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CLARENCE COOK LITTLE

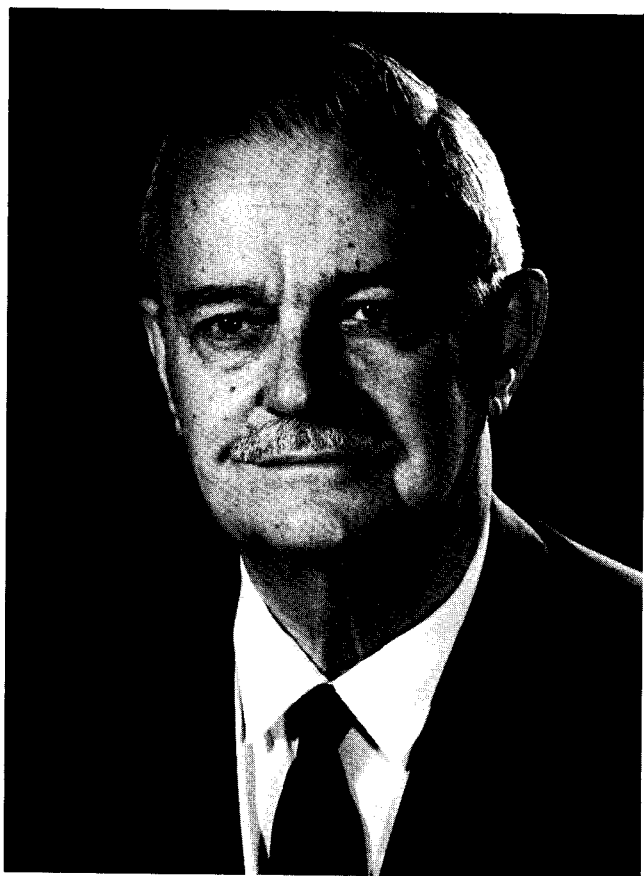
1888—1971

A Biographical Memoir by
GEORGE D. SNELL

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Biographical Memoir

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Clarence Costlette

CLARENCE COOK LITTLE

October 6, 1888–December 22, 1971

BY GEORGE D. SNELL

DR. CLARENCE COOK LITTLE died December 22, 1971, in Ellsworth, Maine, at the age of eighty-three. A leader in education, in the national effort to understand and control cancer, and in the development of mammalian genetics, Dr. Little inspired in the many people who knew him not only admiration but warm personal friendship. He is survived by his wife, Beatrice, two sons, two daughters, and nine grandchildren.

Dr. Little was born in Brookline, Massachusetts, October 6, 1888. He was a member of an old Boston family and a descendent of Paul Revere. His boyhood was spent on the family estate in Brookline, where a variety of animals and pets, including his own mice and prize pigeons, provided an early exposure to biology. He was educated at Noble and Greenough School and Harvard College and continued at Harvard as a graduate student in mammalian genetics under Dr. William E. Castle, who pioneered in the application of Mendelian principles to mice and rabbits. During his senior year at Harvard, Pete, as he was known by his college friends, was captain of the track team. Dr. Castle related later how this handsome team captain signed up for his genetics course and soon had persuaded most of the team to sign up with him.

While still a graduate student at Harvard, Dr. Little became interested in studies being carried out by Professor Tyzzer at

Harvard Medical School on the inheritance of susceptibility and resistance to tumor transplants in mice. This work led him to prepare a paper, published in *Science*, describing a type of multifactor inheritance that anticipated present concepts of histocompatibility genetics. Little's major research interests—transplantation, the cancer problem, and mammalian and especially murine genetics—were established during this period.

Following the award of his D. Sc. in 1914, Dr. Little held various positions at Harvard: secretary to President Lowell, assistant dean of the college, and acting marshal. With the entrance of the United States into the First World War, he enlisted in the army and trained at Plattsburgh, New York. Subsequently he was assigned to administrative duty in Washington with the Signal Corps, later to become the U.S. Air Force. He was discharged in 1918 with the rank of Major. After his war service, Dr. Little spent three years at the Station for Experimental Evolution in Cold Spring Harbor, New York, serving during the last year as assistant director.

Throughout this period Dr. Little maintained his interest in mammalian genetics and cancer. He published numerous papers and even during the war saw to it that his animal colony was maintained. Perhaps his most lasting contribution was the establishment of the first inbred strains of mice. Inbreeding had been extensively studied in corn, and Jennings had examined mathematically the expected increase in homozygosis. The mouse was a logical choice for inbreeding experiments with a mammal, perhaps, in fact, an especially fortunate choice, since wild populations of mice form small colonies with considerable inbreeding so that the accumulation of deleterious recessive genes is restricted. But successful establishment of a homozygous strain required careful selection from a colony of adequate size. Dr. Little's pioneer inbreeding efforts resulted in two highly successful inbred strains, the dilute brown (DBA) strain, begun when he was still at Harvard, and the black

(C57BL) strain, started at Cold Spring Harbor. The genetic uniformity of these and the dozens of other lines subsequently produced in many laboratories makes them a research tool of major importance. The C57BL strain heads the list in popularity—worldwide annual use certainly exceeds one million mice. The DBA strain is not far behind.

The time was less propitious for another project that Dr. Little undertook at Cold Spring Harbor. In collaboration with Halsey Bagg he attempted to induce mutations in mice with X rays. Hermann Muller was to win the Nobel Prize in 1946 for a similar experiment with *Drosophila*, but with mice the number of gametes that it was feasible to test was too small; also the X-ray dose used was probably too low. Two variants appeared, but at least one of these also turned up in the controls.

In 1922, at the age of thirty-three, Dr. Little became president of the University of Maine. He was at this time the youngest college president in the country. Perhaps his most successful innovation during the three years that he held this office was the establishment of Freshman Week. This was held prior to the opening of college and was "designed to instruct all freshmen in methods of study, in choice of courses, and in the aims and value of college work as well as to give an opportunity for the study of the individual freshman in order to recognize, measure, and in so far as possible begin to utilize his particular abilities, and to avoid or to bolster up his weaknesses." The success of this institution is attested to by its permanence and its imitation by other universities. Although there was some growth in the university plant during Dr. Little's term of office, he was not as successful in obtaining money from the legislature as he had hoped to be.

One of Dr. Little's stipulations in accepting the University of Maine presidency was that he have funds and facilities to continue his biological research. Several young men whom he

interested in biology during this period remained associated with him for years. He also succeeded in establishing at Bar Harbor, Maine, a summer laboratory on the site where The Jackson Laboratory was later to be built.

After three years at the University of Maine, Dr. Little was offered and accepted the presidency of the University of Michigan. His appointment provided "an unprecedented \$5000 for research assistance," testimony to his determination to continue his research. He was later able to add substantial support from outside sources. Again his tenure of office was marked by innovation and attempted innovation. A Freshman Week was introduced; a School of Forestry and a Department of Postgraduate Medicine were established; the first faculty research fund was created, and research expanded substantially. A plan to enroll all freshmen and sophomores in a separate University College under its own dean encountered a barrage of faculty criticism and was dropped. Lack of funds rather than active opposition was principally responsible for the demise of a plan for the erection of dormitories housing a few instructors or professors as well as students and designed to serve as small residential colleges.

The latter plan was typical of Dr. Little's interest in the welfare of the undergraduate. A representative group of students met regularly in his home. He worked successfully for better intramural athletic facilities that could serve the student body as a whole. Less popular in some quarters was a ban on liquor in fraternity houses and, with some exceptions, on the use of autos by students.

But probably nothing stirred up more controversy than Little's views on birth control. He spoke out for this boldly and repeatedly. Many people were not ready for such frank talk, and some bitter criticism resulted. The official history of the university refers to his presidency as a "stormy term" and

"brilliant but tactless," but in retrospect it appears that his successes were substantial and his failures prophetic.

The year 1929 was a turning point in Dr. Little's life. In January of that year he submitted his resignation to the Regents of the University of Michigan. He also was divorced from his first wife after eighteen years of marriage and three children. Doubtless his divorce had something to do with his break with the university, as did the antagonism he had aroused in some quarters among the faculty. Perhaps he had decided also that his talent lay in pioneering and not in routine administration. With financial help from the Jackson and Ford families of Detroit and Mount Desert Island, he turned to his first love, research, and set out to create in Bar Harbor a laboratory for the study of mammalian genetics and cancer. When Roscoe B. Jackson, one of the major donors, died, the laboratory was named in his honor.

The laboratory was staffed by a group of six young men and one woman who had worked with "Prexy," as he was still called, during his years as college president. The first major project undertaken by the staff was a study of the genetics of tissue transplantation. Crosses were made between the now highly inbred strains of mice, and data gathered on the growth of transplantable tumors in the parental and various hybrid generations. The existence of multiple genes for susceptibility and resistance, subsequently called histocompatibility genes, was thereby established. Another project took advantage of the great difference in mammary tumor incidence between some of the inbred strains. In a cross between high and low strains, it was found that tumor incidence of the first hybrid generation was determined by the maternal parent. Subsequent foster nursing experiments implicated some agent transmitted through the mother's milk. Dr. Little at the time was under the influence of the antiviral school of thought—the word virus was

taboo, as at least one young staff member discovered—but other laboratories picked up the work and proved the existence of a mammary tumor virus.

In these early days, the research at the laboratory, despite its substantial success, was not carried on in easy circumstances. Nineteen twenty-nine was the year when the stock market broke. After a brief honeymoon, the deepening depression cut off sources of support. The research continued, but on a curtailed basis while the staff turned to fishing, gardening, and canning to provide food. It was at this time that the laboratory initiated the sale of its inbred strains to other investigators, an activity that ultimately became both a major service to researchers all over the world and a much needed source of uncommitted income.

The depression finally passed. Dr. Little initiated a program of modest expansion that ultimately was to change the character of the laboratory considerably, but for the first two decades of its existence its small size and location in "down-east" Maine permitted a mode of life that he and his associates found much to their liking. Dr. Little was an enthusiastic outdoorsman, a knowledgeable ornithologist, and an accomplished fisherman. The Maine countryside provided an ideal setting for these interests. He raised a strain of dachshunds that his father had first brought to this country and was in demand as a judge at dog shows. The life at the laboratory was kept informal. During the winter there were monthly parties, with games and refreshments, in which all employee families participated. If the games lagged, which they seldom did, Dr. Little could always liven the occasion with some good stories. In the warmer seasons there might be a laboratory picnic at which he could still display his prowess in a footrace. World War II took a number of workers away from the laboratory and led to a greatly increased production of mice suitable for the study of

tropical diseases, but the research went on, even though curtailed.

It was during this same early period that Dr. Little started a program of summer training in research for precollege and college students. This program was ultimately to expand considerably. Its numerous alumni, many of them now physicians or engaged in biological research, still refer fondly to Dr. Little as "Prexy."

With the end of the war the laboratory seemed headed for a period of substantial expansion when disaster struck a second time. The main laboratory building was largely destroyed in the forest fire of 1947 that burnt part of the town of Bar Harbor and many summer estates and hotels. The mice were wiped out excepting a few in a fireproof section of the building. Resisting pressure from friends to relocate at some major research center, Dr. Little, with the enthusiastic agreement of the staff, determined to rebuild in Bar Harbor. Part of the staff moved to temporary quarters in other laboratories, part to a remodeled barn on a summer estate that had been donated earlier. The inbred strains of mice flooded back from laboratories around the world, and potential grantors heard, as they never would have otherwise, of their essential value to hundreds of researchers. Within two and one half years the laboratory was housed in far better quarters than it had enjoyed before the fire, and Dr. Little was able to see the staff expand and the research grow and diversify.

One project in which Dr. Little took particular pleasure was the Behavior Study, centered in the barns of the estate already mentioned. Because of the favorable location and Dr. Little's knowledge of genetics and of dogs, Alan Gregg of the Rockefeller Foundation planned with him the creation of a center for the study of behavioral genetics. The project was started with colonies of several breeds of dogs, but inbred mice

were later included with considerable profit. Dr. Little followed the project with interest and found time to study the segregation of canine coat color genes in the second and third generation hybrids of the various breeds.

The founding and direction of a laboratory would have been enough of a career for most men, but Dr. Little found the time and energy for additional major undertakings. In 1929 he became managing director of the American Cancer Society and retained this position till 1945. In the fall of 1930 he traveled extensively throughout western Europe, studying methods of cancer research and care. He was impressed by the long-term view of European cancer workers and urged the desirability of a cancer research program in the United States with similar orientation. He also stressed the need for better facilities for cancer patients and for doctor education in cancer detection and care. In 1935, with these goals substantially attained, he led in the organization of the Women's Field Army, dedicated to lay education concerning cancer. This had a tremendous influence in changing the public attitude toward cancer and in encouraging early diagnoses.

Dr. Little's recognized scientific accomplishments and ability as a leader, his impressive good looks, his warm personality, and his talents as a public speaker and raconteur naturally led him into other positions and activities. He was twice president of the American Association of Cancer Research and was influential in creating *Cancer Research* as its official journal. At one time or another he also served as president of the American Eugenics Society, the American Birth Control League, and the American Euthanasia Society. He was for years a warden in the Bar Harbor Episcopal Church. He was in demand as a speaker and always drew a good audience at local affairs, including the occasional church service at which he gladly filled in for the rector. In 1937 Dr. Little was appointed as one of the six original members of the National Advisory Cancer Council, a

body created by the act of Congress that established the National Cancer Institute. The council played an influential role in setting the policies for cancer research in this country. There were considerable differences of opinion within the council. Dr. Little appears to have been one of the active supporters of the grants-in-aid and peer-review systems that have done so much to further biomedical research in this country.

In 1954, shortly before his retirement as director of The Jackson Laboratory, Dr. Little accepted a position as scientific director of the Tobacco Industrial Research Committee, a position he held until his death. Because of the link between cigarette smoking and cancer, already suspected at the time, he was widely criticized for accepting this position. Doubtless there were many reasons back of his decision. It did have at least two positive aspects. It gave him continuing opportunity, and probably considerable freedom, to influence biomedical research through the disbursement of funds; by providing an outlet for his still considerable energies, it enabled him to make a complete break with the laboratory, giving his successor a free hand.

Dr. Little was a member of the American Academy of Arts and Sciences and the National Academy of Sciences, to which he was elected in 1945, as well as of various scientific societies. He was the recipient of numerous honorary degrees. The Clarence Cook Little Hall at the University of Maine, the Clarence Cook Little Science Building at the University of Michigan, and most recently the Clarence Cook Little Library and Conference Center at The Jackson Laboratory were named in his honor.

In both science and education, Dr. Little was perhaps more the originator than the exploiter of new developments. He preferred the broad view to attention to detail. But despite his diversity of interests, he found the time to be a productive scientist. He was the author of 188 papers, three books on

cancer directed primarily at the layman, and a book on coat color in dogs. Of his scientific achievements, perhaps four stand out: the development of inbred strains of mice and the demonstration of their value in medical and biological research; the formulation of the genetic theory of susceptibility and resistance to tissue transplants; the discovery of the milk-transmitted murine mammary tumor incitor; and the establishment, with Rockefeller Foundation initiative and support, of a study of the genetics of behavior. Of necessity, Dr. Little's personal participation in these projects decreased as his executive duties increased. But if his varied administrative responsibilities narrowed his own opportunities for scientific exploration, he used them, with warmth and wisdom, to open the doors so that younger men could reach for new horizons. Perhaps this was his greatest contribution.

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KEY TO ABBREVIATIONS

- Am. J. Cancer = American Journal of Cancer
 Am. J. Roentgen Radium Ther. = American Journal of Roentgenology and Radium Therapy
 Am. Nat. = American Naturalist
 Ann. Clin. Med. = Annals of Clinical Medicine
 Bull. Am. Soc. Control Cancer = Bulletin of the American Society for the Control of Cancer.
 Cancer Res. = Cancer Research
 J. Am. Med. Assoc. = Journal of the American Medical Association
 J. Cancer Res. = Journal of Cancer Research
 J. Exp. Med. = Journal of Experimental Medicine
 J. Exp. Zool. = Journal of Experimental Zoology
 J. Genet. = Journal of Genetics
 J. Hered. = Journal of Heredity
 J. Natl. Cancer Inst. = Journal of the National Cancer Institute
 Occas. Publ. Am. Assoc. Adv. Sci. = Occasional Publication of the American Association for the Advancement of Science
 Proc. Natl. Acad. Sci. = Proceedings of the National Academy of Sciences
 Proc. Soc. Exp. Biol. Med. = Proceedings of Society for Experimental Biology and Medicine
 Sci. Mon. = Scientific Monthly
 Sigma Xi Q. = Sigma Xi Quarterly

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