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The scientific legacy of Ronald L. Nagel (1936–2016), a true renaissance man

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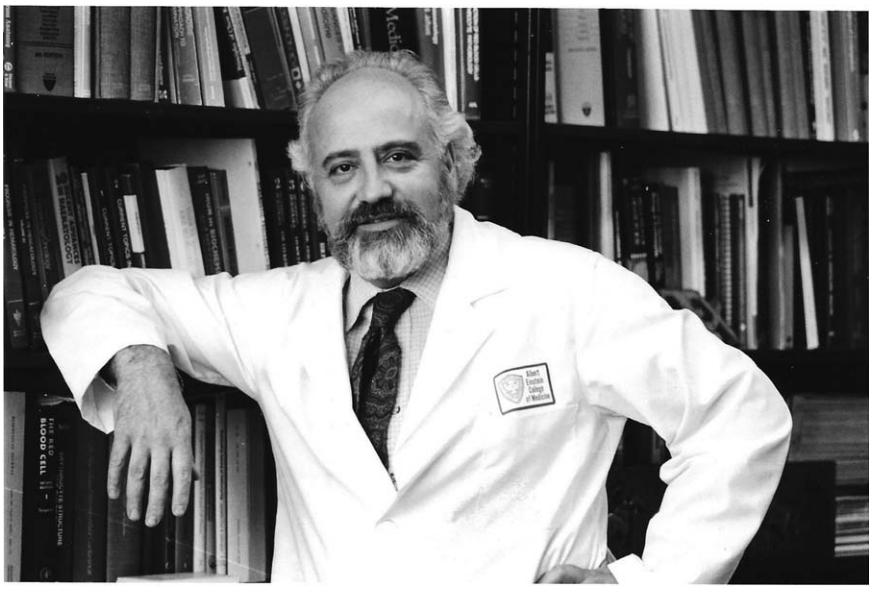

Ronald L. Nagel (Ron) was born in Santiago, Chile, in 1936. His mother was of Spanish and Araucanian Indian heritage; his father had emigrated to Chile from Bratislava, Slovakia. He graduated from the University of Chile Medical School in Santiago in 1960, and completed three years of postgraduate training, both as a resident in the Faculty of Medicine and as a student in the Faculty of Physics and Mathematics at the University of Chile where one of his early mentors was Mitzy Canessa. In 1963, after a stint as a Surgeon in the Chilean Navy, Ron moved to the United States as a Post-Doctoral Fellow at the Albert Einstein College of Medicine under the mentorship of Dr. Helen Ranney, where he acquired clinical and research training on hemoglobinopathies, in particular on sickle cell disease (SCD), to which he would dedicate his career.

Ron's first major findings involved understanding of the molecular basis of polymerization of Hemoglobin S, the mutant hemoglobin that causes SCD. In collaboration with Robert M. Bookchin, Ron cleverly took advantage of naturally occurring mutant hemoglobins to map, at the amino-acid level, the residues that were responsible for hemoglobin sickling. This kind of ingenious research, done well before the development of site-directed mutagenesis techniques, was one of the pioneering efforts to exploit natural variants to study the structural basis of protein function in human physiology and pathology.

As the techniques of molecular biology evolved, Ron, then Chief of Hematology at Einstein, advanced his studies to examine SCD at the DNA level and in particular the evolutionary origin of the sickle cell mutation in Africa. Building on the pioneering work of Kan & Dozy (Science 1980), who described the first restriction enzyme polymorphism in the human β-globin gene cluster, and in collaboration with Dominique Labie, Rajagopal Krishnamoorthy and their team at INSERM in Paris, Ron organized several field trips to the heart of Africa during which he examined the clinical status of SCD patients in relation to their blood parameters. Through extensive use of the newly developed Southern blot methods, the team demonstrated that the sickle cell genes in Africa were genetically linked to different combinations of restriction site polymorphisms (haplotypes) and concluded that the mutation had arisen independently at least three times in Africa and, in each case, had expanded because the heterozygous state of the sickle gene conferred protection against malaria. In addition to their contribution to evolutionary biology, these studies helped clarify at the population level, one of the central mysteries of SCD: the same sickle cell mutation in different patients can associate with

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dramatically distinct clinical courses. We owe Ronald Nagel and his colleagues our current understanding that SCD patients from parts of India and Saudi Arabia, and to a lesser extent from Senegal, exhibit a milder form of the disease than patients from the Bantu ethnic group. These studies were also the direct precursor of much larger international projects such as the HapMap, led by Francis Collins, to map the haplotype structure of the entire human genome to study the influence of genetic variation on human health and disease.

As the technology continued to progress, it became possible to create animal models of human diseases first by transgenesis and later using more powerful homologous recombination methods. Based on pioneering basic science studies from many labs, including those of Dorothy Tuan, Frank Grosveld, Mark Groudine, and Tim Townes, Ron worked with Mary Fabry, Eric Bouhassira, Dhanajay K. Kaul, and John Gilman to create transgenic sickle mice with a variety of phenotypes and elucidated important pathophysiological issues in SCD. These SCD animal models have proved immensely valuable in the field and continue to be used in many laboratories.

As the mouse models were being constructed, the development of viral vectors carrying β-globin transgenes able to infect hematopoietic stem cells was making rapid progress. Excited about the possibilities, Ron organized a multi-disciplinary team to bring gene therapy from the bench to the bedside. The team was designed to cover all aspects of the disease and included Eric Bouhassira and Mary Fabry at Einstein, Irving London and Phillipe Leboulch, at Harvard/MIT, and Connie Eaves and Keith Humphries at The University of British Columbia. That work culminated in the first proof of principle of gene therapy for SCD in the mouse using the animal model developed by Dr. Fabry and a vector carrying therapeutic anti-sickling globin based on the early work of Dr. Nagel on hemoglobin structure/function.

One member of the team, Phillipe Leboulch, continued the studies and, in collaboration with others, led the first successful clinical trial for gene therapy of the hemoglobinopathies in humans. This work has been taken over by a company, Bluebird Bio, who recently reported highly promising clinical trial results.

Ron was at the forefront of what is now called translational research. He understood that patients with SCD, even bearing identical haplotype, could differ in phenotype. He understood, in collaboration with Dr. DK Kaul, that sickle disease involved not only the red blood cells but also other blood cells including vasculature. Ron and Fabry, using density gradients, were able to demonstrate that each patient had their particular red cell density phenotype. In collaboration with Mitzy Canessa and Jose Romero at Harvard, Nagel and Fabry demonstrated a role for cation transport in the hemoglobinopathies. In collaboration with Henny Billett and Chris Lawrence, Nagel showed that the percent of sickle cells, which had been thought to be the determining factor in sickle pathology, was not the major problem, but that instead, sickle cells that could still deform, and therefore adhere, played a significant role in vasoocclusion. Many investigations with Rhoda Hirsch led to the molecular understanding as to why HbC forms an intraerythrocytic crystal in the oxy state while HbS forms a polymer in the deoxy state.

Ron fostered the research efforts in hemoglobinopathies of many other Fellows, Visiting Scientists, and newly recruited faculty including Gene Roth, Seetherama Acharya, Bob Schwartz, Anne Rybicki, Helena Croizat, Hannah Shear, John Greally, and Yelena Ginzburg.

Ronald Nagel was a true renaissance man. History was his hobby. Maybe because he had been touched by greatness from his youngest age, being the godson of Pablo Neruda, the Nobel Prize winning Chilean poet, he had interests in the arts, literature, and in gastronomy and published two volumes of poetry. He is fondly remembered by his former collaborators for his intelligence, encyclopedic memory, his wit, and for the many dinners that he either cooked and hosted at home in New York City or organized at meticulously researched restaurants.

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