Obituary

Maclyn McCarty (1911–2005)

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Co-discoverer of DNA as the material of heredity

Maclyn McCarty, physician and microbiologist, died of congestive heart failure in New York City on 2 January. He was the last survivor of the three-man team that demonstrated that genes are made of DNA.

Previously, most scientists believed that genes must be made of proteins and that DNA lacked the necessary complexity to carry hereditary information. But in 1944, Oswald T. Avery, Colin MacLeod and McCarty published the first paper, in a series of three, that conclusively showed DNA to be the carrier of genetic information. This paper was entitled "Studies on the chemical nature of the substance inducing transformation of pneumococcal types", and the research crowned a 30-year effort, undertaken in Avery's laboratory at Rockefeller Hospital in New York, to understand and combat pneumococcal pneumonia.

The trio's discovery had its origins in the research of an Englishman, Fred Griffith, who in 1928 described the phenomenon of the transformation of pneumococcal types. All of Griffith's work was done *in vivo*, by manipulating pneumococcal bacteria in mice. Transformation involved a heritable change in one type of pneumococcus that was induced by a substance extracted from another type. The change was predictable and permanent, and could be transmitted from generation to generation in laboratory-grown organisms. This finding had, in McCarty's phrase, "all the earmarks of what we would call today, the transfer of genetic information".

We now know that new microbes and new infectious diseases may emerge as a result of genetic mechanisms in pathogens and selective evolutionary pressures. Yet, strange as it may seem, microbial genetic evolution is a new idea that became established long after scientists understood genetics in plants and animals. So it is no surprise that the 1944 paper was greeted with some scepticism. Nevertheless, the paper had an immediate and profound influence on the thinking and the research direction of many scientists. Frank Macfarlane Burnet, for instance, later wrote, "the discovery that DNA could transfer genetic information from one pneumococcus to another heralded the opening of the field of molecular biology". McCarty recounted the history of the discovery in his memoir *The Transforming Principle.*

According to McCarty's mother, medicine and medical research were his ambition by the time he was ten years old. While in high school, his goal was to enter Johns Hopkins School of Medicine. First at Stanford University, then at Johns Hopkins, McCarty excelled at biochemistry. After medical school he was a paediatric house officer for three years, having selected paediatrics "as the best way to promote my interest in infectious diseases".

Later, following his research on pneumococcal transformation and heredity, McCarty remained at the Rockefeller University and was appointed director of the Laboratory of Streptococcal Infections and Rheumatic Fever — the latter being a devastating childhood disease at the time. Like Avery, McCarty accepted only several junior colleagues at a time. But we were a privileged few. In an age of big science, McCarty's laboratory was a cottage industry.

McCarty used the newly emerging techniques and concepts of cell biology in his approach to streptococcal research, delineating the chemical architecture of these bacterial cells and identifying the major streptococcal antigens as constituents of the cell wall. In great detail, McCarty studied the chemistry of the cell-wall 'A carbohydrate'. He surmised that information about the structure of this substance might yield an explanation for the pathogenesis of rheumatic fever. McCarty never put into print his speculation that the immunological crossreactivity between the A carbohydrate and antigens in human connective tissue was related in some way to this pathogenesis. As Avery often said, "stick to the facts" — and McCarty did. The crossreactivity hypothesis is still not proven, but as McCarty recently noted, "it seemed reasonable to pursue at the time".

From 1954, McCarty and his colleagues began intensive studies on the viruses (bacteriophages) that infect streptococci. All efforts to transform group A streptococci had failed. But there was reason to believe that research on bacteriophages would allow entry into the genetics of streptococci and, in particular, into the genetic basis of the toxic substances they produce and the clinical conditions they cause. That expectation has since been proven correct by numerous investigators. We now know, for example, that bacteriophages carry the genes that encode the toxins responsible for scarlet fever. McCarty's work also helped pave the way for genetics research on many other pathogens, including *Vibrio cholerae* and staphylococci, and to further studies of phage-encoded toxins and other microbiological phenomena.

Although McCarty retired in 1981, he continued to go into the laboratory until the end, to discuss research progress with junior colleagues. Retirement also gave him and his wife Marjorie time to travel widely, particularly in France, England and Germany, where they had many friends who treasured their companionship. Often, they rented an apartment in Paris and settled into a daily routine. McCarty read French fluently, but he was reticent about speaking the language. In this regard Marjorie was not so shy, and she would also scan the *Michelin* guide for events that they would attend and for starred restaurants where they would dine. Even in France, dinner was preceded by a Tanqueray Gibson on the rocks. In earlier years, all of us had a Gibson or a gin Martini straight-up. MacLeod related that Avery would announce at the end of a long day in the lab: "Now let's go have 'something else'." — his term for a dry gin Martini.

The 1944 paper on pneumococcal transformation begins: "Biologists have long attempted by chemical means to induce in higher organisms predictable and specific changes which thereafter could be transmitted in series as hereditary characters." All that, and then some, has come to pass: witness the human genome, recombinant DNA technology, and genetically engineered animals that produce complex proteins such as human antibodies.

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