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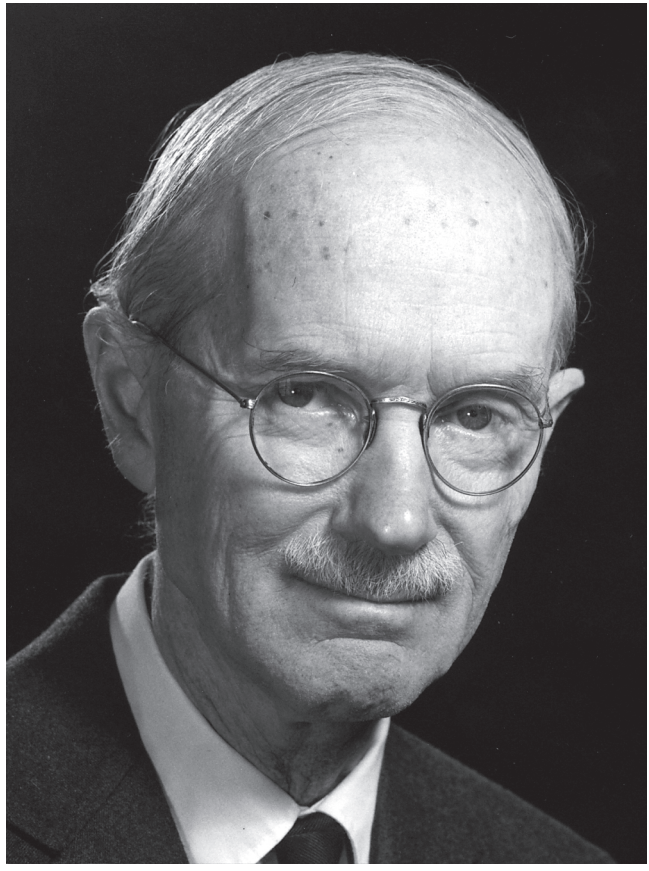

George D. Snell

GEORGE DAVIS SNELL

December 19, 1903–June 6, 1996

BY N. AVRION MITCHISON

GENETICIST GEORGE SNELL is known principally for his part in the discovery of H2, the major histocompatibility complex (MHC) of the mouse and the first known MHC. For this he shared the 1980 Nobel Prize in physiology or medicine. He was elected to the National Academy of Sciences in 1970. Most of his life was spent at Bar Harbor, Maine, where he worked in the Jackson Laboratory.

George was proud of his New England roots, moral and intellectual. His life was passed in the northeast, apart from brief spells in Texas and the Midwest. He was born in Bradford, Massachusetts, and at the age of 19 went to Dartmouth College, where he obtained his B.S, degree in biology in 1926. He went on to Harvard University, where he obtained his D.Sc. four years later at the Bussey Institution. During his last year he served as an instructor back at Dartmouth, and in the following year served again as an instructor at Brown University. He then obtained a National Research Council Fellowship to work at the University of Texas in the laboratory of H. J. Muller (1931-33) and returned there 20 years later to spend a sabbatical year reading up on ethics, as mentioned below. He moved to Washington University in St Louis as an assistant professor

(1933-34). In 1935 at the age of 32 he joined the Jackson Laboratory, then directed by its founder Clarence Cook Little, where he remained until retirement in 1973. His death followed a year after the loss of his beloved wife, Rhoda. They had three sons, who became respectively a manager of a data processing center, a manufacturer of hi-fi loudspeakers, and an architect, all in New England. Sadly, one son suffered an untimely death in 1984.

In an autobiographical note written in 1989 George writes,

> My paternal grandfather, my father, and a brother all held patents; now a son has one. None were big money makers, but in each case at least one had commercial value. I would thus assume that insofar as I have an inclination to invent, this came from my father's side of the family.
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> My mother was . . . a natural planner, a faculty which showed in her carefully designed and tended garden. Gathering and arranging facts are, I think, important antecedents to scientific creativity, and insofar as I have been effective in coping with these antecedents, I think my debt is mostly to my mother.
>
> As a boy, aside from enjoying science and mathematics in school and reading an occasional book on science at home, I don't think I showed any unusual scientific bent. My family spent the summer months in South Woodstock, Vermont, which was then primarily a farming community. Every farmer had a rifle for hunting. . . . I remember trying to devise a mechanism for a repeating rifle that would be different from the two I was familiar with. This never got beyond the thinking stage and I doubt if it had a design that would work, but it was an activity that I enjoyed. In our year-round house in Brookline, Massachusetts, one of my friends and I had a rainy day activity—telling what we called change-around stories—that certainly required some imagination. The idea was to get the hero of the story into the worst possible predicament and then leave it to the other storyteller to extricate him. It was not until I studied genetics with Professor John Gerould at Dartmouth College that I became sufficiently involved in any branch of science to think of making it a career. Even then, it was not until I graduated that I finally decided, with the encouragement of Professor Gerould, to enter a graduate school.

George also mentions his love of ball games, from childhood on. Later his colleagues remember him playing volley ball with enthusiasm—and he was very good.

My own memory of George is of the warm welcome he gave me for a very happy year spent in his laboratory, in the excellent company of Nathan Kaliss, Sheila Counce, and Gustavo Hoecker. George himself was away in Texas writing his ethics book for much of the time, but a rich moment in my life was at the end of the year when he whisked me off into the awesome presence of Little. I vastly appreciated the liberal encouragement that they both gave (but still with a touch of caution on their part about referring to "antigens"), and was duly impressed when George later encouraged me to publish the work on my own.

Personally George was gentle and considerate, but at the same time intellectually stalwart, determined, and creative. Neither flamboyant nor self-assertive, he never built a school or in his formative years published many multi-author papers, and he found little need for technical innovation. He worked within a tradition of classical Mendelian genetics that flourished through most of his lifetime and still connects today with molecular genetics. The Jackson Laboratory with its magnificent mouse facility suited George perfectly, and he provided exactly the foresight and drive that it needed. He was not a good speaker, so the relative isolation there must have been a benefit. In fact, George defined the Jackson phenotype: Stick to your knitting for as long as it takes and let the breeding of mice set your pace. This is well illustrated by his relationship with cellular immunology. George was already working in transplantation at the end of World War II. He realized that immunology would burgeon and that his work on the MHC would help it to do so. He initiated work on immunological enhancement and reviewed developments in immunology on sev-

eral occasions. Yet he never allowed himself to be diverted from his commitment to genetics.

Stories grew around this friendly and unassuming man. Following the 1947 blaze in the Acadia National Forest that destroyed much of the Jackson facility he restarted his research from the remnants that he helped rescue. In the furor after the Nobel Prize the Jackson receptionist denied knowledge of him, and the reporters were told by his neighbors that yes, they had been expecting him to get a prize—for his vegetables. The stock from his prize chives is still handed down among the Jackson geneticists, and his vegetable patch can still be seen on Atlantic Avenue. Jan Klein cites the mice that bear the label "/Sn" as his living monument.

On the advice of Gerould, George went to graduate school at Harvard under the guidance of William Castle, a pioneer of mammalian genetics. George used to say that Castle assigned him to work with mice because he himself didn't like their smell. The mice of the time were domesticated, but did not belong to defined laboratory strains of the modern kind. To start with, George worked on linkage in mice of the "fancy," using mutations collected by amateur breeders, such as short-ear, dwarf, ringed hair, hairless, and naked. By 1996 (his last and posthumous paper) he had studied a total of 26 such visible mutations. This represented a major contribution to formal genetics, whose task it was to establish the linkage groups of selected species such as the mouse. He delighted in the molecular characterization of these genes that began in the last years of his life. Certainly the visible mutations proved very useful later when he came to map his immunological genes.

In the 1930s George developed an interest in the new field of physiological genetics. The control of growth intrigued him, as it did others at the time, including Little. In

retrospect one is amazed at the temerity of the biologists of that era. In Oxford the young Peter Medawar, whose ideas about immunology were later to converge with those of George, had begun his research career by studying the growth of embryos. George collaborated briefly with Douglas Falconer of Edinburgh University, later a great authority on the genetics of mouse growth. Today the quantitative genetics of growth is still regarded as a formidably difficult subject.

While at Harvard, and as was the custom of Harvard biologists, George spent summers working at Woods Hole. There he joined Phineas Whiting, an earlier student of Castle's, in studying the genetics of the parasitic wasp *Habrobracon.* This species is the prototype example of haplodiploidy (i.e., haploid males, diploid females), and his 1932 and 1935 papers are devoted to this subject, in particular to the role of male parthenogenesis in the evolution of the social hymenoptera. The topic was to emerge again later, when Hamilton identified the relative genetic proximity of sisters in haplo-diploid species as a key to the evolution of altruism. George discusses the point in his 1988 book on ethics, and one wonders what part this wasp played in forming his abiding interest in the evolution of social behavior. Might he have become a sociobiologist had the right idea struck him in time?

For his postdoctoral work he joined the laboratory of H. J. Muller at the University of Texas. Muller had discovered that radiation induces mutations in *Drosophila.* In a series of papers between 1933 and 1946 George proved that same effect could be obtained in the mouse, as a representative species of mammal. The most striking effect of radiation, he found, was to produce translocations and other chromosomal abnormalities, which often reduced fertility. His careful analysis helped establish that these effects resulted from

chromosome entanglements formed at meiotic pairing that interfere to a variable extent with chromosome segregation. The 1946 paper shows George scrupulously citing the work of a student of his who had been drafted for military service, as well as that of his competitor Peter Hertwig, who had continued to publish papers on mouse genetics in Berlin until 1942! George's pioneering work on translocation in mammals pointed in three future directions. Mis-segregation of rearranged chromosomes was found to underlie the weird phenomena displayed by the t-alleles at H2. Radiation-induced chromosomal rearrangements provided fundamental insight into the life span of human T cells. And postwar studies of the genetic consequences of the atomic explosions hinged largely on chromosomal rearrangements. The advent of nuclear weapons make his 1937 paper on the genetic effects of neutrons seem remarkably prescient. Indeed it was fortunate for immunology that George came to feel that radiation genetics had reached the point of diminishing returns, as otherwise he might have been sucked into the post-1945 resurgence of the subject.

In 1941 the first edition of *Biology of the Laboratory Mouse* appeared, edited by George and largely written by staff of the Jackson Laboratory. It became the standard work on the subject, along with the second edition published in 1966 that contained no less that nine chapters coauthored by George.

George's entry into immunogenetics, in 1943, came in the form of a study of sperm iso-agglutinins (i.e., strain-specific antibodies made in one mouse strain are able to agglutinate sperm of another strain). This approach was natural to him, as he had long been interested in breeding mice, and similar antibodies had long been known against red blood A cells. In his previous work he had encountered male sterility induced by radiation and had studied several

of the aspects of reproduction relevant to running a large mouse colony. In retrospect it is worth noting that these anti-sperm antibodies have since become one of the few human immune responses that show clear-cut regulation by the major histocompatibility complex.

In the same year George published a joint paper with A. M. Cloudman that marked his debut in tumor transplantation, a field of research that he came to dominate and in which he made his great discovery of the major histocompatibility complex. Cloudman had long been working with Little at the Jackson Laboratory. In 1914 Little (*Science* 40:904-906) proposed a genetic theory of tumor transplantation postulating that the susceptibility to a tumor transplant was determined by several dominant genes. And he and Tyzzer (*J. Med. Res.* 33(1916):393-453) went on to estimate the number of these factors by challenging an F2 population with grandparental tumor. Thanks to Little's foresight Jackson Laboratory proceeded to collect and inbreed numerous strains of mice and has ever since served as the world center for the distribution of mouse strains. Using the collection, George formulated the "fundamental rules of transplantation": that tumors could be transplanted freely within an inbred strain, into its F1 hybrids with other strains, and into a Mendelian proportion of an F2. They were however rejected by other strains, as were tumors that originated in F1 hybrids and were transplanted into one of the parental strains. Inbred mouse strains, they concluded, differed by only a few rejection-inducing genes.

Opinion grew that these rules must reflect an immune response to antigens expressed by the tumors, as well as by normal transplanted tissue. From the early years of the twentieth century it was known that transplanted tumors were often rejected, and that this might represent a response to something specific to cancer—a possibility that was to prove

an enduring hope of cancer research. W. Woglom in his influential 1929 review rejected that view and argued instead that tumors and normal tissue share a similar ability to elicit immunity. Later J. B. S. Haldane visited Little and brought back to London on the pet deck of the liner *Mauritania* some of the new inbred strains. In his 1933 lecture to the Royal Institution he suggested that each of Little and Cloudman's rejection genes might be "responsible for the manufacture of a particular antigen, as in the case of the red corpuscles." He encouraged his young colleague Peter Gorer to search for such antigens.

Gorer worked in parallel with Irwin and Coles, who had coined the term "immunogenetics" to describe their work on antigens of avian red cells. Gorer raised rabbit antisera to red blood cells of mice, which upon absorption distinguished two antigens present in different strains. He then joined George in demonstrating that his antigen II segregated in F2 mice together with the gene fused (Fu), which George had found to be linked to transplant rejection. On this basis the gene encoding the antigen was named H2 (H for histocompatibility and 2 for antigen II) and represents the first sighting of what later came to be called the major histocompatibility complex. It is worth noting that their 1947 paper wisely refrains from claiming that the antigen expressed on red blood cell antigen caused the rejection, or that antibodies of the iso-agglutinin type were responsible. For another five years at least, George continued to refer to histocompatibility factors rather than antigens. After all, 20 years earlier Woglom had cited evidence that antibodies did not mediate transplant rejection.

George at this point made the wise decision to split the effort of his laboratory. To Nathan Kaliss he left the problem of characterizing the histocompatibility factors, while his own group concentrated on the genetics. The isolation

work had originally begun in collaboration with Cloudman. They sought simply to preserve tumors by freezing. Next they discovered that the new trick of freeze drying could be used to preserve the immunizing material in tumors, although to their surprise this material often prolonged (enhanced) rather than shortened the survival of subsequent transplants. Kaliss took up the problem with only limited success. Although the conditions under which enhancement takes place were defined, little progress was made with characterizing its mechanism. In 1960 Henry Winn showed that lymphocytes could transfer the effect. In retrospect the effect joins other assorted down-regulatory phenomena such as the transfusion effect (suppressing rejection of transplanted tissue by prior transfusion of donor blood) and the activity of various regulatory T cells.

A development of this work sees that rare occurrence, George abroad. During the "Prague spring" of 1968 he visited Prague to collect the Mendel medal, the first international recognition of his contributions to immunogenetics. He received a warm welcome from Milan Hasek, whose group he recognized for its scientific excellence, its stalwart devotion to science through difficult times, and the extent to which it shared his interest in immunogenetics. After the sad ending of the "spring" Hilgert and Dement joined George's laboratory for a while. Hilgert attempted to carry on the work of Kaliss but with little success: The field was waiting for better biochemical methods.

Meanwhile, the genetics of the MHC, the work for which George received the Nobel Prize, steamed ahead on an expanding scale. The work depended on two simple but ingenious procedures. One was to type existing inbred lines at H2 by means of the linkage with the Fused gene (as described in 1951). The second was to make new congenic lines (originally termed "isogenic resistant," abbreviated to

IR), in which various histocompatibility alleles were backcrossed onto the same background. The H2 alleles were later termed "haplotypes" after the composite nature of this genetic region was discovered. Each step of the backcrossing required 2 generations, and George decided that up to 20 generations were needed to establish a new line. Over a decade this prodigious task proceeded steadily. By 1953 a total of 102 typings had yielded 9 H2 alleles, by 1958 the number rose to 12 alleles, and by 1969 to 18, encompassing all the main laboratory strains. With his colleague Graff, George later showed that a congenic line would also reject skin grafts from its pair.

In the meantime Donald Shreffler and Jan Klein began to employ antibodies to explore H2 and divide it into its components within George's congenic lines. In this quest they sought and found recombination between end markers of H2 and began to construct the map of the H2 region that figures in modern textbooks. The term "major histocompatibility complex (MHC)" was coined to describe this series of closely linked genes. In parallel Hugh McDevitt discovered that genes of the MHC had the unexpected function of controlling the level of the immune response. In collaboration with George these two approaches converged in 1972 to map Ir-1 (immune response gene one, now identified as H2A and H2E) within H2. With the advent of monoclonal antibodies and later of DNA sequencing the mapping proceeded rapidly, curtailed only by Shreffler's untimely death in the midst of his work on the C4 complement (Ss, Slp) locus. Ian McKenzie from Australia contributed to this effort during his sojourn in George's lab, in collaboration with the main serological work conducted there by Peter Demant and Marianna Cherry.

The prodigious polymorphism of H2 required explanation, since obviously it did not exist merely to bother trans-

plant surgeons. George in his 1981 "Future" paper rightly identified regulation of the immune response as the function of the MHC. He saw resistance to viral infection as the main driving force in its evolution, and its polymorphism as sustained by the wider range of reactivity enjoyed by heterozygotes. Both these views are now generally accepted.

Not all congenic pairs differed from one another at H2, as judged by the linkage test with the Fused gene. Differences at the remaining "minor" H loci resulted in a weaker and more variable rejection that often required pre-immunization to prevent tumor growth. Good quantitation of the difference was obtained by Winn's transfer test. Consecutive numbers were assigned to these minor loci (e.g., H1, H3, H4). By this and similar methods some 60 minor H loci have now been mapped. The frequency of single nucleotide polymorphisms in the genome suggests that there may be many more.

The H3 complex is of particular interest, as shown in George's 1964 and 1967 papers. As Roopenian and Simpson write, "Snell and his collaborators' masterful exploitation of the fortuitous linkage of H3 to agouti and other visually detectable linked loci . . . proved that there were a minimum of two H genes within the H3 segment."

Since then minor transplantation antigens have proved valuable tools for probing the working of the immune system, notably in delineating the role of T-cell subsets and in studies of anergy and other forms of peripheral tolerance. They are considered likely to have a therapeutic future, as contributing to the so-called graft-versus-leukemia effect after bone marrow transplantation.

As George's retirement approached, Cherry and McKenzie contributed to the discovery of non-H2 antigens on the surface of mouse lymphocytes, defined by antibodies. The unfortunate name "cluster of differentiation" (CD) is now

given to these molecules, which turn out to have important functions, as George predicted in his 1981 "Future" paper.

Snell had an abiding worry about the contradiction between evolution and ethics. He relates that this first struck him while teaching genetics and evolution at Washington University in 1933-34. He found the genetics easy, but the survival of the fittest did not seem compatible with his New England upbringing. In 1953-54 he took a sabbatical to read further at the University of Texas in Austin and at Dartmouth College, leading eventually to his book *Search for a Rational Ethic* in 1987. This is an extensive survey of human evolution from a genetic and anthropological standpoint, which argues that the origins of ethical behavior can be traced to particular periods and structures of human society.

The book is hard going. The *mea culpa*, surely due to human genetics as practiced in the twentieth century, is missing (could George have been unaware of the ridiculous views about the genetics of human merit expressed by his one-time collaborator R. A. Fisher, a grand old man of genetics?). Mussolini gets favorable mention, for what we would now call anti-terrorist activity (against the Mafia in Sicily) but not Hitler or Stalin. The Old Testament and the Koran receive attention but not the Israeli-Arab conflict. A sensible discussion of kinship in ethology gets mixed up with some far-fetched sociobiology. From this book the author emerges as a true scholar, expert in biology but confused by ethics and the social sciences and quite unconcerned with urgent problems of the day.

George's discovery and characterization of the MHC is of fundamental importance to immunology and medicine. It enabled the MHC to be subdivided into sets of genes of different type. It allowed the normal function of these genes to be determined, and led eventually to the structural and

molecular characterization of the proteins that they encode. It prepared the ground for HLA (the MHC of man), which rapidly gained importance in organ and bone marrow transplantation and has saved many lives. Today it is also important in predicting disease susceptibility and in the design of peptide vaccines. Well did it merit its Nobel Prize.

Science moves on. Immunogenetics, in man and mouse, is now a sub-specialty of molecular genetics and genomics. The laborious methods of immunogenetics in the past are being replaced by DNA sequencing. Worldwide the bone marrow transplantation groups are engaged in deciding whether sequencing HLA-class genes is worthwhile in practice. The old transplantation tests and serology now seem old hat. Nevertheless it was those older methods that laid the foundations on which we now build, and *in vivo* transplantation tests will remain the endpoint for clinical transplantation.

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