontosil in 1935 augured a new era in treating bacterial infections, and led Mac to focus on infectious diseases and pediatrics. Upon graduation in 1937 he began three years of house staff training in pediatrics at the Harriet Lane Service at Johns Hopkins. But to really understand his love of pediatrics was to watch that special light in his eyes when he spoke of it. To him each sick child was a new puzzle that came as a small bundle unable to explain what was amiss, waiting for a physician to draw conclusions based on careful examination, observation and astute analysis of all the clues available. He published his first paper as an assistant resident under the direction of Horace Hodes on the effect of sulfapyridine on pneumococcal pneumonia in children. This was a review of 71 cases and provided not only the opportunity for the clinical management of patients, but also the isolation and serotyping of the offending pneumococci. Thus Mac gained familiarity with the laboratory aspect of handling this organism that was to become central to his later research.

New York University

In July 1940, to initiate his career in research, he joined William Tillet at NYU. They wished to determine the *in vivo* role of leukocytes in the efficacy of sulfapyridine in pneumococcal infection. They planned to render rabbits leukopenic by injection with benzene (the only agent with leukotoxic properties available at that time), infect the animals, and then test the efficacy of sulfapyridine treatment. Instead, they found that sulfapyridine prevented the development of leukopenia in response to benzene. It was known that the toxic effect was not due to benzene per se, but rather to phenolic compounds resulting by *in vivo* oxidation. Mac and William Tillet demonstrated that sulfapyridine did in fact suppress this oxidative reaction as measured by the excretion of phenolic compounds in the urine.

In order to seek support for further research training, Mac late in 1940 applied for a National Research Council fellowship in the medical sciences, and in the spring of 1941 he was selected for the award to begin in September 1941. However, the letter from the chairman of the Medical Fellowship Board urged that he consider moving to another laboratory, and suggested he work with Colin MacLeod at The Rockefeller Institute. Since Colin was leaving the Rockefeller Institute to become the head of bacteriology at NYU, Dr. Tillett contacted Oswald Avery, with whom he had worked for several years, and Mac received a position in Avery's laboratory starting September 1, 1941.

The major scientific challenge to the Avery lab at that time was to define the chemical nature of the transforming principle. This problem arose from studies published in 1928 by the eminent bacteriologist Fred Griffith in Britain. He, as well as others, had shown earlier that upon subculture in vitro in immune serum encapsulated virulent pneumococci would give rise to progeny that lacked the capsule and was less virulent or avirulent when injected into mice. This was accompanied by a change in colonial morphology on agar surfaces from smooth to rough and it became laboratory shorthand to call them respectively S and R. The R form upon injection into mice either was avirulent or could revert to the S form, but always of the original serotype from which the R form was derived. However, Griffith modified the experiment by challenging the mice by co-injection with a small inoculum of a type II derived R strain together with a large inoculum of heat killed type I pneumococci. He found that the mice succumbed to infection with type I organisms. If the co-inoculum consisted of heat-killed type III organisms, then type III organisms were found in the mice that died. Controls included in the experiments definitively excluded the possibility that there were rare survivors in the heat-killed S inocula. Hence the conclusion was that some transformation of the R

strain had occurred and the unknown factor responsible came to be called transforming principle (TP).

These induced changes in pneumococcal serotypes were utterly contrary to more than 20 years' experience with this organism that had established the fixity of the capsular serotypes, and indeed the chemical nature of the specific soluble substances (SSS) antigens as polysaccharides. Yet Griffith was a highly respected investigator, and his observation was confirmed within less than a year by Neufeld and Levinthal in Berlin and Reimann at Peking Union Medical College. Martin Dawson in Avery's laboratory confirmed all of the essential aspects of Griffith's study in a publication in 1929.

Dawson, after his move to Columbia University, continued these studies and was able to obtain transformation in vitro, but only if he used small inocula of the R form. The biological basis for this was not understood until many years later when pneumococcal transformation competence was found to be a property arising in rapidly growing pneumococci. Lionel Alloway in Avery's lab did succeed in producing soluble extracts that were able to be passed through a Berkefeld porcelain filter to remove all particles, conclusively proving that no living bacteria were involved. However, despite these clear advances published in the *Journal of Experimental Medicine* in 1932 and 1933, the assay of TP activity remained extremely unreliable.

Colin MacLeod came to Avery's laboratory in 1934 and worked on this problem, making steady progress. He identified strain R36 as being more readily transformable than other rough strains. He used the SSS III degrading enzyme to remove the type III capsular polysaccharide from TP extracts and introduced the method of Otto Sevag—shaking with chloroform—to remove proteins. He noted that the TP was very sensitive to UV radiation.

In 1940 Colin began to grow 30 to 45 liter lots of virulent type III pneumococci as starting material for the purification. This was made possible by the use of an enclosed continuous flow centrifuge called a Sharples. He derived from strain R36 a subclone named R36A that was even more reliable as a recipient R strain. The test system was improved when pneumococcal broth was absorbed with activated charcoal. He demonstrated that crystalline trypsin did not affect the activity of TP, and introduced the use of RNAse digestion to remove RNA. As part of testing for RNA contamination he used the Bial reaction, and January 1941 also tried the diphenylamine reaction, which was positive and an indication of the possible presence of DNA. In March 1941 he noted that first inactivating the cells with heat and then extracting with deoxycholate produced

extracts with much lower levels of contamination with pneumococcal antigens and equal or better transforming activity. Despite the impending move to NYU Colin prepared a dozen more large cultures in May and June and the last four were preserved under alcohol for the fall.

In mid April 1943 Avery sent his annual report to his Board; in it he stated that TP (transforming principle) was nucleic acid and that the phenomenon was genetic since the transformation of the cells was a lasting property propagated in the progeny of the transformants.

Mac joined the laboratory September 2, and Avery returned from Maine September 15, 1941. By the second week of October, Mac was fully engaged in the project. On October 21, with Colin present, he did his first Sharples run. Then for several months he did runs almost every week, By the end of January 1942 he had material from several hundred liters lyophilized after having done detergent extraction, ethanol precipitation and removal of protein by shaking with chloroform. By the end of November 1942 Mac had shown that SSS III could be completely eliminated with SIII enzyme and dialysis without affecting activity. In December 1941 he determined that adding glucose to the medium to enhance growth of the organisms was counterproductive, and that the TP activity was enhanced with much lower contamination by SSS. He also found that washing the cells before the detergent extraction greatly reduced contamination with RNA and SSS.

By January 1942 by using the SSS III enzyme TP preparations free of SSS were obtained, but upon ethanol precipitation these still gave rise to stringy precipitates that the Mac and Avery had always assumed to be due to SSS. In mid April 1942 Mac did ultracentrifugation experiments and found TP to have a high molecular weight. Upon preparative ultracentrifugation at 30,000 rpm for a few hours he found that the activity was in a small gelatinous pellet at the bottom of the tube. At this time Mac and Avery also modified the assay to always include four replicate tubes for each dilution to get clearer results in titrations.

Alfred Mirsky had developed a method for extraction of high molecular weight DNA from animal tissues such as calf thymus glands using a mild salt extraction protocol followed by removal of proteins and provided a sample. Mac found that the appearance of the ethanol precipitate of this material was remarkably similar to TP. Mirsky was given a Sharples lot and performed his salt extraction method after heat killing and obtained a

low yield of a fibrous precipitate that had good TP activity . The same lot yielded a great deal more TP after detergent extraction.

By November 1942 Avery and Mac had material from three Sharples runs (about 45 mg) for an elemental analysis and it matched the theoretical composition of DNA. They repeated this with two more runs, one of them of 300 liters. They also repeated the analytical ultracentrifugation and found that the material gave a very sharp boundary characteristic of a highly asymmetric large molecular weight material and that the activity coincided with this material. Similarly, electrophoresis revealed only a single electrophoretic component of relatively high mobility. The UV spectrum was also characteristic of nucleic acid. In mid April 1943 Avery sent his annual report to his Board; in it he stated that TP was nucleic acid and that the phenomenon was genetic since the transformation of the cells was a lasting property propagated in the progeny of the transformants.

The drafts of the paper for publication were prepared individually during the summer of 1943, with Mac writing the methods and results section while Avery wrote the introduction and discussion section. In the fall they spent many hours in the library away from interruptions rewriting the manuscript. It was submitted by hand November 1, 1943 to Peyton Rous, editor of the *Journal of Experimental Medicine*. The paper was published on February 1, 1944. Avery and Mac felt that for further evidence an enzyme specifically inactivating the TP was needed. Moses Kunitz had crystallized RNAse in 1940 from beef pancreases. Mac decided to isolate the DNAse from this source and succeeded, although crystallization was only achieved a few years later. This resulted in the submission of a second and third paper by McCarty and Avery October 10, 1945. The second paper demonstrated the susceptibility of the TP to the highly purified DNAse in the presence Mg++ or Mn++. The third paper described major improvements in the purification of the DNA, first by use of citrate to inhibit the endogenous pneumococcal DNAse during lysis with deoxycholate at room temperature. This extract was then shaken with chloroform to remove proteins, and then ethanol precipitated with two volumes and the fibrous precipitate rapidly fell to the bottom and the remainder was decanted away. The final purification step was to add CaCl2 to 1% and precipitate the DNA with 20% ethanol. This selective precipitation procedure allowed him to produce pure DNA from type II and VI capable of inducing transformation.

The Rockefeller Hospital and Streptococcus

In March 1946 Thomas Rivers, the head of the Rockefeller Hospital, anticipating the retirement of Dr. Homer Swift, who had led the Laboratory of Streptococcal Diseases

since 1922, offered Mac this position. Mac accepted the offer and took over this new responsibility on July 1, 1946.

Despite the whirlwind of five years of work only remotely related to clinical research, he welcomed the opportunity to extend his work to include direct contact with clinical problems.

Maclyn McCarty (with glasses) with his son Colin Avery McCarty, the younger of the two boys presenting New York Mets manager Gil Hodges (in uniform) with the New York Heart Association's Heart of Gold Citation. Far left is Mets broadcaster Ralph Kiner. The citation on the award reads "In recognition of his courageous battle against heart disease and his inspiration to those who face this challenge."

It was well established that in a subset of children and young adults acute rheumatic fever was a disease that occurred a few weeks following group A streptococcal infections, that it was due to intense inflammation leading to arthritis and the carditis, but the inflamed sites did not contain living streptococci. Because of the absence of the bacteria in the inflamed sites, these have been called the non-suppurative sequella of streptococcal pharyngitis. Frequently the carditis led to permanent deformities of the mitral and the aortic valves and impairment of cardiac function. Indeed, at that time the leading cause of death in the age group 40 to 50 years old was post-rheumatic heart disease. How a self-limited throat infection could lead to the sterile inflammation weeks later was an intellectually challenging mystery that as yet has eluded a clear solution.

Mac established at the Rockefeller Hospital a clinic for patients with acute rheumatic fever that over the next three decades closely followed more than 400 patients. This clinical material was supplemented by an extraordinary collection of clinical histories, sera and streptococcal strains isolated from recruits stationed at the Great Lakes Naval Station in 1946 during an epidemic of scarlet fever. With Harold Anderson and Henry Kunkel, Mac developed a quantitative procedure for determining antibodies to streptokinase, a streptococcal protein that promotes lysis of fibrin clots. They followed the antibody response of recruits with scarlet fever, including those who developed rheumatic

fever. There was a trend that patients who developed rheumatic fever exhibited a greater antibody response. Early penicillin therapy eliminating the infecting organism promptly from the nasopharynx either entirely prevented or greatly decreased the expected antibody response to streptokinase and streptolysin O.

In 1947 Mac reported the crystallization of human C-reactive protein (CRP) discovered in 1930 as a protein that reacted with the C-carbohydrate common to all pneumococci derived from the cell wall following autolysis. The prior work by Tillet and later MacLeod had indicated that this protein was present in serum during the acute phase of pneumonia, but rapidly disappeared when the patient recovered. This protein would also appear in other infections or in non-bacterial inflammatory diseases such as rheumatic fever. The exquisite purification afforded by the crystallization permitted the development of highly specific antisera to CRP with which Mac followed the course of the patients with acute rheumatic fever, and found it to be a very a useful clinical indicator because it rapidly and accurately reflected the level of inflammation. This test has become a standard clinical parameter in clinical medicine, particularly in rheumatology and in the past decade has captured much attention as a predictor of heart attacks.

In parallel with the clinical and immunological studies Mac initiated an in depth analysis of the chemistry of streptococci. His initial efforts were characterizing enzymatically active extracellular products produced by group A streptococci. He found that they produced both DNAse and RNAse. The DNAse activity was very high when compared to culture supernatant of pneumococcus, *Bacillus subtilis*, or *Escherichia coli*. Mac purified the DNAse and then determined that patients produced antibodies able to inhibit the activity of the enzyme and in some instances at very high titer. Applying this test to the sera obtained during the Great Lakes scarlet fever epidemic, he found that only 38% demonstrated anti-DNAse activity whilst most of them had significant ASO titers and streptokinase antibodies. The mean anti-DNAse response was higher in those recruits who developed rheumatic fever. The finding that only a subset of patients developed anti-DNAse antibodies stimulated Lewis Wannamaker, to look at streptococcal DNAse more closely and led to the identification of two additional distinct DNAses with different immunological properties.

The studies just cited suggested that as a group patients developing rheumatic fever had a heightened response to several streptococcal antigens. Are individuals that progress to rheumatic fever prone to excessive response to any antigen, or is this limited to streptococcal antigens? In collaboration with Kuhns, Mac determined the immune response to

diphtheria toxin of healthy individuals compared to patients after recovery from rheumatic fever. They found no significant difference in pre-existing neutralizing antibodies as determined by the Schick test (the skin reaction that ensues upon intradermal injection of a minute amount of active diphtheria toxin). They then tested the magnitude and the promptness of the antibody response to immunization with the diphtheria toxoid vaccine and found no difference between the two groups. Thus, the propensity to develop rheumatic fever is not due to a generalized immunological hyper-reactivity, but one limited to streptococcal antigens.

Beginning about 1950 Mac turned his attention to the study of the cell wall of streptococci. The Rockefeller Institute for Medical Research was pioneering the new technology of electron microscopy in the study of cell biology, but its use in the study of bacterial anatomy was just beginning. Gram+ cells walls are very sturdy structures, and mechanical disruption of the cells was challenging and initially was performed by rotating dried streptococci in heavy glass flasks with stainless steel marbles. By this method followed, by a series of washing and centrifugation steps, the cell walls could be freed of the cytoplasm. Later, the rupture of the cells was performed in a Mickle disintegrator that was essentially an electrically driven tuning fork with small vessels attached at the ends that could be filled with streptococcal suspensions and fine glass beads and oscillated. The soluble material obtained from the purified cell walls by digestion with the bacteriolytic enzymes produced by *Streptomyces albus* yielded about one third protein and two thirds carbohydrate. The later consisted mainly of N-acetyl glucosamine and rhamnose and serologically was identical to the group A antigen identified by the classic Lancefield acid extraction technique.

However, Lancefield had identified streptococci that did not react normally with group A typing sera that appeared during mouse or rabbit passage of group A strains and these had been named A variant strains. Mac investigated these strains and found that their cell walls consisted of a carbohydrate like group A, but with reduced content of N-acetyl glucosamine. To get a deeper understanding of the relation of the A to the Avar carbohydrate Mac isolated two soil organism producing enzymes respectively able to abolish the serological reactivity of the carbohydrates with their specific antibodies. The A enzyme released N-acetyl glucosamine from the group A antigen, while the V enzyme released rhamnose from the variant carbohydrate. With the use of these enzymes Mac characterized the group A carbohydrate as a polymer of rhamnose that was capped with N-acetyl glucosamine residues. Later studies with more modern techniques have confirmed the proposed structure.

McCarty (center) with fellow Academy members Richard Krause (left) and Robert Austrian (right).

Working with Richard Krause, Mac examined the cell wall carbohydrate of group C streptococci and found that it was analogous to group A except that the capping of the rhamnose backbone was with N-acetyl galactosamine. At this time another method to extract streptococcal cell walls became available, namely extraction at 170°C with formamide. The insoluble residue of the formamide extraction still had the appearance of ghosts of cell walls by electron microscopy and was composed of N-acetyl-muramic acid, N-acetyl-glucosamine and the amino acids alanine, glutamic acid, lysine, and glycine. However, this residue could be solubilized by the Streptomyces albus enzyme, or lysozyme, a characteristic of linkages that are part of the mucopeptide fraction of the cell wall and not the group carbohydrate.

These were landmark studies that gave a unified and coherent accounting of the anatomy, the chemistry and the immunology of the cell walls of group A and C streptococci, important pathogens for human beings. With this background information, Mac investigated an oddity of streptococci, the variation of colonial morphology grown on agar known as the blue <-> opaque variation. He expected to find some difference in cell wall chemistry or antigen expression, but a detailed analysis revealed no difference. The sole difference was that the opaque variants grew in abnormally long chains, suggesting a defect of separation of the individual cocci during growth. A subsequent electron microscopic study by Mac with John Swanson showed that while the cells walls had a normal thickness, the individual cells remained stuck to each other because the intercellular division septa failed to mature to complete division.

Mac encountered antisera prepared to a group A streptococcus that cross-reacted with extracts of most other streptococcal serogroups, staphylococci and some other Gram+ organisms, but not Gram- bacteria. He purified this antigen from acid extracted strepto-

cocci and found that it was a polymer of glycerophosphate (PGP). In a subsequent study he demonstrated by a milder extraction method that the PGP contained ester linked D-alanine, and that this was able to serve as an antigenic epitope recognized by some streptococcal antisera.

In the course of the first 20 years of Mac's leadership of the laboratory and the period while he was personally involved at the bench, the group A streptococcus became one of the best understood organisms in science, and served as a model for an inclusive analysis of chemistry, immunology and anatomy of a human bacterial pathogen. These studies were paralleled by clinical inquiry of patients with rheumatic fever admitted in the hospital and led to major advances in understanding the immune responses in this disease.

Beyond research

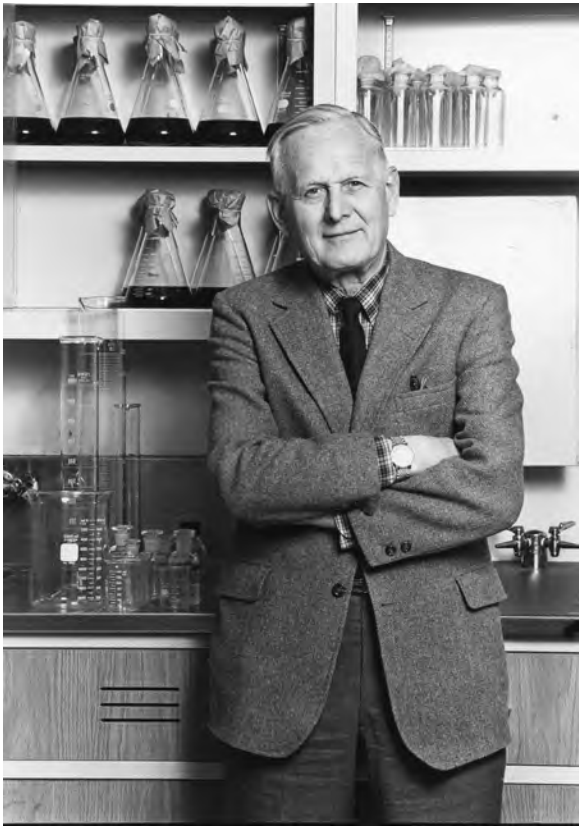
The door between Dr. McCarty's office and lab was always open. He always seemed to have time to stop what he was doing to talk to whoever entered from the lab. Midmorning coffee was an important occasion where he would enter into the laboratory with his beloved pipe and a cup of black coffee. He would be joined by Rebecca Lancefield, his fellows, and during summers by Stuart Elliott. The conversation would range over the current work, it was low key and warm, yet everyone there became familiar with what the others were doing and trying to uncover. Dr. McCarty didn't assign problems, he encouraged and helped fellows to find and develop their own problems.

It was a very gentle almost imperceptible mentorship that fostered independence of his trainees and ultimately was very effective. His example and his style of mentorship that emphasized independence right from the start ensured that the laboratory retained its excellence during the years that his many administrative responsibilities curtailed his direct work at the bench. At Mac's retirement in 1981, the lab originally started in 1922 remained active, led first by the author, and currently by Vincent Fischetti. It remains a world-leading center for microbial pathogenesis.

As Mac's scientific contributions, high scientific standards and his personal integrity became more broadly known his advice was increasingly sought. At Rockefeller University he led the clinical research program as Physician-in-Chief of the Rockefeller Hospital for 14 years. He also served as vice president for 13 years. Perhaps his most satisfying obligation was his service as editor for the Journal of Experimental Medicine

for 41 years starting in 1963. His co-editors greatly prized the scientific incisiveness of his opinion and his always seeking the meritorious aspects of the contributions that he distilled into carefully hand written reviews.

Mac was appointed to the Armed Forces Epidemiological Board as an associate member of the Commission on Streptococcal and Staphylococcal Diseases, and served from 1948 until 1972. This coincides with a remarkably productive period of research on streptococcal diseases in the military that among many advances included the demonstration that early treatment of streptococcal pharyngitis was able to prevent the development of rheumatic fever and that subsequent streptococcal infections could be prevented with very modest doses of penicillin administered orally on a daily basis.



McCarty at Rockefeller University, circa 1982. (Photo by Ingbert Grüttner.)

He was elected as a member of the National Academy of Sciences in 1963 and served as Chairman, Section of Medical Sciences 1971-74, as Member of Council 1973-76, and as Member of Report Review Committee 1974-78. In 1978, with the founding of the Institute of Medicine of the NAS, he was elected as a charter member.

Mac always felt a great satisfaction from being involved as a mentor or advisor to young people at the initiation of their scientific careers. Hence he took particular pleasure and pride in being part of The Helen Hay Whitney Foundation since 1956. From 1963 to 1996 he served as the scientific advisory committee chair of the foundation, and also as a member of the board of trustees from 1964 until 2005. The number of outstanding scientists that had their initial support from this foundation is a testament to the good

judgment and high standards set by Mac's leadership. Mac also cherished his contributions to the Public Health Research Institute of the City of New York, and served for 40 years on their board of directors starting in 1965, and as chair of the board from 1984 to 1992. He also led the institute's research council as chairman from 1969 to 1977, when New York City's funding crisis terminated direct support by the city.

Mac, with Frederick Seitz and James A. Shannon, served as a visiting committee for a grant giving program in the biomedical sciences supported by the R. J. Reynolds company, then headed by J. Paul Sticht, who also served as a member of the board of trustees of the Rockefeller University. Institutions were invited to present a few research programs for consideration and these would be reviewed during a site visit by the visiting committee. This program was funded for about six years, and dispensed about 10 million dollars annually in the form of generous RO1 type grants, none on tobacco-related research. Its most prescient choice was to support, beginning in 1979, the program of Stanley B. Prusiner on the scrapie agent that led to the recognition of prions as totally novel protein based etiologic agents for a number of diseases. The research was recognized in 1997 by the award of the Nobel Prize in Medicine. Stan Prusiner and Mac jointly wrote an article entitled "Discovering DNA Encodes Heredity and Prions are Infectious Proteins," published in 2006 in the *Annual Review of Genetics*, that muses on the similarity of the initial reluctance of acceptance that both of these discoveries encountered before becoming part of the scientific canon.

Mac traveled extensively all over the world for important professional trips. Among these were two trips to Iran. The first was a week long visit in November 1974 as part of a team from the Rockefeller University that served as an advisory group for advancement of medical research in that country. This was followed by a second trip in March 1975 by Mac, Frederick Seitz, and Rodney Nichols to plan the establishment of a biomedical research institution. However, increasing opposition to the Shah, culminating in the Islamic Revolution in 1979, put an end to this initiative. Mac also participated as member of a Rockefeller University advisory board in an 18-day trip to the Peoples Republic of China in May 1977, one of the earliest scientific contacts following the Cultural Revolution.

Mac's advice was sought by a large number of institutions, who made him a member of their advisory boards. Among these were the Stanford University School of Medicine, the Scripps Clinic and Research Foundation, the C. V. Whitney Laboratory of Experimental Marine Biology and Medicine, the Massachusetts General Hospital, and the Biomedical

Marjorie and Mac McCarty at their wedding, 1966.

Research Center for Infectious Diseases in Cairo, Egypt. His strength as an advisor was Mac's unusual combination of modesty and self-confidence; healthy skepticism mixed with tolerance and optimism; strong convictions without doctrinaire rigidity; and high personal standards. He was extremely discrete, with no need to self-aggrandize or seek credit for decisions he participated in.

Following his retirement in 1981, with a decrease in day-to day-responsibilities and at the urging of Lewis Thomas at the Commonwealth Fund, Mac revisited the events leading to the identification of DNA as the stuff of heredity. He began a meticulous review of annual reports, laboratory notes, the prevailing scientific thinking at that time and, of course, his memory as the last living participant. Mac wrote his book *The Transforming Principle* in language addressed to the lay reader, recounting the long path of the research that led to this stunning discovery. It is a highly readable account that conveys vividly the staggering amount of work, the intensity of this pursuit, and the resourcefulness needed to marshal the evidence to prove the role of high molecular weight DNA in pneumococcal transformation.

Personal life

Mac McCarty's first marriage, to the former Anita Alleyen Davies in 1933, ended in divorce. They had three sons and a daughter: Maclyn, Jr., Richard, Dale, and Colin. In 1966 he married the former Marjorie Fried. He is survived by his wife, his son Richard of Baltimore, his daughter Dale Dinunzio of Bradenton, Fla., eight grandchildren, and five great-grandchildren. Mac was very close to his family, and while his mother was alive

he and his three brothers, Von, Bruce, and Stuart would meet at least annually at her home in Winter Park Florida. When their mother died, they decided to continue this tradition. Their first meeting in the subsequent year was at South Bend, in the family's original home. Subsequently they met at least yearly, usually for a three day weekend or longer in various cities such as Charleston, Savannah, Boston and later, when Mac was not as well, in New York.

McCarty receiving the Robert Koch Gold Medal, 1981

He continued his love of traveling, and for many years Mac and his wife Marjorie would leave mid-December for London to catch some theater, move on to Paris, and then celebrate Christmas and the New Year in a French countryside inn. He had a particular fondness for Paris and loved to aimlessly stroll its boulevards.

Mac was a reserved person, but had a warm and winning persona and a large circle of fast friends all over the world who treasured his and his wife's companionship. With these Mac shared his love of Dickens novels, the theater, the fine arts and especially calligraphy, classical symphonic music, and nice dinners preceded by a Tanqueray gibson on the rocks and capped by whichever dessert had chocolate as the main active ingredient. He loved puns, and in his mouth these were by no means a low form of humor.

Honors and awards

Fittingly, many awards and honors were bestowed on Mac. Among these was the Eli Lilly Award, the Wolf Prize in Medicine, the Kovalenko Medal, the Kober Medal, the Albert Lasker Special Public Health Award, the Order of the Republic in the First Degree by the Egyptian Government, Commander's Cross of the Order of Merit of the Federal Republic of Germany, the Waterford Biomedical Sciences Award, and the Robert Koch Gold Medal. He also received honorary degrees: from Columbia University, the University of Florida, the Medical College of Ohio, Emory University, the University of Cologne, Mt. Sinai School of Medicine, Harvard, Jefferson University, Johns Hopkins University and his academic home, the Rockefeller University. He was also honored by election as a member of the American Philosophical Society, the American Academy of

Arts and Sciences, the National Academy of Sciences and as a charter member to the Institute of Medicine.

As Alexander Bearn and Richard Krause recalled in *Proceedings of the American Philosophical Society,* "He will be long remembered…as a man who combined undeviating integrity in science and every other aspect of his life, with a sense of pleasure and fun. For those who knew him, he will remain one of the most remarkable and accomplished biological scientists of the twentieth century."[1]

ACKNOWLEDGEMENTS

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Unless otherwise credited, photos in this memoir were provided by Marjorie McCarty.

1 Alexander G. Bearn and Richard M. Krause. Maclyn McCarty, 9 June 1911 · 2 January 2005. *Proceedings of the American Philosophical Society*, Vol. 151, No. 2 (Jun., 2007), pp. 247-253.

SELECTED BIBLIOGRAPHY

1939 With H. L. Hodes, W. C. Stifler, Jr., E. Walker, and R. G. Shirley. The use of sulfapyridine inprimary pneumococcic pneumonia and in pneumococcic pneumonia associated with measles. *J. Pediat.* 14:417-446.

1941 With W. S. Tillett. The inactivating effect of sulfapyridine on the leukotoxic action of benzene. *J. Exp. Med.* 74:531-544.

1944 With O. T. Avery and C. M. MacLeod. 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. *J. Exp. Med.* 79:137-158.

1946 Purification and properties of desoxyribonuclease isolated from beef pancreas. *J. Gen. Physiol.* 29:123-139.

With O. T. Avery. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. II. Effect of desoxyribonuclease on the biological activity of the transforming substance. *J. Exp. Med.* 83:89-96.

With O. T. Avery. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. III. An improved method for the isolation of the transforming substance and its application to pneumococcus types II, III, and VI. *J. Exp. Med.* 83:97-104.

1947 The occurrence during acute infections of a protein not normally present in the blood. IV. Crystallization of the C-reactive protein. *J. Exp. Med.* 85:491-498.

1948 With H. C. Anderson, H. G. Kunkel. Quantitative antistreptokinase studies in patients infected with group A hemolytic streptococci. A comparison with serum antistreptolysin and gamma globulin levels with special reference to the occurrence of rheumatic fever. *J. Clin. Invest.* 127:425-434.

1950 With H. C. Anderson. The determination of C-reactive protein in the blood as a measure of the activity of the disease process in acute rheumatic fever. *Amer. J. Med.* 8:445-455.

1952 The lysis of group A hemolytic streptococci by extracellular enzymes of Streptomyces albus. II. Nature of the cellular substrate attacked by the lytic enzymes. *J. Exp. Med.* 96:569-580.

1954 With W. J. Kuhns. Studies of diphtheria antitoxin in rheumatic fever subjects: Analysis of reactions to the Schick test and of antitoxin responses following hyperimmunization with diphtheria toxin. *J. Clin. Invest.* 33:759-767.

1956 Variation in the group specific carbohydrate of group A streptococci. II. Studies on the chemical basis for serological specificity of the carbohydrates. *J. Exp. Med.* 104:629-643.

1958 Further studies on the chemical basis for the serological specificity of group A streptococcal carbohydrate. *J. Exp. Med.* 108:311-323.

1959 The occurrence of polyglycerophosphate as an antigenic component of various Gram-positive bacterial species. *J. Exp. Med.* 109:361-378.

1961 With R. M. Krause. Studies on the chemical structure of the streptococcal cell wall. I. The identification of a mucopeptide in the cell walls of group A and A-variant streptococci. *J. Exp. Med.* 114:127-140.

1962 With R. M. Krause. Studies on the chemical structure of the streptococcal cell wall. II. The composition of group C cell walls and chemical basis for the serological specificity of the carbohydrate moiety. *J. Exp. Med.* 115:49-62.

With R. M. Krause. Variation in the group-specific carbohydrate of group C hemolytic streptococci. *J. Exp. Med.* 116:131-140.

1964 Missing links in the streptococcal chain leading to rheumatic fever. T. Duckett Jones Memorial Lecture. Circulation 29:488-493.

The role of D-alanine in the serological specificity of group A streptococcal glycerol teichoic acid. *Proc. Nat. Acad. Sci. of U.S.A.* 52:259-265.

1969 With J. Swanson. Electronmicroscopic studies on opaque colony variants of group A streptococci. *J. Bacteriol.* 100:505-511.

1971 The streptococcal cell wall. (Harvey Lecture, delivered 12/18/69). In Harvey Lectures, Series 65, pp. 73-96. Academic Press, New Y.ork.

1979 With B. Hosein and V. A. Fischetti. Amino acid sequence and structural similarities between streptococcal M protein and mammalian tropomyosin. *Proc. Nat. Acad. Sci. of U.S.A.* 76:3765-3770.

1981 With A. Bouvet and I. van de Rijn. Nutritionally variant streptococci from patients with endocarditis: Growth parameters in a semisynthetic medium and demonstration of a chromophore. *J. Bacteriol.* 146:1075-1082.

1985 *The Transforming Principle: Discovering that Genes Are Made of DNA.* (252 pages.) New York: W. W. Norton.

2006 With S. B. Prusiner. Discovering DNA encodes heredity and prions are infectious proteins. *Annu. Rev. Genet.* 40:25-45.