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George Snell and the Gold Medal

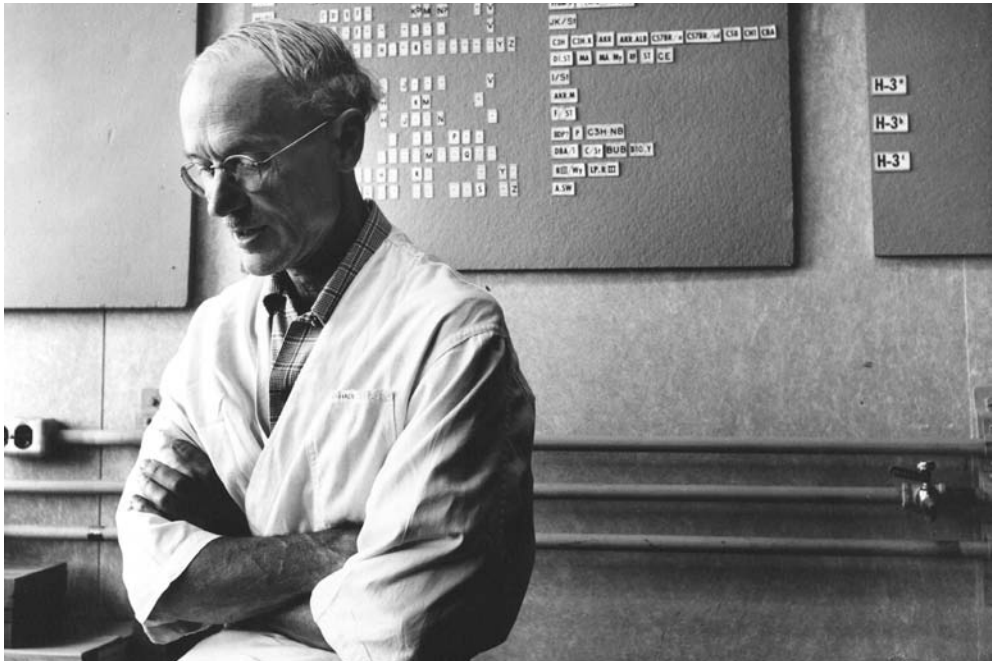
By Joyce Dall'Acqua Peterson

Before dawn on October 10, 1980, the phone rang at 21 Atlantic Avenue in Bar Harbor, Maine—a compact, white, split-level house, with a columned front porch. It was a breezy night, but not too cold, so the last of the tomatoes in the tidy vegetable garden would make it through without freezing.

But the occupants weren't home. George D. Snell, Sc.D., a scientist at the Jackson Laboratory in Bar Harbor (JAX), and his wife, Rhoda, were in a hotel room in Newburyport, Massachusetts, near the home of their son, Peter.

The call was from Sweden, and, had Snell answered, he would have heard firsthand that he and two other scientists had won the 1980 Nobel Prize in Physiology or Medicine. It was Peter (second on the Nobel Committee's phone list) who first received the news, and he delivered it in a phone call to his father at the hotel, conferencing in his brother Thomas, in Wentworth, New Hampshire, and his brother Roy, in South Woodstock, Vermont.[1]

Hearing the first words of congratulations from his son, Snell would later tell friends, he initially thought he had received an award for his garden. "And you got the impression he would have been even more pleased with a garden trophy,"[2] says Jackson



George Snell ca. 1960 in his lab, in front of a chart of the H2 genes he was tracking for his work to understand the immune system. *Photo by Bernard Cole courtesy of The Jackson Laboratory*

Laboratory Professor Lenny Shultz, Ph.D., who, as a postdoc, had worked in the lab next to Snell's.

Professor David Serreze, who, like Shultz, was a young JAX scientist when Snell was winding down his research career, keeps Snell's vintage stapler on his desk as a treasured parting gift from the Nobel laureate. Serreze recalls that Snell generously shared much of the produce from his garden: "We got our kids to eat carrots, because we sold them as Nobel carrots."[3]

Lauded by all who worked with and around him as both brilliant and humble, Snell is acknowledged worldwide for establishing the foundation of immunological research.

The immune system provides the major line of defense against infectious microorganisms. However, immune defenses can also attack normal tissues, resulting in autoimmune diseases such as lupus or rheumatoid arthritis, or rejection of a transplanted organ.

During his four decades at JAX, Snell performed the painstaking experiments that established our understanding of the method by which the body's immune system recognizes the difference between its own tissues and foreign invaders—work that has enabled every successful organ transplantation ever conducted.

The Harvard Connection

Snell was born in Bradford, Massachusetts, in 1903, and his family moved to Brookline three years later. He spent his childhood summers in South Woodstock, Vermont, at his family's farmhouse on their seventy acres. "The summers I spent at 'the farm' were among the delights of my childhood and youth," Snell related in his official Nobel Prize autobiography.[4] "An interest in gardening, farming and forestry have been a permanent legacy of the experience this home provided." Snell also had an early interest in mathematics and science, and enjoyed sports most of his life: touch football as a youngster, skiing and tennis as an adult.

While an undergraduate at Dartmouth College, Snell took a course in genetics that captured his interest and set him on the path for his future career. The professor of that course, John Gerould, advised him to do his graduate studies at Harvard University's Bussey Institute, directed by William Castle. Castle was the first American biologist to look for Mendelian inheritance in mammals. And an earlier student of Castle's, Clarence Cook Little, would have an outsized influence on Snell's life.

In 1922, at the extraordinarily young age of thirty-three, Little became the president of the University of Maine. In the summers, he would bring students to Mount Desert Island, on land owned by a family friend, George Dorr, for biology field studies. At thirty-six, he was recruited to be the president of the University of Michigan. A charming visionary, and himself from a prominent Boston family, Little was comfortable socializing with the wealthy automobile barons of Detroit, most of whom (such as Edsel Ford and Roscoe B. Jackson, president of the Hudson Motorcar Company) also summered on the island.

But Little was a contentious figure at Michigan, he was at odds with the regents on many topics, ranging from finances to his progressive views on birth control and the equality of the sexes. Divorcing his wife added to the controversy.[5] He

resigned in January 1929, and immediately began work on his next move.

Little had two big and prescient ideas that would transform science. The first was that mice are a good model for human disease. Modern genomic sequencing reveals that mice and humans share up to 98 percent of genes. Thus, mice get the same diseases as humans, for the same reasons. Little was also responsible for developing inbred mouse strains, populations of genetically identical mice that provide a stable platform for experiments to meet the scientific gold standard of reproducibility. Today, mice are far and away the most widely used model for biomedical research, and nearly ten thousand strains are available from JAX.

Little's other big idea was that cancer has a genetic component and was not, per the early-twentieth-century consensus, an infectious disease. He had noticed that certain strains of his inbred mice were more likely than others to develop tumors. This idea has also been confirmed in the present century: while only a few cancers are inherited, every cancer involves faulty genetic processes.

In May of 1929, Little established the Roscoe B. Jackson Memorial Laboratory, with seven other scientists (including a female trailblazer, Elizabeth Fekete) as one of the world's first cancer genetics research institutions. Funding came from Jackson, Ford, and other supporters. Meanwhile, Dorr, who would assemble the acreage that would become Acadia National Park, set aside the parcel of land that would be the footprint for JAX.

Coming to Maine: "Almost Inevitable"

By 1934, Little's laboratory had grown to thirteen people, including caretakers for the research mice, and Little was working on building the research staff. Little had maintained a correspondence with Snell as a fellow Bussey Institute alumnus, and, aware of Snell's interest in working with laboratory mice, recruited him to join the faculty. "Despite small salaries and financial insecurity, the research character of the Jackson Laboratory was attractive for young scientists such as Snell, who joined the staff in 1935," an institutional history recounts.[6] Snell would later describe JAX as "almost the inevitable selection as a place to work."[7]

The modesty of Snell's new surroundings were in stark contrast to the grand Ivy League universities of his past, and to the prestigious international institutions where most Nobel laureates conduct their work. The young "JAX," as the scientific world already referred to it (it was the laboratory's telex address) consisted of a single building, smaller than most of the nearby "cottages," the mansions of the rich summer visitors to Bar Harbor.

"My first summer I slept in a tent on top of a platform behind the Lab," Snell would recount in 1984. "There were a number of these platform tents used by students or summer visitors. There was a shower in the basement of the Lab, which everyone shared. Things were very primitive."[8]

But, Snell said, by 1935, the laboratory's financial situation was beginning to emerge from the depths of the Great Depression. "The staff had by that time stopped having a communal garden to grow vegetables," he reported, likely with some regret.[9]

George Snell photographed in the 1940s with the wooden mouse boxes of the day. *Photo courtesy of The Jackson Laboratory*

Of Mice and Maine, and Immunology

In his first years, Snell focused on inducing and analyzing chromosomal changes in laboratory mice, and subsequently worked on the issue of standardizing the names of genes and mouse strains for the international research community.

In 1944, Snell decided to study the genetics of tumor transplantation. By then, Little and other scientists had already established that genes controlled the immune response; tissue transplantation from one mouse to another was successful only when both mice were from the same inbred strain. But what were these genes, and where were they located on the chromosomes?

Today, in order to study the effects of a gene in health and disease, it's possible to engineer a genetic change in a single generation of mice, using technologies such as CRISPR-Cas9. But in Snell's and Little's day, the only way to isolate a specific genetic variant was by cross-breeding mice over multiple generations, and this process often took years.

And in the days before genetic sequencing, mice were a "black box," genetically speaking. It was not possible to tell just by looking at a mouse whether or not it was carrying the invisible genetic trait that was needed—which, in Snell's case, were the genes that confer immune resistance—until the experiments were actually performed, such as testing whether the mouse rejected tumors or other tissues from another animal.

But sometimes the early geneticists got lucky, and the gene for an invisible trait was passed along with a visible physical trait such as coat color. Snell was lucky,

George Snell receives his Nobel Prize from Sweden's King Carl XVI Gustaf. *Photo courtesy of The Jackson Laboratory*

his very first cross yielded a "clear and close association" of tumor rejection or acceptance with a dominant inherited trait, a loop or kink about halfway down the length of the tail, known as a fused tail.[10]

The gene for the fused-tail trait was already known to be located on Chromosome 17. The gene site turned out to be a complex of multiple genes that would become known as the major histocompatibility complex, or MHC. And the MHC would turn out to be the immune system machinery that orchestrates the body's reactions to foreign tissues.

Amazingly, the 1947 fire that wiped out JAX and thousands of acres on Mount Desert Island had spared Snell's research records. An assistant of Snell's, Dick Desjardens, had recently come home from World War II and was waiting to be accepted into medical school. "Dick had the very good sense to take my records, which were in a steel filing cabinet, out of the old part of the building, which burned to the ground, and move them into the fireproof part," Snell said.[11]

Snell continued to study the genetics of immunology for two more decades. The younger scientists around him admired him for his "very sharp mind and giving nature," Shultz says. "If you looked for George you would find him in the lab. That's where he was, that's where his mind was. George's breakthrough technology was his mind."[12]

From the Vegetable Patch to the World Stage

Once he retired in 1976, Snell settled into a quiet routine of gardening and a bit of correspondence with fellow scientists. The news

of the Nobel was a considerable jolt. "I was completely overwhelmed," he told *The New York Times*, adding that he had "not the slightest idea" that he was even being considered for the prize.[13]

On December 10, 1980, at a ceremony at the University of Oslo in Norway, Snell and fellow immunologists Baruj Benacerraf and Jean Dausset received the Nobel Prize in Physiology or Medicine "for their discoveries concerning genetically determined structures on the cell surface that regulate immunological reactions."[14]

When it was Snell's turn to accept the award, he walked up to Sweden's King Carl XVI Gustaf. As the men shook right hands, the king passed Snell his Nobel diploma, written on parchment and enclosed in a red leather cover, and on top of the diploma was the prize medal itself, encased in a gray woven paperboard box lined in pigskin suede.

The 1980 Nobel medals were the first to be made from 18-carat gold plated with 24-carat gold (previously, they were made from 23-carat gold). It glows with a matte, not shiny, finish, and it weighs 175 grams, or about the same weight as a smartphone.

A profile portrait of Alfred Nobel and the dates of his birth and death in Roman numerals are on the front side of the medal. On the reverse is a sculpted image of two females, representing "the Genius of Medicine holding an open book in her lap, collecting the water pouring out from a rock in order to quench a sick girl's thirst," according to the Nobel website.[15] Around the edge of the medal is the Latin inscription, "Inventas vitam iuvat excoluisse per artes" (And they who bettered life on earth by their newly found mastery).

The original medal is in the possession of Snell's son, Thomas. The Jackson Laboratory archives hold official facsimiles of the medal and diploma.

Snell died at his Bar Harbor home on Thursday, June 6, 1996 at the age of ninety-two.[16] His work at JAX is acknowledged as the foundation of modern immunological research. Today, new generations of scientists at JAX and around the world are exploring the role of the immune system in cancer, neurodegeneration and cardiovascular disease, as well as infectious disease and autoimmune diseases such as type 1 diabetes and lupus, with the goal of developing new and effective clinical therapies.

But for those who knew him, Snell's legacy was his kindness, generosity, and modesty. "He was a gentle giant," says JAX Professor Derry Roopenian, "more interested in encouraging young scientists than in accolades of his own monumental achievements."[17]

Joyce Dall'Acqua Peterson is now in her third decade at the Jackson Laboratory, where she began as the public relations manager and recently moved to an all-writing role. Except for a short stint at a Washington, D.C. publisher, and the two years when she and her husband lived in northern Italy running a vineyard and an Arabian horse farm, her entire career has been in nonprofit public affairs, including at the Smithsonian Institution's National Air and Space Museum, the erstwhile Corcoran Gallery of Art, and the American Farmland Trust.

Acknowledgments: Jackson Laboratory scientists, including Barbara Knowles, Lenny Shultz, Dave Serreze and Derry Roopenian, have been eager to share with me their reminiscences of the kindly George Snell over the years. No look at Jackson Laboratory history is possible without the help and resources of archivist Doug Macbeth. I salute the late Jean Holstein, who worked in the Snell lab and who later wrote a painstaking history of the lab's first fifty years. This article is dedicated to the scientists who move to Bar Harbor from all over the world to find cures for human diseases and who, along the way, also make our island community a better place.

1. "Sketches of Three Winners of Nobel Prize," *The New York Times*, October 11, 1980.

2. Interview with author, November 2, 2017.

3. Interview with author, November 2, 2017.

4. "George D. Snell — Biographical," Nobelprize.org, last modified February 12, 2018, https://www.nobelprize.org/nobel_prizes/medicine/laureates/1980/snell-bio.html.

5. James F. Crow, "C. C. Little, Cancer and Inbred Mice," *Genetics* 161 no. 4 (August 1, 2002): 1357-1361.

6. Jean Holstein, *The First 50 Years at The Jackson Laboratory* (Bar Harbor, Maine: The Jackson Laboratory, 1979).

7. George Snell, oral history interview with Patricia Harrison, October 23, 1984.

8. Harrison, oral history.

9. Harrison, oral history.

10. Holstein, *The First 50 Years at The Jackson Laboratory*.

11. Harrison, oral history.

12. Interview with author, November 2, 2017

13. "Sketches of Three Winners of Nobel Prize," *The New York Times*, October 11, 1980.

14. "The Nobel Prize in Physiology or Medicine 1980," Nobelprize.org, last modified February 12, 2018, https://www.nobelprize.org/nobel_prizes/medicine/laureates/1980/.

15. "The Nobel Medal for Physiology or Medicine," Nobelprize.org, last modified February 11, 2018, https://www.nobelprize.org/nobel_prizes/medicine/medal.html. Nobelprize.org, "George D. Snell—Biographical."

16. "George Davis Snell, 92, Dies; Won Nobel for Genetics Work," *The New York Times*, June 8, 1996.

17. Interview with author, November 4, 2017.