Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

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C. C. Little, Cancer and Inbred Mice

James F. Crow

Genetics Department, University of Wisconsin, Madison, Wisconsin 53706

IN January 1929 the Regents of the University of Michigan accepted the resignation of C. C. Little as President. He had become increasingly controversial during his tenure and was often at odds with the Regents. He was a great innovator and always wanted more than they were able to deliver. Often he was ahead of his time. In the words of George SNELL (1975), "His successes were substantial and his failures prophetic." The difficulties were not just financial. He loudly and repeatedly advocated birth control, euthanasia, and eugenics, not the best public relations for a university president. He was also an outspoken proponent of equal rights for women and minorities. Although he was handsome and had a charming personality, he could also be stubborn and tactless in his numerous controversies. The faculty strongly opposed his suggestion of a separate undergraduate college for freshmen and sophomores, and the Regents were further annoyed by his approaching the Governor and Legislature directly. He tried to ban automobile driving by students, which put him at odds with undergraduates. A further reason for his departure was an attention-getting divorce at about that time. It is not surprising that his resignation, if not forced, was at least welcomed by many.

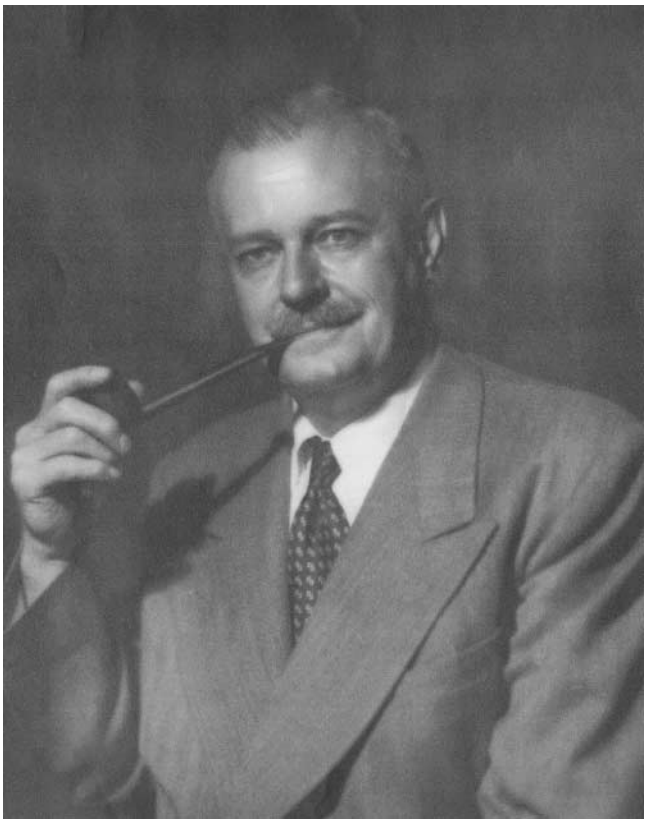
What was a welcome relief for some at the University of Michigan was a great opportunity for research in genetics. Starting in 1923, Little had conducted summer research programs at Bar Harbor, Maine. Now, in 1929, he decided to make the most of being jobless by converting this to a year-round institution. That was the beginning of the Jackson Laboratory, soon to become a world center of mouse genetics (HOLSTEIN 1979). It may well be that this is what Little really wanted. Clearly his interests were in mouse research, so a fulltime laboratory was far preferable to having one conflict after another as a university president. From the beginning, he was deeply interested in cancer. He was convinced that the best way to study cancer was with genetics, the best way to study genetics was with mice, and the best way to study mouse genetics was with inbred lines (HOLSTEIN 1979, p. 218).[1]

Clarence Cook Little was born in Brookline, Massachusetts, on October 6, 1888, a direct descendant of Paul Revere. As a child he enjoyed animals and had his own mice. He was also an athlete and later captained the Harvard track team. Using his popularity and powers of persuasion, he inveigled a number of his teammates to enroll with him in William E. Castle's genetics course. Little remained physically active and years later at the Jackson Lab took part in foot races. When he completed an undergraduate degree at Harvard in 1910, he remained as a graduate student of Castle (PROVINE 1986; SNELL and REED 1993; WEIR 1994). In addition to his work with Castle, he became interested in acceptance and rejection of tumor transplants in mice, work being pursued at Harvard by Edward E. Tyzzer.

Little started doing mouse research with Castle in 1907 while still an undergraduate. He had long had an interest in dogs and later wrote a book on canine color inheritance (LITTLE 1957). Castle persuaded him that dogs were too large and too slow breeding for productive genetic study and that he should work with mice, which he did. Castle continued to study rabbits and rats, while another student, John Detlefson, worked with guinea pigs. After Detlefson left, in 1912, Sewall Wright came to Harvard. Castle assigned him the guinea pig work, and he stayed with them the rest of his laboratory life. He enjoyed guinea pigs, but recognized their limitation for genetic research; consequently, his students worked with mice and Drosophila.

I have often wondered what the world of genetics would be like if Little had studied guinea pigs and if Wright had studied mice. Wright was a much deeper thinker than Little. Undoubtedly mouse genetics would have advanced at a faster pace. The studies would have been more physiological, more developmental, more chemical, and much more quantitative. Castle's assign-

[1]As an instance of the vagaries and occasional surprises from using a search engine, my hunt for more information about C. C. Little revealed "Little cc," which turned out to be a calico kitten cloned at Texas A&M University. The letters cc stand for carbon copy.



C. C. Little. Blackstone photo, courtesy of The Jackson Laboratory.

ment was unfortunate in this way, for Wright was handicapped all along by the much greater difficulties of studying genetics in guinea pigs rather than in mice. He did, however, take advantage of several long-time sib-mated lines in the U.S. Department of Agriculture to do a beautiful study of inbreeding (Wright 1922). He might have had an interest in developing inbred lines in mice, for his knowledge of inbreeding was deep; but this is not clear. What *is* clear, however, is that he would never have established the Jackson Lab. Wright's shy, introverted manner would have been totally incompatible with organizing a research institution. He would have been a miserable failure at money-raising. Little, in contrast, had an optimistic, gregarious manner. He was a great public speaker, and he undoubtedly charmed potential donors, something Wright could never have done. So the way things worked out is not so bad. It might, however, have been still better if Little and Wright had *both* worked on mice. With their complementary interests, the field would surely have advanced much faster than it did.

Most of Little's work with Castle was on color inheritance, but he did write an early paper related to graft rejection. Tyzzer had thought that his data could not be explained by Mendelian principles. However, Little (1914) pointed out that traits determined by a large number of loci could appear non-Mendelian. This was a significant step in understanding the genetics of transplantation in mammals. Later the two (Little and Tyzzer 1916) made the fundamental discovery that transplants from inbreds to hybrids were successful, whereas the reverse transplants were rejected. Little was ahead of his time in realizing the importance of inbred lines and showed great zeal in developing them. The two most famous lines, still highly popular, came from his early work. The *DBA* (dilute brown) strain was developed while he was still at Harvard, and the *C57BL* (black) shortly afterward. The mouse was particularly good for developing inbred lines. Commercial strains were already somewhat inbred, being descended from small colonies kept by mouse fanciers, so that many harmful recessive alleles had been purged. Also, mouse fanciers in Europe and Asia had bred recessive mutants; Little used Japanese waltzing mice in his transplantation studies (Little and Tyzzer 1916). Furthermore, wild mice were known to have a deme structure with small local breeding populations. Finally, the ability to rear large numbers permitted strong selection in a large colony, a necessity for getting highly viable inbreds.

After graduation from Harvard, Little was secretary to President Lowell and assistant dean, in addition to his active research program. This pattern continued throughout his life; usually he was simultaneously involved in several jobs. Also, while still a graduate student, he began a lifelong habit of getting into controversies. The first to be published was his criticism of Dr. Maud Slye, who, he said, had oversimplified cancer inheritance and had even misinterpreted the inheritance of albinism. For many years Slye maintained that cancer resistance is a simple dominant allele, and Little did not let this pass unnoticed.[2]

Little received his Ph.D. in 1914 and soon after was involved in World War I. He served in the U.S. Army Signal Corps (later the Air Force) and graduated with the rank of Major. During this time he was stationed in Washington while his Harvard stocks were kept by the Tyzzer lab. After the war he spent three years at Cold Spring Harbor. Again, his engaging personality and administrative skills were recognized and he soon became assistant director. During this period came one major failure: he tried to induce mutations with X rays. Unfortunately, the experimental design and small numbers were inadequate to the problem. A few years later, H. J. Muller was able to develop methods in Drosophila that ensured success (Crow and Abrahamson 1997), but once again Little's ideas were ahead of their time.

Administration soon called again. In 1922, Little be-

[2]Since full disclosure is now *de rigueur*, let me confess that as a college student I was taken in by Maud Slye's work. Thinking of perhaps going into genetics, I discovered in the public library a then-new book that began with the work of T. H. Morgan (Jaffe 1935). The book also included a chapter on Slye, which I found utterly fascinating.

came president of the University of Maine, the youngest college president in the United States. He was innovative—often too innovative for the job. He started one custom that many other universities followed: a freshman week, in advance of the academic year, so that incoming students could learn university ways and how to fit into them. He also insisted on having a laboratory and doing research while holding the presidency. Soon, his outspoken manner got him into trouble. His ambitions and continuous desire for more funds ran afoul of the Governor, Percival B. Baxter, with whom he carried on a public feud in the press. Not surprisingly, he left in 1925, this time to accept the presidency of the University of Michigan.

As I mentioned above, his stay at Michigan was highly controversial. As earlier at Maine, he demanded as a condition for accepting the job that he have a laboratory and an unprecedented $5000 for research support. This wasn't all the money that he got, for he had made the acquaintance of several Detroit automobile executives who summered at Bar Harbor. In their home territory of Michigan, they were sitting targets for Little's fundraising blandishments, and he soon had additional support for his research. He continued to emphasize the summer program at Bar Harbor and took several students with him. I think it is likely that, while at Michigan, he already had ideas for a full-year program in Maine.

In any case, he left the Michigan presidency with a running start toward expanding the Bar Harbor activity to a full year. Again he used his contacts with wealthy automobile manufacturers to get a laboratory started. The land was donated by a family friend, George B. Dorr. In the early stage of the lab's development, Roscoe B. Jackson of the Hudson Motor Car Corporation, who had been a major donor, died. This led to the immediate decision to call the new institution the Roscoe B. Jackson Memorial Laboratory. Several years later the name was changed to The Jackson Laboratory. As usual, Little held more than one job. In September 1929 he accepted the half-time position as managing director of what was later to become the American Cancer Society.

The full-year Bar Harbor program was formally organized and running in the summer and fall of 1929 with a staff of seven. Little administered the Lab in a highly informal way. He left each researcher free to sink or swim and, although he occasionally gave advice or criticism, for the most part his policy was one of benign neglect. Although the researchers worked separately, there was nonetheless a policy that all the work was to be discussed openly. The Laboratory members were very close socially; for example, they had a monthly party in which all, with their families, participated. Prexy, a name that stayed with him after his university presidencies were over, was always an active participant. His athletic prowess, his magnetic personality, and his abilities as a speaker and raconteur all generated the respect and affection that the staff members held for him. Later, of course, the Laboratory grew to be much larger, but most of this happened after his retirement. I think he liked the intimacy and informality of a small group of like-minded mouse enthusiasts. A notable achievement during this period was publication of *Biology of the Laboratory Mouse* (Snell 1941), which was a group endeavor. Little was the mortar that held the bricks together when the edifice was in danger of crumbling. Under his leadership the Lab survived during its formative years and the hard times soon to come.

The Laboratory was just getting going in October 1929 when the stock market crashed. Soon after, the large gifts from Michigan fell to near nothing and the Laboratory went into a hand-to-mouth existence. Little's fundraising skills were put to a severe test. Salaries had to be greatly reduced, and staff members made ends meet by a community garden and fishing expeditions. Fortunately, the Cancer Society position supported a secretary. Such things as carpentry were part of the job. By 1933, there was considerable doubt each month about the next payroll. The staff was considerably reduced. But, almost miraculously, the program held together, and beginning in the fall of 1933 it got along much better. In a few years it was growing. Little's money-raising skills were finally bearing fruit so that funds for Laboratory expenses were less tight. Fortunately a new source of income emerged: the Laboratory started selling mice, and eventually this became a major part of the organization.

Three of the best known appointees came soon after. George Snell, who had worked with H. J. Muller at the University of Texas, joined the Laboratory in 1935. He adapted some Mullerian Drosophila-like techniques to analyze histocompatibility and the H-2 locus (Klein 2001). Later he was to win the Nobel Prize for his work. Elizabeth Russell, soon to become widely recognized as a leader in hemoglobin and pigment genetics, arrived in 1937. She came with her husband Bill Russell. Later they were divorced and Bill started the large-scale radiation ("megamouse") experiments at Oak Ridge (Davis and Justice 1998).

During this time the National Cancer Institute was formed, and in 1938 one of its first grants went to the Jackson Laboratory. Mouse sales continued to rise. By 1941 the Laboratory was shipping some 2500 mice per week, and in the next three years the number grew to more than 9000. For comparison, the current weekly number is about 44,000. In 1946 the research staff numbered 13. In the 1940s the Laboratory received additional income by performing fee-generating Ascheim-Zondek pregnancy tests.

Meanwhile Little was continuing his work as Director of the American Cancer Society, and, as always, he was not a silent partner. His forceful and direct speaking style was what this organization needed, dependent as it was on leadership and drive. Under his direction the

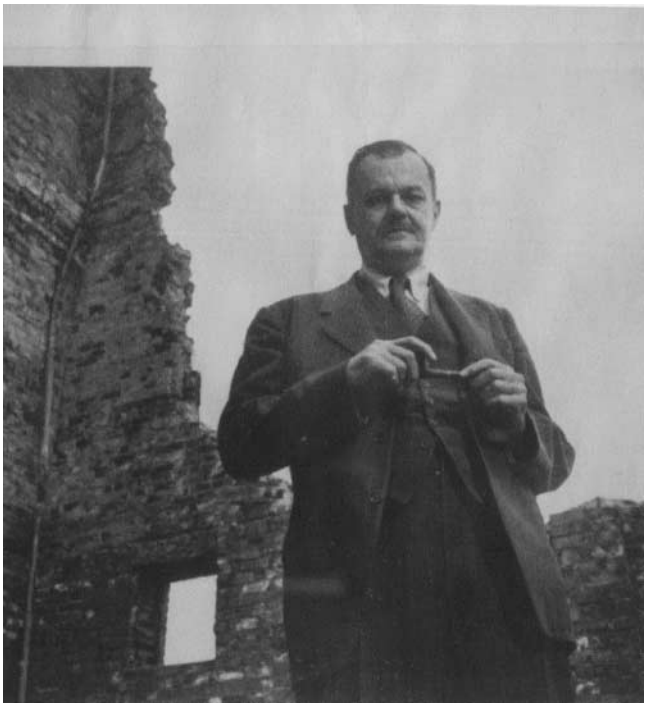
Society expanded into a strong national organization with regional divisions, and money rolled in.

By 1947 the Laboratory was thriving. The research staff now numbered 19. Grants were coming in. The depression and war years were over. Then tragedy struck again. In October 13 a brush fire was discovered some 8 miles from the Laboratory, but over the next few days it seemed to be under control. Elizabeth Russell (1987) remembers seeing a small plume of smoke. Then, on October 23, a combination of a changed wind direction and an unusually dry summer combined to turn a local brush fire into a devastating conflagration. Any attempts to save the mice were given up and the priority changed to saving human lives. Several buildings were utterly destroyed, and almost all the mice were lost. Immediately afterward, C. C. Little presided over a meeting of the staff. Some, along with several trustees, had wanted to move the laboratory elsewhere, but Little was insistent on rebuilding the Laboratory in its existing location.

Happily, tragedy was turned into opportunity. It was easy to raise money for reconstruction. The National Cancer Institute and the American Cancer Society contributed generously, and soon a rebuilding project was underway. Very few mouse strains were permanently lost, for laboratories all over the world offered to return mice of special strains that they had earlier obtained from the Jackson Lab. The whole experience brought renewed vigor, and in five years the research staff had increased to 33. By 1950 the Laboratory was back to normal operation. Growth in both numbers and diversity has continued ever since. More than 60 inbred strains were maintained at the Laboratory, of which about 30 were in demand and produced in large quantities. In addition to inbred lines, the Laboratory supplied F_1 hybrids, notable for vigor and uniformity. Enormous numbers of these were used for the large chemical surveys instituted by the National Cancer Institute.

In 1954 the Laboratory celebrated its 25th anniversary with William Castle, then 86, as special guest. Two years later, C. C. Little resigned and was replaced by Earl Green, who was far more interested in administrative details. The result was a tighter ship, and more growth, which still continues. Whereas Little was a dreamer and innovator, Green was an organizer and consolidator. Nevertheless, Green carried on a fairly extensive research program in radiation genetics, whereas by this time Little did hardly any hands-on research.

When Little retired, he quickly moved to a position that enabled him to sever completely his connection with the Laboratory. After years of being at the center of controversies, he got into the biggest controversy of all. He became chairman of the Scientific Advisory Board of the Tobacco Industrial Research Committee, later becoming Scientific Director and continuing this for the rest of his life. His acceptance of the position made him appear to condone smoking, just at the time when the controversy over cigarette smoking and lung cancer was heating up. Although the evidence was becoming stronger, he continued to maintain that a causal connection had not been established. An experimentalist through and through, he distrusted statistical evidence. He was vilified by epidemiologists and by the press. An example is a strongly critical article in the form of an open letter to him. Written by Dr. D. D. Rutstein of the Harvard Medical School, it appeared in The Atlantic Monthly (October 1957). Perhaps the best thing to say about this period is that the position gave him the opportunity to support research in the effects of smoking, an opportunity that he seized with vigor (Snell 1975). His career ended as it began—in the eye of the storm.



C. C. Little in front of burned out buildings after the 1947 fire. Photo courtesy of The Jackson Laboratory.

Despite eventually being heavily criticized in each university presidency, he is memorialized by Clarence Cook Little buildings at both Maine and Michigan, buildings that are still in active use. The Conference Center at the Jackson Laboratory is also named after him. He received many honors, including several honorary degrees. In his lifetime, he wrote 188 papers and three books (Snell 1975).

Little's greatest accomplishment is undoubtedly his founding the Jackson Laboratory and, with sheer will and personality, carrying it through hard times to its eventual success. His greatest scientific accomplishment was seeing the potential value of inbred lines for genetic and cancer research and developing a number of them. It is hard to imagine mouse genetics without the Jackson Lab inbreds! A second great accomplishment was his

early development, with colleagues, of a theory for the genetic control of transplant acceptance and rejection. Taking advantage of partially inbred lines, Little and Tyzzer (1916) found that grafts from parent to F_1 were accepted, whereas reciprocal grafts were rejected. Subsequent crosses gave a minimum estimate of the number of histocompatibility loci. Out of this grew the great work on the H-2 loci, leading to a Nobel Prize for Snell. A third great accomplishment under his leadership was the "milk factor," a maternally transmitted breast cancer, discovered by Bittner and worked on by many at the Laboratory. It is one of the earliest and most striking examples of a virus-induced cancer. And all along he was busy encouraging his staff to study various aspects of mouse genetics. As he had been earlier in his University positions, he was especially helpful to young scientists.

Characteristically, Little's societal activities never let up. He seemed totally incapable of holding only one job. In addition to his work advocating birth control and cancer research, he was president of the American Eugenics Society and the American Euthanasia Society, both unpopular. He never shunned controversy; rather, he seemed to welcome it. Throughout his life he was in demand as an organizer and speaker. I had only one chance to become personally acquainted with him. But from this brief experience, I can attest to his charming, even charismatic personality. His presence was immediately felt and could light up a whole room.

Finally, I would like to repeat something that I wrote on the occasion of the Jackson Lab's fiftieth anniversary (Russell 1981, p. 323):

> I once read an anthology of Sherlock Holmes stories in which the collector thanked the would-be patients of the young Dr. A. Conan Doyle for *not* seeking his services, thereby converting him into a writer. In the same vein, I should like to thank those people at the University of Michigan whose opposition to Little's personal and administrative decisions led to his resignation as President and to the founding of the Jackson Laboratory.

My greatest debt is to Don Bailey, who supplied an abundance of information about the early days. Ben Taylor helped by reading the manuscript and making useful suggestions, Joyce Peterson aided in getting photographs of C. C. Little, and Tyra Young provided several useful details.

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