

OBITUARY

James V. Neel, M.D., Ph.D. (March 22, 1915–January 31, 2000): Founder Effect

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James V. Neel (1915–2000) preparing blood film for malaria, Patanowä-teri (Yanomama), 1968.

We write as a tribute to Jim Neel, whose accomplishments during his long and full life were a major factor in the development of modern human genetics. Although battling a string of formidable ailments, he was active and typically feisty to the end. Shuffleboard in the sun was not for him. It is more than a little ironic that the first two pages of the new millennium in this *Journal*, which he helped found, are devoted to his last paper

(Neel 2000). As demonstrated by his other papers published in 1999, even at 84 he was articulate, forthright, and knowledgeable as ever.

Personal History (see Neel 1994)

James van Gundia Neel was born on March 22, 1915, in Hamilton, Ohio. He graduated in 1935 from the College of Wooster (Ohio), where, under Warren Spencer, he investigated natural genetic variation in *Drosophila*. This laid the foundation for the scientific inquiry into the role of evolutionary forces—particularly mutation—in the genetic complexities of natural populations, which was to be the hallmark of his entire career. Jim did his graduate work at the University of Rochester (New York), pursuing genetic variability in *Drosophila* under Curt Stern, who was also happy to indulge his young student's desire to learn about human genetics. At that time, there was relatively little to know; but it whetted Jim's interest, and he would rapidly become one of our foremost human geneticists.

In 1939, with a newly minted Ph.D., he accepted a post at Dartmouth. There he discovered a *Drosophila* strain in which variability in bristle number seemed to be driven by a high mutation rate. This stimulated his lifelong general interest in mutation as a potent evolutionary force. However, with his leanings toward human genetics in particular—and with war being imminent—Jim modified his career path by entering medical school at Rochester and was inducted into the U.S. Army. As a young clinician, he became conversant with a number of heritable clinical issues, notably the hemoglobinopathies such as thalassemia. However, it had been known since the turn of the century that most diseases were not “genetic” in the usual sense of the term, and, because human genetics had also been stained by its recent role in eugenics, it was considered a dubious field for an ambitious young physician to enter (Neel 1994). But genes are key to human life, and Jim—never one to shy from a challenge—became a human geneticist anyway.

Jim and Priscilla Baxter married in 1943 and successfully raised three children, Frances, James, and Alexander. After residency in Rochester and a stint with the Atomic Bomb Casualty Commission (ABCC) in Ja-

pan, he assumed his lifelong post at the University of Michigan. Jim had high professional standards and did not seek personal attention, but he nonetheless quickly attained scientific prominence and eventually became the recipient of most of the important academic honors that can be bestowed on a biomedical scientist: member of the National Academy of Sciences since 1963 and recipient of the Lasker and Allen Awards and of the National Medal of Science. Over the years, he was called on for considerable national and international advisory service, although he had a remarkable ability to say no to things that he did not deem important.

Professional Human Genetics: A Founder

It is a sign of the times that, as the century turned, all too few readers of this journal might have recognized the name of James V. Neel and its significance for our Society and *Journal*. Like other founders, his achievements were being eclipsed by the explosive success of contemporary human genetics. He was an instigator of the 1947 meeting that led to the foundation of the Society in 1948, and his career was inextricably entwined with the Society: board of directors (1948–50, 1968–70), vice-president (1952–57), and president (1953–54). He wrote the first paper published in the *Journal* (immediately following Herman Muller's preface), and just this January he provided a firsthand review of its history (Neel 2000).

Over his long career, Jim helped bring to prominence many of the research activities that preoccupy our members today. In founding the Department of Human Genetics (DHG) at Michigan, one of the first in the country, Jim bestowed a distinguished intellectual depth that generally set rather than followed scientific fashion. Technology and topicality were important, but always in service to broader questions. Rather than constrain the DHG's focus to rare Mendelian disease (Neel 1950), Jim took a broader, population view, querying whether we had "forgotten to set up the team which has as its concern the species as a whole?" (Neel 1958a; 1994, p. 32). To this end he recruited an impressive diversity of scientists to the DHG, who had skills ranging from phage genetics through statistical genetics to somatic-cell genetics. It was noteworthy that a strong sense of evolution permeated the DHG, relatively unusual in those days and perhaps even more so today. Jim's preoccupation with evolutionary processes may have stemmed from his premedical training, but it found a receptive audience in the staff and students in the DHG and formed the keystone of most of the major studies that came from the DHG. In our technology-driven times, in which students are rapidly specialized, a medical school department with a preoccupation with evolution may seem quaint. But nature will out: the dif-

faculty of making sense of the flood of sequence data that now confronts us is a salutary reminder that adherence to the basic biological processes that generate that variation is essential—as Jim would have told us, had we asked.

The DHG has been home to many prominent geneticists, but for many of its early years it was synonymous with the close partnership that Jim forged with Jack Schull. For 20 years they were intellectual fellow travelers who, among other contributions, helped found the field of "genetic epidemiology" and largely introduced the modern context of genetic approaches to complex chronic disease (Neel and Schull 1954; Neel et al. 1965). A mark of the times is that during that period they regularly *walked* home together after work, providing years of extensive, leisurely time to discuss the issues of the day. Although it is easy to romanticize the past, in its heyday the DHG displayed an intellectual depth that elevated it above most of its peers and that represented a living monument to its founder.

Research Legacy

Hemoglobinopathies

Jim's first major contribution to human genetics involved the inheritance of sickle-cell anemia. In our molecular age, it is difficult to appreciate how difficult it was to discern the inheritance of these complex phenotypes, characterized by variable clinical severity in individuals of African descent. Using earlier insights from his thalassemia studies, Jim solved the problem by detailed analysis of phenotypic segregation. Controlling for ascertainment in carefully identified families, he showed that the sickle trait was the heterozygous condition—and that sickle-cell disease was the recessive homozygous condition—at a single Mendelian locus.

Shortly after Jim's analysis, Linus Pauling's group presented molecular confirmation of this conclusion. But how could one account for the high frequency of this deleterious condition in African Americans? Jim approached this problem as he did natural variation in *Drosophila*. Ironically, he was to some extent thwarted by his earlier success with *Drosophila*, since most of his effort was spent examining evidence that a high recurrent mutation rate, or even admixture with Caucasian genes, could be responsible for the apparently elevated frequency of sickle-cell disease in North America compared with that in Africa, despite his awareness of Beet's early observations about the differential rate of malarial infection. Although Allison and Beet deserve credit for recognizing the overdominant fitness of the sickle-cell trait, without Jim's groundwork this understanding would have taken far longer to achieve.

Mutation and Harmful Variation in the Human Species: Japan

Just as he was starting his tour of duty in a U.S. Army hospital, Lieutenant Neel was summoned to Washington and was whisked onto a plane to Japan, to begin studies of the effects of radiation exposure in survivors of the atomic bombings. He had probably been identified for this role through his mutation work with Stern and Spencer. He arrived in 1946, just 15 months after the bombing, was a key person in the development of the scientific program, and was asked to stay on as acting director after his initial tour of duty. He thus played a leading part in establishing the ABCC (now known as the “Radiation Effects Research Foundation,” or RERF) in Hiroshima, and he continued working there for decades, although from Michigan as his base.

Radiation dangers were paramount in the public mind at the end of the war. Muller had shown that ionizing radiation was mutagenic to the individual (e.g., see Muller 1947, 1950), and, for population geneticists, there were additional grounds for concern. In the prevailing theory of the time, mutation pressure was expected to introduce only a small number of deleterious mutations. These were predicted to be largely recessive (Fisher 1930), but, in small populations such as had characterized our ancestry, the high probability of homozygosity would rapidly eliminate them. However, in the large, heterogeneous outbred human populations of today, with their diminished probability of homozygosity, a mutational “load” of recessive mutations could accumulate before the burden of their harmful homozygous effects was borne (e.g., see Haldane 1937; Muller 1947).

The specter of nuclear weapons having been loosed as a significant contributor to the mutation rate in humans, causing long-term damage to the gene pool, “wonderfully concentrated” the public mind (Morton 1997). Even the survivors of nuclear holocaust would bear a legacy of death for human posterity. It had been difficult to quantify the radiation risk from therapeutic or occupational exposures, because of the need for excessively large samples and longitudinal data. But such data would be available in Japan, and the measurement of the consequences of exposure became a high-visibility endeavor, somewhat as is the urgent study of AIDS today. The ABCC was probably the first nonmilitary megascience biological project in history.

At the time there was no direct test for mutations (the DNA era had not yet dawned). Instead, in a “model of design and execution” (Morton 1997), the investigators developed a set of surrogate criteria related to birth defects and estimated the frequency of the various defects in offspring born to survivors, in relation to dose (published by Neel and Schull 1991). In a more recent and direct attempt to estimate mutation rates in the exposed,

Jim helped lead a study of ~500,000 tests, mainly of protein polymorphisms, in each of two cohorts of exposed and nonexposed individuals and their offspring—the largest such comparison that had been done in humans. This involved his only real “genomics” effort, a collaborative effort to develop two-dimensional electrophoretic polymorphism and mutation-detection systems (Neel et al. 1984; Rosenblum et al. 1984).

Although the indicators were in the expected direction, the most striking result of this 40-years work was that “in no instance is there a statistically significant effect of parental exposure” (Schull et al. 1981, p. 1220). Similarly inconclusive results were found in another classic mutation study, in which Jack and Jim used the comprehensive Japanese genealogical record-keeping system to estimate the prevailing burden of recessive mutation, on the basis of the excess frequency of defects expected in offspring of inbred matings (Schull and Neel 1965, 1972; also see Morton et al. 1956; Morton 1997). Even the huge sample sizes available were insufficient for characterization of rare mutational events, especially with indirect and incomplete detection technology.

Research on the effects of the atomic-bomb exposures continues, but the question has changed in a biologically interesting way. Over the postwar decades it was realized that cancer was essentially a disease of somatic mutation. Meanwhile, systematic lifelong increases in cancer risks began to appear in the RERF cohorts decades after the exposures (e.g., see Shimizu et al. 1990). One major reason that the risk of cancer to exposed individuals is much greater and more easily detected than that of germinal mutation is that many more somatic than germinal cells are exposed. Thus, if the feared threat to distant human posterity is less than was thought, high doses of radiation are a substantial threat for the duration of an exposed person’s life.

Overall, an important inference from the inability to detect a clear signal is that humans are less sensitive to heritable radiation damage than they had been thought to be (largely on the basis of a mouse model). Interestingly, Jim had long acknowledged that, in this area of great practical importance, the working assumptions are so uncertain that a statistical significance level cannot even be reliably placed on the results. This raises serious and still-unanswered questions for determination of radiation safety standards (Schull et al. 1981; Neel et al. 1990; Neel and Lewis 1990; Neel 1999)—even for cancer—especially at low or chronic doses.

It is worthwhile to note the caution with which these expensive, highly visible studies were begun. A prospectus published in *Science* clearly laid out the serious sample-size limitations, even in the Hiroshima and Nagasaki material, in this study being led by a young Dr. Neel. “Even after a long-term study, such as that outlined below,” the report wrote, “it still may not be possible

to determine just how much genetic damage was done at Hiroshima and Nagasaki” (Genetics Conference 1947, p. 331). Nobody likes to spend his or her career chasing a negative result, especially one clearly predicted in his youth. Such candor would be death to any funding opportunities today, but could anyone suggest that this effort was a waste? Jim expressed a “twinge of envy” (Neel 1994) for the more quick-hitting science that is common today. But his twinge “didn’t last long. . . . If one commits oneself to the field of human population genetics, one must be prepared to pay the price” (Neel 1994, p. 246).

Mutations and Genetic Variation in Natural Human Settings

Jim’s concern with the natural load of mutational effects—and his realization that human population history was responsible for their amount and dispersion—led to an interest in the study of humans in a more evolutionarily natural state, where those processes could be observed. He placed particular stress on the understanding of local microdemographic events through which the human evolutionary processes occurred.

Jim recognized that the cultural changes accompanying the progression from tribal society to urbanization had created novel environments for selection—and that this contrast might reveal selective pressures, with consequences for human health (Neel 1958*b*, 1966). Reflecting this view was his “thrifty genotype” hypothesis, suggesting that in modern society susceptibility to diseases such as diabetes might be a deleterious consequence of genotypes that had formerly been advantageous in human ancestral environments (Neel 1962)—arguably one of the most influential hypotheses in genetic epidemiology.

Jim soon put his view to the empirical test. He realized that recently contacted tribes would be least affected by traits of the outside civilization, such as diet and infectious diseases. The Amazon basin was one of the best available places in which to find such groups. Working with South American colleagues, beginning in the 1960s, he made an initial foray into the recently contacted Xavante in the Brazilian Mato Grosso. That provided remarkable demographic and phenotypic data and suggested unsuspected amounts of genetic difference between small, geographically adjacent villages. He then turned his attention to the much larger tribal group, the Yanomama, on the Brazilian-Venezuelan border. Over a 30-year period his work in a large number of Yanomama villages and in at least 20 other tribes in South and Central America generated a formidable set of data providing unparalleled and perhaps unrepeatable insight into the evolutionary biology of our species (summarized in Neel 1994).

Jim was directly involved in all phases of the opera-

tions, showing a natural flair for fieldwork under difficult conditions—including the need to spur on cantankerous, younger colleagues. A wide variety of polymorphisms have been defined, initially blood groups and protein isozymes and continuing, today, to DNA-sequence variation. These data revealed a wholly unexpected magnitude of genetic variation in human populations, just when the merits of Kimura’s neutral theory were being hotly debated. The many analyses of these data have been influential in shaping our perception of human genetic diversity, highlighting in particular the role that sociocultural practices such as culturally defined kinship relationships within and among local villages have in the shaping of human genetic diversity at the micro scale (e.g., see Neel 1966, 1970). The continued existence of 15,000 or so samples collected 30 or more years ago ensures that this scientific legacy will be profitably mined for many years to come.

Jim and his colleagues also provided important phenotypic data from the Amazon. As he had predicted, the forces of cultural change are eliminating the last vestiges of “tribal physiology” at a much more rapid rate than they are destroying the patterns of genetic variation. The ecology of tribal societies gave rise to very different physiological profiles and disease patterns: blood pressure and glucose levels were radically lower than those in contemporary urban populations, the distribution of infectious disease was influenced by the same cultural factors that magnified genetic microdifferentiation, and the detection of new pathogens, such as retroviral elements, shed new light on infectious-disease ecology. There can be little doubt that the selective pressures 10,000 years ago were substantially different from those of the recent past, a concept that has implications for how we design studies of the genetic contribution to common disease.

A Few Personal Notes

Jim kept his private life private, and we will honor his feelings—but will note that his was a life of high personal standards. His professional interactions were insistent, and he could be demanding. He was assertive within his academic realm and highly competitive. We have numerous times seen him hold his own in discussions with persons of high technical skills, on issues within their areas of expertise, by dint of personality and a penetrating ability to focus on the main issues. He could intimidate the timid, and one had to defend one’s point of view. But to those of us fortunate to be among his students he gave considerable freedom of action. He could, of course, also be compassionate and helpful, and it is a mark of his character that he inspired a fierce loyalty, especially among his staff. Although he spent most of his academic life at one institution and trained relatively few students, Jim had a profound impact on the international scene. This was especially so in Japan

and parts of Latin America, where, as a consequence of his intense collaboration, he assisted the development of a number of scientific groups. Nearly to the end of his last year of life, he continued to foster the careers of junior colleagues and students.

Conclusion

Except for the few and the lucky, leadership goes beyond discoveries. Historians will trace the development of human genetics, now one of the most prominent of sciences, to a few determined and dedicated people. Jim Neel was a driving force among them. He was motivated by intellectual rather than by material capital. Lists of patents, citations, number of genes mapped will not tell his story. His legacy is the emphasis that he placed on the application of basic biological and evolutionary principles to genetic variation in natural populations and to the understanding of genetic etiology. This has shaped our science in a manner probably not wholly appreciated by those rushing pell-mell into biotechnology. Yet, without Jim's contributions, their opportunities might not exist.

In his biography (Neel 1994), as a "physician to the genome" Jim lays out his vision for the future of our species. His views have received considerable attention. When one of us (K.M.W.) was asked to review the manuscript of this biography, he suggested to Jim that the section be toned down, since it seemed to be an elder statesman's predictable petulance about the state of the world. Characteristically, Jim refused. As we have rediscovered, on rereading his papers while preparing this tribute, he had been saying many of the same things for at least 30 years, long before the current genomics explosion. When placed in context they merit serious examination.

Taking a natural historian's perspective, Jim noted the current belief that genetic knowledge will contribute to public health by tailoring the genome to the environment. He warned that this will be a wasteful and probably losing proposition. As he repeatedly pointed out, the essential facts have been known for a century or more. Most of the complex multifactorial diseases really are just that—complex, *not* "genetic" in the usual sense. Their expression is heavily dependent on interaction with rapidly changing environments. Much more effective and cost-efficient improvements to human well-being can be made by tailoring the environment to the genome. Lifestyle interventions are more practical than genetic ones. Prevention, based on an understanding of the nature of *normal* human genetic variation, has the best chance of contributing to society. To understand the nature of genotype interactions, an evolutionary perspective is required.

However, as Jim also warned, success in any such strategy could lead to an increasingly aged society with

much greater health burdens. He suggests that we keep our current love affair with mapping and cloning in perspective. In particular, he warns that excessive concern about genetic disease will become a trivial luxury if we do not avoid the specter of global overpopulation of the species to whose welfare he was so long dedicated (Neel 1994, 1996, 1997).

Were these his salad days, Jim would be right at the front of the technological edge (but with his yellow pad and pencil), working on his next paper and badgering some poor colleague to get his part done. But we think that he would be arguing for a very different kind of genome project. Instead of a preoccupation with disease mining, he would be urging that effort be primarily directed toward an understanding of the evolutionary interactions within our naturally varying genome. Perhaps, if we paid greater heed to these ideas of his, we would advance the cause of genomics in a much more useful and meaningful way.

Acknowledgments

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