Oscar L. Miller

1925–2012

BIOGRAPHICAL *Memoirs*

A Biographical Memoir by
Joseph G. Gall

NATIONAL ACADEMY OF SCIENCES

OSCAR LEE **MILLER, JR.**

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By Joseph G. Gall

Oscar Miller, Jr., was a pioneering cell biologist who, during a long career of teaching and breakthrough research, gained his greatest renown by creating electron micrographs clearly showing genes in the process of transcription. The photos displayed serially repeated ribosomal RNA genes that were individually recognizable, resembling a string of "Christmas trees" with transcription just beginning at the top of the "trees" and nearly complete at the bottom. These stunning images proved what molecular biologists had only postulated about actively transcribing genes. Starting with this signal triumph, he led two laboratories where, over a 25-year period, he and small, select groups of doctoral candidates, post-docs, and faculty associates turned out a vast array of groundbreaking discoveries.

Miller earned his bachelor's (1948) and master's (1950) degrees in agronomy from North Carolina State College (now University). From 1950 to 1956 he was a tobacco farmer, after which he enrolled in the doctoral program at the University of Minnesota and was awarded a Ph.D. in plant genetics in 1960. He set up his first lab in 1961 at the Oak Ridge National Laboratory, where he continued his research until 1973. That year he became chair of the University of Virginia's biology department, simultaneously directing another cell biology lab for the next six years, before giving up his administrative duties to devote himself wholly to teaching and research till his retirement in 1995.

In the fall of 1960 Oscar Miller joined my laboratory as my first postdoctoral student. He was three years my senior, almost to the day. These simple statements hide much more than they reveal. I had joined the Zoology Department at the University of Minnesota as a freshly minted instructor in 1952, immediately after obtaining my Ph.D. at Yale, and I was still feeling my way as a teacher and independent scientist in 1956, when Oscar became a doctoral candidate in the Agronomy Department.

As part of the requirement for the Ph.D. Oscar was required to pass a foreign language course, but there was a loophole by which he could substitute a "techniques" course instead. Oscar decided that French and German were not for him, so he arranged with me, sometime in 1957, for a one-on-one course on chromosome structure. I don't remember exactly what he did—something to do with the giant salivary-gland chromosomes of flies, I think—but we soon found that we shared the same love of chromosomes and hands-on research. We decided that it would be good to extend his work in my lab after he completed his Ph.D., and so Oscar applied for and obtained a one-year postdoctoral fellowship from the NIH, which began in the fall of 1960.

The university had a generous sabbatical leave policy then, and I had already decided to spend a year abroad, half in Scotland with H. G. "Mick" Callan and half in Germany with Wolfgang Beermann. Callan was already a close colleague, being one of the few other people at that time working on the giant lampbrush chromosomes—named for their unique shape—of salamanders. Beermann was a rising star in cytogenetics, working on the equally giant polytene chromosomes of the fly *Chironomus*. I don't remember now the details of my discussions with Oscar, but we came to the unusual arrangement that he would take care of my laboratory while I was away. At that time there were no other students in my group, so he had a free hand to choose his own project, primarily looking at lampbrush chromosomes with our newly-acquired electron microscope. And so, while I was overseas, my first postdoc was taking care of the laboratory and training himself! And to make things complete, he and his young family moved into my house and took care of that as well.

Shortly after I returned from Europe, Oscar left my lab for his first independent position, at the Oak Ridge National Laboratory in Tennessee. All of this was before he came up with his famous chromatin spreading technique, for which I take no credit whatsoever. Indeed, I remember that when Oscar sent me the first electron micrograph of an active gene without telling me what it was, I had no clue what I was looking at. So, perhaps he was my first postdoc, but in fact he was a thoroughly self-directed brilliant experimenter who only needed to be left alone to work his wonders. I am proud to have been linked to him at the start, even tenuously. Through the years we kept in close contact and my respect for Oscar only grew stronger as he and his students made seminal discoveries one after another.

Early life

Until I began to research this biography I knew nothing about Oscar's early life except for the few details that he told me himself. He was proud of the fact that after getting a degree (actually both B.S. and M.S.) in agronomy at North Carolina State College (now University), he had been a tobacco farmer for six years before deciding to go for further education. When recently I asked for details from his former students and associates, I found that the experience as a farmer is about all that anyone had been told by him directly. It seems clear in retrospect that he wanted to project an image of humble origins—a simple rural farmer who decided to better himself. Without in any way detracting from Oscar's incredible career, I have to say that a few clicks on my computer revealed a more complex and illuminating history of the man.

Oscar Lee Miller, Jr., was born April 12, 1925, in Gastonia, North Carolina, son of Oscar Lee Miller and Rose Evans Miller. His father was an orthopedic surgeon who had received his medical degree in 1912 from the Atlanta College of Physicians and Surgeons (later part of Emory University). The elder Miller moved with his family from Georgia to Gastonia in 1921 after being appointed the first surgeon-in-chief and director of the North Carolina Orthopaedic Hospital for crippled children. Two years later he opened a private clinic in Charlotte, later to be known as the Miller Clinic. His influence in orthopedics throughout the state and nationally was profound (Frankel and Raney, 1971). One continuing evidence of his stature is the existence of an annual "Oscar Miller Day Symposium" sponsored by OrthoCarolina Research Institute (OCRI), in its 37th year at the time of this writing (2017). Oscar, Jr., had three siblings: an older sister, Mrs. Caroline Miller McClintock; an older brother, Dr. Robert Evans Miller, who like his father, was an orthopedic surgeon; and a younger brother, the Reverend John Neel Miller. It is clear, therefore, that young Oscar came from an established and well-to-do family of professionals, and his subsequent rise to prominence as a scientist was not without precedents.

In early 1943 Oscar entered North Carolina State as a freshman. He soon turned 18 and was faced with being drafted into the army, since this was at the height of the Second World War. He chose instead to join the navy's V-12 College Training Program, which he attended at the University of Virginia from July 1943 to October 1944. After finishing the V-12 program Oscar entered the Naval Reserve Midshipmen's School, earning his commission as an ensign in March 1945. Although the war ended shortly thereafter, he was stationed aboard the U.S.S. Midway and served as a machine gun battery officer from January until June 1946. He was discharged from active duty not long thereafter.

He then returned to North Carolina State, where he received his B.S., cum laude, and M.S. There then followed the famous six years as a tobacco farmer, from 1950 to 1956. One slight hint that this was not entirely a hardscrabble existence comes from a C.V. that Oscar himself put together, which lists this period as "Manager of Commercial Farm, Horry County, S.C." In other words, Oscar and his new wife, Mary Rose, were not struggling against all odds to make ends meet by cultivating a few acres of tobacco by themselves. It is likely that Oscar did work some in the fields, but as farm manager he undoubtedly had other duties that occupied much of his time and required managerial skills.

Whatever the exact circumstances, Oscar decided to acquire a higher degree in agronomy and ended up in a Ph.D. program with Charles Burnham at Minnesota, beginning in 1956. Burnham was a corn geneticist, one of the famous group of like-minded scientists who had trained in the 1920s and 30s at Cornell University under the tutelage of Rollins Emerson. Among those who worked together at that time were also Marcus Rhoades, George Beadle, and Barbara McClintock. Both Beadle and McClintock went on to become Nobel Laureates.

Oscar's thesis problem was to examine a mutant in corn called *asynaptic* (*as*) (Miller, 1963). Asynaptic refers to the fact that homologous chromosomes—that is, the two similar chromosomes derived from the maternal and paternal parents— were not paired at meiosis, as they are in normal plants. The mutant had been around for a number of years, but the precise basis for the lack of pairing was not known. Oscar carried out a detailed cytological analysis of all stages of meiosis, showing that homologous chromosomes did pair early on, but later tended to fall apart. One can see from the published paper that Oscar was already a superb technician whose images of chromosomes were not only scientifically revealing but aesthetically pleasing.

Lampbrush chromosomes

Oscar did his Ph.D. work in the Agronomy Department, which was located on the "Ag" campus, across town from the Zoology Department. He then moved to my laboratory for his postdoctoral work. During the year I was away Oscar used the electron microscope in my lab to examine the giant lampbrush chromosomes (LBCs) found in developing oocytes of the American newt (salamander) *Notophthalmus viridescens*. My thesis at Yale had focused on these wonderful chromosomes, and I continued to study them after taking my first independent position at Minnesota in 1952. Although I had done a little electron microscopy on LBCs for my thesis, it was not until 1958 that

I obtained an EM for my own lab, only the second at the University of Minnesota. The first one was in the Anatomy Department and was operated by a talented postdoctoral fellow, Marilyn Farquhar, who was extremely helpful to me in my early EM studies. Marilyn became an internationally known cell biologist, currently (2017) at the University of California, San Diego.

During his postdoctoral year in my lab Oscar began looking at newt LBCs, and he continued to do so after moving to Oak Ridge in 1961. Unless one has tried personally to place the giant LBCs from a single, hand-isolated oocyte nucleus onto a tiny electron microscope grid, one can have little idea what skill is required. To further subject these chromosomes to various experimental manipulations requires both talent and patience, both of which Oscar had in abundance. His seminal studies on the fine structure of lampbrush chromosomes were finally published in 1965 (Miller, 1965). They had been presented as part of an "International Symposium on Genes and Chromosomes: Structure and Function," held in Buenos Aires, Argentina, in late 1964. This symposium and several others held in various Latin-American institutions were the brainchild of Alexander Hollaender, then director of the Biology Division at Oak Ridge.

Nucleoli

The next Oak Ridge symposium was held in late 1965 in Montevideo, Uruguay, and was entitled, "International Symposium on the Nucleolus, Its Structure and Function." Oscar and I both attended this symposium. He presented a paper entitled "Structure and Composition of Peripheral Nucleoli of Salamander Oocytes" (Miller, 1966), based on his studies at Oak Ridge. I presented a paper on "Nuclear RNA of the Salamander Oocyte" (Gall, 1966), my first real foray into hard-core biochemistry, carried out in my new lab at Yale. Oscar's paper contained the best evidence to that date that the extrachromosomal nucleoli in the amphibian oocyte contained amplified ribosomal DNA. The Montevideo Symposium was remarkable in that it brought together, for the first time, classical cytologists working on the structure of the nucleolus and the new breed of molecular biologists who studied gene structure and function. This was just a year or two before the revolutions in gene cloning and DNA sequencing occurred. Montevideo was Oscar's second trip to South America, and it helped solidify an enduring interest he and his wife, Mary Rose, had for South American, Central American, and Mexican science and culture.

Christmas trees

Few scientists are so completely identified by a single revolutionary finding as Oscar and his famous images of transcribing genes, published in 1969 in *Science* with only him and his technician Barbara Beatty as co-authors (Miller and Beatty, 1969). I was, of course, familiar with the EM images of LBCs and nucleoli from the newt oocyte that Oscar had already published. But I was unprepared when he sent me an image of ribosomal RNA transcription units and asked me to guess what they were. I had no clue and told him so.

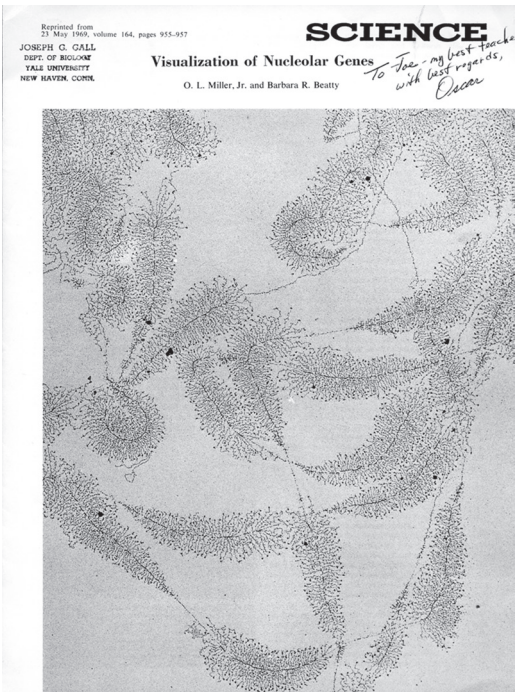

Figure 1. The famous cover of *Science* (May 1969) showing an electron micrograph of actively transcribing ribosomal RNA genes, from an oocyte nucleus of the salamander *Triturus (Notophthalmus) viridescens*. (Presentation copy from Oscar Miller to the author.)

It is quite remarkable what a difference a small change in isolation medium had made. When GV (germinal vesicle) contents were spread in a saline of about 0.1 M, the lampbrush chromosomes maintained their "normal" contours and the extrachromosomal nucleoli remained as compact objects showing little internal detail. But when Oscar isolated a GV in distilled water with a small amount of detergent, producing what became known as a "Miller spread," the ribosomal genes spilled out of the nucleoli in a most remarkable manner (Fig. 1). No longer tightly wound up inside the nucleoli, the serially repeated ribosomal RNA genes were individually recognizable. They looked like little Christmas trees all in a row, separated from each other by a thin strand. Oscar recognized that each Christmas tree was a gene with its nascent transcripts still attached to the DNA template. The short transcripts, at the top of the tree, were just beginning transcription, whereas the longer transcripts at the bottom were nearing completion. For the first time ever, his electron micrographs provided striking confirmation of what molecular biologists had postulated about actively transcribing genes. We were able to see "genes in flagrante transcripto," as Oscar amusingly dubbed his images (Miller, 1972).

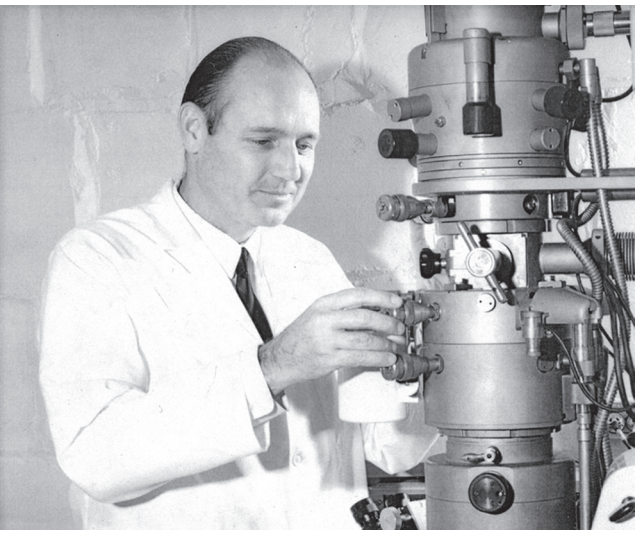

Figure 2. Oscar Miller operating his electron microscope at the Oak Ridge National Laboratory, before 1973.

The next 25 years saw a remarkable outpouring of manuscripts from Oscar's lab, first at Oak Ridge (Fig. 2) and, after 1973, at the University of Virginia, where Oscar went as chair of the Biology Department. Most of these manuscripts were co-authored with only one or a few of his graduate students, postdocs, or associates. His was clearly a small operation of highly skilled and dedicated individuals, determined to use this marvelous new technique to illuminate all aspects of gene structure, transcription, and gene replication in eukaryotes and prokaryotes alike. In all, about 75 original reports and reviews appeared until Oscar essentially closed his lab and ceased publication in the mid-1990s. It would be impossible in the confines of this biography to discuss all of these papers, but I will try to give a flavor of this work by highlighting some of the major issues addressed.

The first papers dealt with transcription of the repeated ribosomal genes in the amphibian oocyte. In the late 1800s and early 1900s cytologists had examined oocytes from many animals and had demonstrated that the oocyte nucleus could contain up to 1000 "nucleoli" that were not associated with the chromosomes. The significance of this fact remained obscure until Oscar showed that each of these nucleoli contained a small amount of DNA (Miller, 1966). Not only that, the DNA in these extrachromosomal nucleoli was made up of tens to hundreds of copies of a specific gene, that coding for ribosomal RNA (rDNA). Thus, in 1969, when his famous *Science* paper appeared, Oscar already knew that each amphibian oocyte nucleus contained at least 100,000 active copies of the rDNA genes. His genius lay in recognizing that each "Christmas tree" represented one of these actively transcribing genes. Oscar's discovery beautifully illustrated Pasteur's classic statement that "chance favors only the prepared mind."

Then came a series of outstanding papers that described transcription in bacteria (including simultaneous transcription and translation), transcription and gene amplification of the chorion genes in *Drosophila* (fruit flies), rDNA replication in yeast, polysome structure in sea urchins, simultaneous transcription and replication in a *Drosophila* gene, and on and on (Miller, et al., 1970; Hamkalo, et al., 1974; McKnight and Miller, 1976; McKnight and Miller, 1977; Martin, et al., 1980; Beyer, et al., 1981a; Beyer, et al., 1981b; Osheim and Miller, 1983; Jamrich and Miller, 1984; Saffer and Miller, 1986; French and Miller, 1989; Osheim, et al., 1996). Each of these papers was a small gem, attesting not only to Oscar's wide-ranging interests, but also to the remarkable group of young investigators whom he attracted to his small lab. An incomplete list of the individuals involved includes Barbara Hamkalo, Aimee Bakken, Steve McKnight, Ann Beyer, Linda Saffer, Yvonne Osheim, Milan Jamrich, Sarah French, Marina O'Reilly, and his long-time assistant, Martha Sikes. Given the time-frame involved—the early 1970s to the early 1990s—a noteworthy feature of this group is the high percentage of female graduate students, postdocs, and associates, several of whom went on to distinguished independent careers. Thus, among his other praiseworthy traits, Oscar was an early and strong advocate for women in science.

Oscar held his position as chair of the University of Virginia's biology department for six years. It is remarkable that not only did his output of good science not decline during this period, but arguably some of his best work was carried out while he had significant administrative duties. Those who witnessed these years remember him as both an intellectual and a social leader. He made strong appointments of young faculty, who found themselves in an exciting and nurturing environment. Because of his scientific contacts both at home and abroad, Oscar brought many outstanding speakers to the department.

During the same period that he and his colleagues were publishing one informative study after another, Oscar was also on the lecture circuit. In some years he presented his findings in as many as 25 lectures, both in the United States and abroad. He spent most of 1980 as a visiting professor at the Max-Planck-Institut für Zellbiologie (Ladenburg bei Heidelberg), half of 1984 as a visiting professor at the University of California, Irvine, and half of 1986 as a Senior Fulbright Scholar, Division of Molecular Biology of the Commonwealth Scientific and Industrial Research Organisation (CSIRO), New South Wales, Australia.

Recognition from his peers naturally followed his scientific accomplishments. Among many other honors, Oscar was elected to the National Academy of Sciences in 1978,

received the Cell Biology Award from the German Society for Cell Biology in 1980, was Senior Scientist Fellow of the Alexander von Humboldt Foundation in 1980, and received the Outstanding Achievement Award and presented the commencement address to the Graduate School, University of Minnesota, in 1994.

Oscar closed his laboratory in 1995, at age 70, and no longer accepted students. However, he maintained an active interest in the Biology Department at Virginia until his death in 2012 at the age of 86.

Epilogue: Oscar and Mary Rose

It would not be appropriate to recount Oscar's success as a scientist without mentioning his wife (and muse) Mary Rose. The Millers married in 1948 and until Oscar's death they were inseparable. Mary Rose was not a scientist herself, but she was supportive in all aspects of Oscar's career, and she shared his interest in gardening, travel, and entertainment. Ask any of Oscar's students, friends, or associates what they remember best about Oscar, and they will invariably mention the parties at the Millers' home in Charlottesville. Let me quote here from Ann Beyer, one of Oscar's postdoctoral fellows and then long-time colleague at Virginia (with her permission).

> *The frequent dinners at their Charlottesville home for visiting speakers were legendary. There were usually 20 or so in attendance, including the entire lab group, additional biology faculty members, and always someone you couldn't predict but who enlivened the evening, such as a neighbor or a University dean, or an esteemed humanities professor. Everyone's spouse/significant other was included. Dinner was buffet style and featured the delicious southern dishes that Mary Rose was famous for, often with vegetables from their garden. (Oh, that sweet corn!) The evenings were quite informal and went on for hours, always with music and sometimes with dancing. For those who stayed till the end, Oscar would bring out his stash of moonshine and steer the conversation to controversial topics (e.g., politics or sticky ethical situations) and encourage a friendly but heated exchange. These were really wonderful evenings.*

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