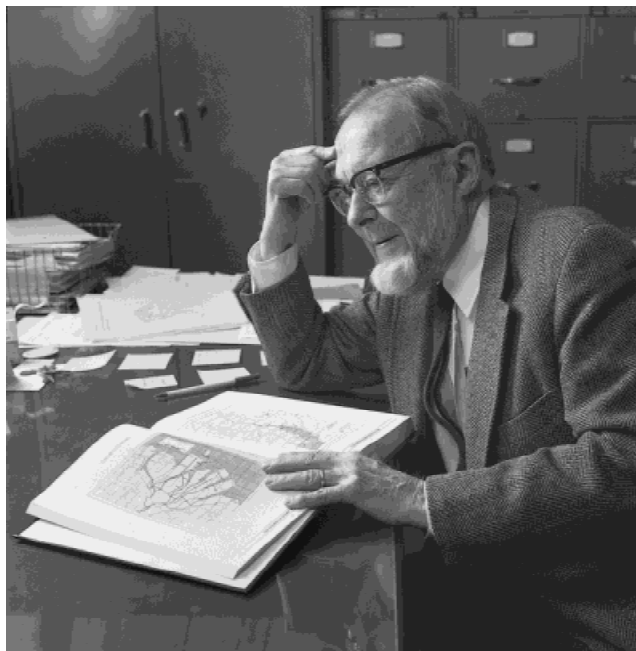


In Memoriam

James V. Neel, 1915–2000



The celebration of insight, responsibility, and intellect that marked Jim Neel's life ended with his death on February 1, 2000. Jim Neel was a key founder of human and medical genetics and a significant force in the development of the field. He remained an active investigator in human genetics until his death at age 84. James Van Gundia Neel, M.D., Ph.D., Professor Emeritus of Human Genetics and Internal Medicine of the University of Michigan, was born on March 22, 1915, in Hamilton Ohio, and died of cancer at his home in Ann Arbor. His wife, Priscilla (Baxter) Neel, his daughter, and his two sons survived him; additional survivors included a granddaughter, two grandsons, and a sister. His integrity, determination, energy, wit, and commitment to excellence will be long remembered.

During his undergraduate studies at the College of Wooster (Ohio), James Neel was introduced to genetics by Warren Spencer. It was there that he began to investigate natural genetic variation in *Drosophila*, and

this particular area of investigation—natural variation within a population and the contribution of mutations to maintaining or modifying variation—would serve as a lasting fount of inspiration for the remainder of his career. Jim did his graduate work at the University of Rochester (New York) under the direction of Curt Stern. There, he continued to investigate the genetic variability in the fruit fly; but it was also there, with Curt Stern's support and guidance, that Jim began to explore the potential of human genetics. It is important to bear in mind, that in contrast to the excitement and attention that developments in human genetics are currently afforded, in 1939 human genetics was a largely discredited field. Immediately before World War II, human genetics was severely stigmatized by the careless and biased studies associated with the American and German eugenics movement. This disrepute would grow considerably when the European war atrocities came to light. Jim Neel's strong sense of social responsibility, however, played a significant part in his decision to study human genetics. As the war approached, Jim reasoned that he could make his greatest contribution to society by becoming a physician. Combined with his love for genetics, his dedication to medicine firmly established Jim Neel's course toward his career in human genetics.

After obtaining his doctoral degree in 1939, before entering medical school, Jim Neel accepted a teaching position at Dartmouth. There he discovered and studied a hypermutable *Drosophila* strain. Investigations into the genetic basis for this phenotype further stimulated his lifelong interest in mutation as an influential evolutionary force. Later, he obtained a National Research Council postdoctoral fellowship at Columbia University where he was supervised by Theodosius Dobzhansky and L.C. Dunn. During these years, Jim also became acquainted with Miloslav Demerec while continuing his analysis of the hypermutable fruit fly during summers at the Carnegie Institute Laboratory for the Study of Experimental Evolution in Cold Spring Harbor. Jim Neel would value and maintain these personal and professional contacts throughout his professional career.

Jim Neel enrolled in the University of Rochester Medical School as a second-year student in 1942, and received his M.D. degree in 1944. After completing his internship and residency at the Strong Memorial and Rochester Municipal Hospitals, Jim sought an opportunity to thoroughly integrate his background in genetics and training in medicine to generate a medical subspecialty in medical genetics. Such an opportunity presented itself to Jim when Lee R. Dice recruited him to the University of Michigan. Neel joined the faculty of

*Correspondence to: Jerome L. Gorski, M.D., Division of Pediatric Genetics, Room 3570 Medical Science Research Building II, Box 0688, Departments of Pediatrics and Human Genetics, University of Michigan Medical School, Ann Arbor, MI 48109-0688. E-mail: jlgorski@med.umich.edu

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the University of Michigan in 1946 as an assistant geneticist in the Laboratory of Vertebrate Biology. After serving in the Army Medical Corps and directing field studies for the Atomic Bomb Casualty Commission of the National Research Council, Neel returned to the University of Michigan in 1948 to direct the Institute of Human Biology's Hereditary Clinic. This was one of the first clinics (if not the first) specifically devoted to providing medical care and genetic counseling to patients and families with inherited disease. Neel subsequently established the University of Michigan Medical School Department of Human Genetics in 1956, the first academic department of human genetics in the United States, and a department he chaired for 25 years. He was named the Lee R. Dice University Professor of Human Genetics in 1966, a position he held until his retirement on June 30, 1985.

Jim Neel was devoted to using the power of genetics to better understand the basis of human inherited disease and improve medical care, and his accomplishments are a testimony to the full measure of his commitment to the new field he helped found. While a medical student, Neel used his insight to elucidate the genetics of β -thalassemia, and in a relatively brief time, he also established the genetics of sickle cell and hemoglobin C anemias. These seminal studies initiated the extremely fruitful analyses of the human hemoglobinopathies, a paradigm for human biochemical genetics. These studies also determined the mutation rate and the then surprisingly high heterozygous carrier frequency of these mutant genes, results that had considerable impact on modifying the care of affected homozygous infants and in organizing newborn screening programs to detect these mutations. Neel also determined the genetics and mutation rate for neurofibromatosis type I (NFI). To complete these studies, he also derived the clinical criteria to diagnose individuals carrying a mutant NFI allele; these are largely the same criteria that are widely used to make the clinical diagnosis of NFI today. Jim Neel also described the natural history and genetics of Huntington disease. In addition to these investigations, Neel studied the genetics and mutation rates of a variety of human diseases including multiple polyposis of the colon, retinoblastoma, aniridia, and glucose-6-phosphate dehydrogenase deficiency. His impact on medical genetics, however, extended beyond the analysis mutation rates and carrier frequencies. Neel was sensitive to the many needs of the patients and families evaluated and treated in the Hereditary Clinic, and the non-directive genetic counseling provided to the families evaluated in this clinic became a model for future medical genetic clinics. Neel was also instrumental in the formation and organization of the American Society of Human Genetics. He was an organizer of the 1947 meeting that led to the formation of the Society in 1948; he served on the board of Society directors (1948–50), served as vice-president (1952–57), and was president (1953–54).

Neel was preoccupied with the role of mutation on the variation of natural populations throughout his career, and this interest formed the foundation of most of his major studies. From late 1946 to 1947, he served in the Army Medical Corps and directed field studies for

the Atomic Bomb Casualty Commission (ABCC) of the National Research Council and played a leading role in establishing the direct descendent of the ABCC, the Radiation Effects Research Foundation. These studies were directed toward identifying changes in the rate of mutational frequency subsequent to radiation exposure. Although these studies were conducted with indirect and incomplete detection technology, the results of these long-term studies showed that parental radiation exposure had no statistically significant effect on observed mutation frequency, findings in marked contrast to those previously observed in mice. These studies played a central role in Neel's scientific life and significantly altered our understanding of mutational frequencies and human susceptibility to radiation. Using the same Hiroshima population base, Neel also studied the genetic consequences of consanguineous marriage.

Perhaps Neel's most significant contributions to human population genetics were his studies on the timing of human migration into North America and his analysis of the genetic characteristics of isolated Amerindian tribes in the Amazon rain forest. Over a 30-year period his work in a large number of Yanomama villages on the Brazilian-Venezuelan border produced an unparalleled and, with societal pressures, perhaps unrepeatable set of data that provided unique insights into the evolutionary biology of our species. These studies showed that as a consequence of tribal social structure individual Yanomama tribes manifested marked genetic variability. Through these studies Neel also identified cells manifesting severe chromosomal damage, or "rogue cells." He subsequently showed that rogue cells occurred in epidemics and that the chromosomal damage was the result of viral infection. Jim Neel was investigating the significance of these chromosomal rearrangements and their possible contribution to oncogenesis at the time of his death.

The Yanomama studies also showed that tribal members differed significantly from contemporary urban populations in disease patterns and physiological profiles. For example, compared to the urban population, tribal members had drastically lower levels of sodium intake and excretion and significantly lower blood pressures and blood glucose levels. These studies strongly suggested that modern urban selective pressures differed considerably from those of the Amerindian tribal people and, presumably, from those selective forces acting on the human species 10,000 years ago. In large part, these observations led Jim Neel to make the "thrifty gene" hypothesis. This hypothesis stated that genetic alleles favoring survival in an environment of limited resources would be detrimental in the modern environment of relative nutritional excess. This hypothesis also suggested that the susceptibility of modern society to many common diseases, such as obesity, diabetes mellitus, and hypertension, was largely the result of altered environmental genetic interactions. These studies illustrated the importance of considering environmental solutions for common or "multifactorial" genetic diseases of modern society, an issue that Jim Neel would stress in his autobiography "Physician to the Gene Pool."

Jim Neel's numerous awards and honors highlight his diverse intellectual interests and illustrate the many ways he touched and influenced medical genetics. These awards also serve as a testimony to his strong and lasting commitment to public service. Jim Neel was elected to the National Academy of Sciences and was the recipient of the American Public Health Lasker Award, the Atomic Bomb Casualty Commission Distinguished Service Award, and the American Society of Human Genetics Allen Award. Neel was the recipient of the Michigan Scientist of the Year Award from the Michigan State Legislature, and he received the University of Michigan Henry Russell Award. Neel also received the National Medal of Science, the Smithsonian Institution Medal, the James D. Bruce Memorial Award from the American College of Physicians, the International Genetic Epidemiology Society Distinguished Service Award, and the March of Dimes Colonel Harlan Sanders Award.

Over the course of his distinguished career, Jim Neel conducted seminal research and helped bring to prominence many of the research and clinical activities that occupy medical geneticists today. In contrast to technologically driven investigations, Jim's research was based on broad fundamental themes. In establishing the University of Michigan Department of Human Genetics, Jim Neel provided a fertile intellectual field for broad scientific growth. In developing his department, rather than taking a narrow view or focusing on a particular family of disorders, Jim recruited faculty from a

variety of disciplines. These faculty including investigators in bacteriophage genetics, somatic cell genetics, biochemical genetics, statistical genetics, and mouse genetics, for Jim was interested in human genetics in the broad sense—the genetics of the human species. Throughout his career, Jim Neel consistently used a physician's perspective to view the problems and issues of human genetics. He also had a keen sensitivity to the societal implications of knowledge discovered. Later in life, Jim was troubled by the complex issue of how to reconcile a rapidly increasing population with limited sustainable resources in a genetically equitable manner. Jim was a vocal and insistent advocate of realistically considering societal resources and needs in allocating medical services. He was also concerned that the current hope of tailoring the genome (gene therapy) to cure inherited disease would prove wasteful and not generally applicable; alternatively, he advocated the low-tech strategy of modifying the environment to suit the genome. Jim firmly believed that the activities of medicine and genetics should be distributed to best provide for the needs of the total human population—the human gene pool. His common sense, vitality, thoughtfulness, rigor, and social commitment will be sorely missed.

Jerome L. Gorski*

Department of Human Genetics and Pediatrics
University of Michigan
Ann Arbor, Michigan