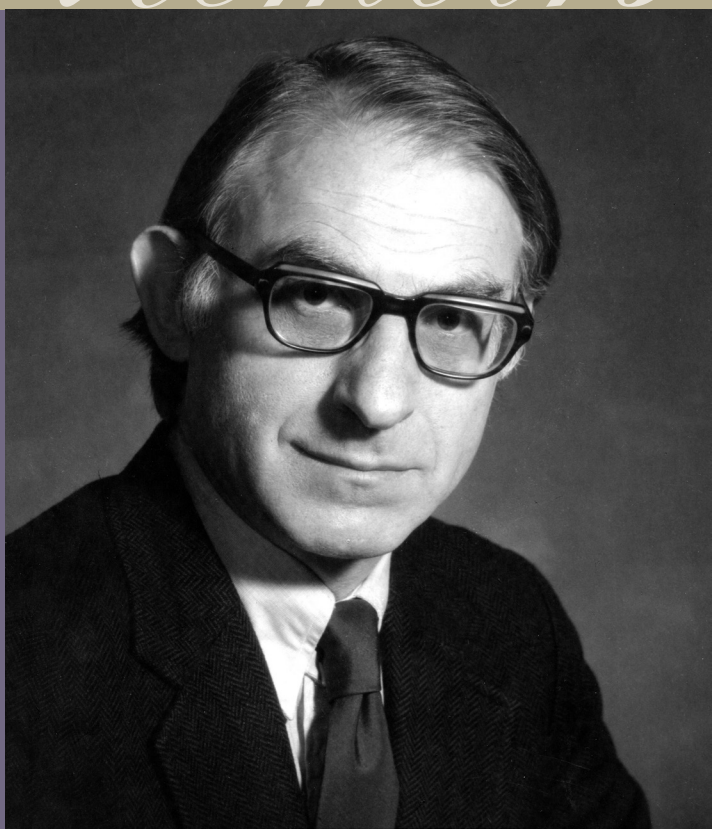
Arno G. Motulsky

1923–2018

BIOGRAPHICAL *Memoirs*



A Biographical Memoir by
Stanley M. Gartler
and Gail P. Jarvik

NATIONAL ACADEMY OF SCIENCES

ARNO GUNTHER **MOTULSKY**

July 5, 1923–January 17, 2018

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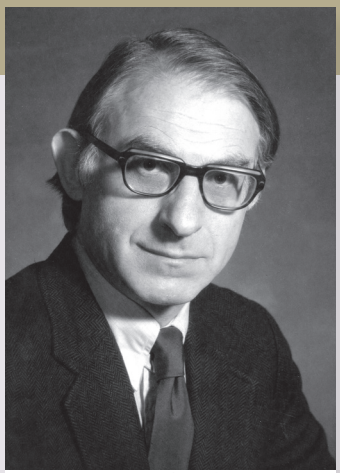

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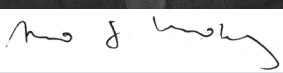

By Stanley M. Gartler and Gail P. Jarvik

Arno G. Motulsky, a founder of modern human genetics and creator of pharmacogenetics, was born in Fischhausen, Germany, on July 5, 1923, and died in Seattle, Washington, on January 17, 2018. Hitler and his Nazi Party had come to power in 1933, and anti-Semitism was a centerpiece of the Nazi platform. By 1939, many German Jews had already left or were making plans to leave Germany, as was the Motulsky family. Arno's father had a brother in Chicago, so in 1939 Arno's father left for Cuba, planning to establish the family there before heading to the United States and Chicago.

Conditions for Jews in Germany continued to deteriorate. Arno's mother became concerned about remaining in Germany and obtained a tourist entry card for the family to join his father in Cuba. In May 1939, Arno, his mother, and two younger siblings boarded the German ship, the *St. Louis*, for the two-week trip to Havana. As Arno wrote aboard the *St. Louis*, "spirits (of passengers) were high because everyone was glad to escape the hell of Hitler."[1] After arrival in Cuba, however, few were allowed to disembark because the tourist entry cards were not considered valid.

Arno's father was among the many on the dock who were in a state of shock—"so close and yet so far." The ship's captain tried to get U.S. and Canadian authorities to intervene, but to no avail. After five days and being also denied entry to the US, the *St. Louis* left Cuba and headed for Hamburg. Two days before the ship would have arrived in Hamburg, a message was received that England, France, Holland, and Belgium were willing to give temporary refuge to the passengers. Arno, his mother, and two younger siblings were given refuge in Belgium, where Arno attended his one and only year of high school.

The following year, the Germans invaded Belgium and Arno was arrested by the Belgians as a German enemy alien and, thus, separated from his mother and siblings. Barely sixteen-years old, he was packed into a freight car, forced to stand with no food or water

for over two days as the train travelled. Eventually, the train reached an internment camp run by the French at St. Cyprien in the south of France. Conditions were horrific, with little food, no sanitation or running water, and regular sandstorms. Many prisoners died, most from typhoid fever or starvation. And this would go on for almost two years. In all this misery there was one highlight. The prisoners were allowed to bathe in the Mediterranean Sea and very briefly forget their misery. After six months, Arno and the rest of the camp were moved to the Gurs internment camp. Living conditions were even worse than in St. Cyprien, with deep mud everywhere. Although there were no formal classes in the internment camps, there were teachers and former professors among his fellow prisoners. Arno wrote that "We didn't have books, but we had our brains. So I learned quite a lot."[2]

Finally, those prisoners with U.S. visas were allowed to go to another camp near Marseilles where there was an American consulate. Arno got a new visa, and in June 1941, only ten days before his 18th birthday and after nearly two years in the internment camp, he left France legally, crossed Spain into Portugal and sailed for the States a short time later.

Arno arrived in America in August 1941 and soon joined his father in Chicago. Two years later, they learned that Arno's mother and his brother and sister had (with the help of Belgian friends) escaped to neutral Switzerland and remained there for the duration of World War II. The family was reunited in Chicago in early 1946.

In Chicago, Arno passed an exam, got a high school certificate and attended a local college, where he took biology, chemistry, and mathematics and met his future wife, Gretel Stern. In 1943, he applied for medical school and was accepted at the University of Illinois at Chicago. That year, he also became a U.S. citizen, joined the Army, and was assigned to a special program that included a year of premed courses at Yale University for the rapid training of young physicians. The war ended, and he finished medical school. It was clear well before Arno had finished medical school that he was not going to be an ordinary physician. He started medical school at the end of 1943 and finished in 1947. His publication list when he finished medical studies was comparable to that of an assistant professor. He had numerous opportunities when he finished his formal medical school studies, and the one he took was the teaching position at the new medical school in Seattle at the University of Washington. In the 1950s, genetics was not taught to medical students. He assumed that he would be able to teach medical genetics on the side and eventually get the department to officially support his interest in medical genetics. He was right on this point.

He quickly became involved with the group working in hematology under Clement Finch. Eloise Giblet was a new medical fellow working with Finch, and she was destined to take over the Seattle Blood Bank. She would become an important colleague for Arno as he developed genetic interests. Arno was building up his own interest in medical genetics and would soon have his own unit in the Department of Medicine.

Arno hired two technicians and spent a year with Lionel Penrose in London. Penrose, at that time, was considered to have the most advanced unit of formal medical genetics in the world. In the meantime, Arno visited places in the United States where genetics research was being carried out. At Columbia University in New York City, he visited the Institute for the Study of Human Variation. This is where he met Stanley Gartler, a young PhD in genetics, who was looking for a position. The year was 1956. Arno had a long talk with Gartler and invited him out to Seattle. Gartler made the trip to Seattle. He liked the set up and was hired by Arno as the first appointee to the Division of Medical Genetics. The first year in Seattle was financially difficult; Arno had big ideas for the Division but was short on funds.

The year of Gartler's move to Seattle, 1957, was the year of "Sputnik," the world's first satellite, developed by the Russians. Once the U.S. Congress became aware that the Russians were significantly ahead of the United States in scientific research, federal research grants were there for the asking. Arno took advantage of this and in the early years of the Division of Medical Genetics, funding was no longer a problem.

One of Arno's earliest interests was in what he was the first to call pharmacogenetics,[3, 4] the differential reaction to drugs among individuals based on their genotypes. One of the best examples of this was the relationship between X-linked glucose-6-phosphate dehydrogenase deficiency (G6PD) and primaquine sensitivity. Males have either a normal or deficient type of enzyme, but females with two X chromosomes can be heterozygotes. G6PD deficient males were sensitive to a variety of drugs. About 10 percent of African American men, as well as many men with origins in India and the Mediterranean region, are G6PD deficient. The sickle cell trait had a similar distribution. Arno developed the idea that malaria was the major selective factor underlying the persistence of G6PD deficiency. He visited populations in Africa living in areas of high or low malaria frequency. There was a correlation between the frequency of falciparum malaria and the frequency of G6PD deficiency in populations.

Arno also spent time in Sardinia with Marcello Siniscalco testing the same hypothesis with respect to thalassemia. In Sardinia, malaria was frequent in valleys and rare at high

elevation where there were no transmitting mosquitoes. The same general idea was examined in Greece, where Arno worked with George Stamatoyannopoulos.[5] These combined results grouped sickle cell trait, G6PD deficiency, and thalassemia as evolutionary responses to malaria.[6]

During the 1960s it became clear that elevated lipids in individuals are significant risk factors for coronary heart disease. Joseph Goldstein was a medical fellow in Arno's division at that time. Arno set him up in a study, involving a large number of hospitals in Seattle, to enroll patients who had myocardial infarction (MI) and measure their cholesterol and triglycerides levels three months after their attack. Goldstein then selected patients with the highest cholesterol levels, or highest triglycerides levels, or both and enrolled their family members and measured their lipids as well. About 5 percent of the MI patients had very high cholesterol levels that segregated in their families in a clear, autosomal dominant way. They named this condition familial hypercholesterolemia.[7] Another 8 percent of MI patients had familial hypertriglyceridemia, characterized by extremely high levels of triglycerides that segregated in their families in a clear, autosomal dominant way. And yet another 15 percent of MI patients had elevated levels of both cholesterol and triglycerides both segregating in their families. They named this condition, controlled by a third autosomal dominant gene, familial combined hyperlipidemia.[8]

Goldstein moved to Dallas after his fellowship, where he worked with Michael Brown at the University of Texas Southwestern Medical Center. The Brown and Goldstein studies led to the identification of the low density lipoprotein (LDL) receptor gene and its pathogenic variants; to the development of statins; and of course, to the Nobel Prize.[9] As Arno noted, "when we become discouraged about whether identifying the gene for a trait will ever lead to a medical intervention, we should remind ourselves that this one did… It took a long time—more than twenty years."[2]

One of the other areas of human genetics in which Arno worked emphasized color vision as a model for perception. The character is controlled by a complex locus with one gene for red pigment and a variable number of genes for green pigment.[10] Arno collaborated with Samir Deeb, a biochemical and molecular geneticist who joined Arno's group in the 1980s. They studied both color vision defects and normal polymorphic variation in these genes. They discovered a serine-alanine polymorphism in the red pigment gene with a distribution of approximately 60 percent serine: 40 percent alanine in males. While the

polymorphism did not affect color vision, the individuals with the serine polymorphism and those with the alanine polymorphism perceived red differently.[11]

Arno was as interested in training medical geneticists as he was in the various research projects he pursued during his career. This was already evident early in his career when he started medical school as a private in the army. He said that he was profoundly affected when he walked into Yale's Sterling Library, looked around, and remembered his experiences in the concentration camp in France not long before. He said he'd "thought that I'd died and gone to heaven."[2] An even more profound effect on him was the course in genetics he took from Donald Poulson in 1943 at Yale. Arno foresaw that somehow his career would combine his medical training with genetics, and this proved to be his guiding light throughout his career. In 1979, he and Friedrich Vogel published the first edition of their now-classic textbook, *Human Genetics: Problems and Approaches*, which went through three editions before Friedrich Vogel passed away and a fourth edition after.[12] Additionally, the training program he began at the University of Washington continues to train new generations of medical geneticists.

Arno's numerous honors include election to the American Society for Clinical Investigation, the Institute of Medicine, the National Academy of Sciences, the National Academy of Medicine, the American Philosophical Society, Fellow in the American Association for the Advancement of Science, The Alexander von Humboldt Award, a Lifetime Achievement Award from the American College of Medical Genetics, the William Allen Memorial Award of Excellence in Education Award, and the Victor A. McKusick Leadership Award of the American Society of Human Genetics.

NOTES

1. Motulsky, A. G. 2018. A German-Jewish refugee in Vichy France 1939-1941. Arno Motulsky's memoir of life in the internment camps at St. Cyprien and Gurs. *Am J Med Genet A* 176(6):1289–1295.
2. Motulsky, A. G. and M. C. King. 2016. The great adventure of an American human geneticist. *Annu Rev Genomics Hum Genet* 17:1–15.
3. Motulsky, A. G. 1957. Drug reactions, enzymes, and biochemical genetics. *JAMA* 165(7):835–837.
4. Motulsky, A. G. 1964. Pharmacogenetics. *Prog Med Genet* 23:49–74.
5. Fraser, G. R., G. Stamatoyannopoulos, C. Kattamis, D. Loukopoulos, B. Defaranas, C. Kitsos, L. Zannos-Mariolea, C. Choremis, P. Fessas, and A. G. Motulsky. 1964. Thalassemias, abnormal hemoglobins and glucose-6-phosphate dehydrogenase deficiency in the Arta area of Greece: Diagnostic and genetic aspects of complete village studies. *Annals of the New York Academy of Sciences* 119(2):415–435.
6. Motulsky, A. G. 1964. Hereditary red cell traits and malaria. *Am J Trop Med Hyg* 13(1):147–158.
7. Schrott, H. G., J. L. Goldstein, W. R. Hazzard, M. M. McGoodwin, and A. G. Motulsky. 1972. Familial hypercholesterolemia in a large kindred. Evidence for a monogenic mechanism. *Ann Intern Med* 76(5):711–720.
8. Goldstein, J. L., H. G. Schrott, W. R. Hazzard, E. L. Bierman, and A. G. Motulsky. 1973. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 52(7):1544–1568.
9. Motulsky, A. G. 1986. The 1985 Nobel Prize in Physiology or Medicine. *Science* 231(4734):126–129.
10. Nathans, J., D. Thomas, and D. S. Hogness. 1986. Molecular genetics of human color vision: the genes encoding blue, green, and red pigments. *Science* 232(4747):193–202.
11. Winderickx, J., D. T. Lindsey, E. Sanocki, D. Y. Teller, A. G. Motulsky, and S. S. Deeb. 1992. Polymorphism in red photopigment underlies variation in colour matching. *Nature* 356(6368):431–433.
12. Speicher, M. R., A. G. Motulsky, and S. E. Antonarakis, eds. 2010. *Vogel and Motulsky's Human Genetics: Problems and Approaches*. 4th ed., Springer: Berlin, Heidelberg.

SELECTED BIBLIOGRAPHY

1954 With W. H. Crosby and H. Rappaport. Hereditary nonspherocytic hemolytic disease: A study of a singular familial hemolytic syndrome. *Blood* 9:749-772.

1956 Genetic and haematological significance of haemoglobin H. *Nature* 178:1055-1056.

1957 Drug reactions, enzymes and biochemical genetics. *J. Am. Med. Assoc.* 165:835-837.

1960 With R. Anderson and R. R. Huestis. Hereditary spherocytosis in the deer mouse. Its similarity to the human disease. *Blood* 15:491-505.

1961 With M. Siniscalco, L. Bernini and B. Latte. Favism and thalassaemias in Sardinia and their relationship to malaria. *Nature* 190:1179-1180.

1964 Current concepts of the genetics of the thalassemias. *Cold Spring Harbor Symp. Quant. Biol.* 29:399-413.

1965 With W. E. Hodgkin, E. R. Giblett, H. Levine, and W. Bauer. Complete pseudocholinesterase deficiency: Genetic and immunologic characterization. *J. Clin. Invest.* 44:486-493.

1966 With J. Vandepitte and G. R. Fraser. Population genetic studies in the Congo. I. Glucose-6-phosphate dehydrogenase deficiency, hemoglobin S and malaria. *Am. J. Hum. Genet.* 18:514-537.

1967 With R. Lisker. Computer simulation of evolutionary trends in an X linked trait: Application to glucose-6-phosphate dehydrogenase deficiency in man. *Acta Genet.* 17:465-474.

1968 With A. C. Morrow. Rapid screening method for the common atypical pseudocholinesterase variant. *J. Lab. and Clin. Med.* 71:350-356.

1969 With A. Yoshida. A pseudocholinesterase variant (E. Cynthiana) associated with elevated plasma enzyme activity. *Am. J. Hum. Genet.* 21:486-498.

1973 With J. L. Goldstein, W. R. Hazzard, H. G. Schrott, and E. L. Bierman. Hyperlipidemia in coronary heart disease: II. Genetic analysis of lipid level in 176 families and delineation of a new inherited disorder. *J. Clin. Invest.* 527:1544-1568.

2010 With M. R. Speicher, and S. E. Antonarakis, editors. *Vogel and Motulsky's Human Genetics: Problems and Approaches*. 4th edition. Berlin: Springer.