Arno G. Motulsky

The Great Adventure of an American Human Geneticist*

Arno G. Motulsky as told to Mary-Claire King

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Abstract

It is my great pleasure to have been asked by the Editorial Committee of the *Annual Review of Genomics and Human Genetics* to write a short autobiography of my life in genetics over the past 70 years. It has been a great adventure. I came both to America and to human genetics by a circuitous and ultimately very fortunate route. I hope the next generation of geneticists will enjoy reading about it.

COMING TO AMERICA

Between 1923 and 1939, I was a happy kid in the then-German town of Fischhausen on the Baltic Sea. I liked to read and did pretty well in school. By age 15, I was interested in psychology, in psychiatry, in psychoanalysis—in general in what makes people tick—and thought to become a psychiatrist. But history intervened. By early 1939, my parents realized we would need to leave Germany. My dad had a brother in Chicago, so we hoped to go there, but in order to get out of Germany and into America, one needed a visa, which required a quota number that took a while to come up. So my father went to Cuba, where immigration permits were available, with the idea that we would join him later in Chicago. But over the next few months, as the situation deteriorated in Germany, my parents decided it would be best for my mother and brother and sister and me to join my father in Cuba and go to Chicago later.

We left Hamburg in May 1939, on a ship named the *St. Louis*. There were almost a thousand Jewish refugees on board. The voyage from Hamburg to Havana was normal. But before we could disembark in Havana, the Cubans declared our permits void and refused to let us land. The ship was German, but the captain, Gustav Schröder, was very sympathetic to us and sailed all over the Caribbean in search of a friendly port. Of course, we asked to land in America, but were denied. When we sailed close to Miami, US Coast Guard cutters and planes shooed us off.

So ultimately the ship had to return to Europe. I was 16, so still a little naive, but many of the passengers had been interned previously and knew what awaited us on our return. Some attempted suicide by jumping overboard. Telegrams were sent all over the world asking that we be allowed to disembark anyplace other than Germany. Miraculously, a few days before we would have arrived back in Germany, four other countries—England, France, Holland, and Belgium—each agreed to take one-fourth of the passengers. By luck of the draw, my mother and brother and sister and I were assigned to Belgium. So in June 1939, I started high school in Brussels.

Eleven months later, on May 1, 1940, my dad got his visa to move from Cuba to the US and went to Chicago. On the same day, our US visas came through as well. But by May 10, we hadn't yet gotten out of Belgium, and the Germans invaded. Leaving was impossible. Since I was now 17, I was arrested by the Belgians as an enemy alien—ironically, as a German—and sent to an internment camp in France. As the Germans invaded France, we prisoners were moved further and further south, until we ultimately were interned in a camp in the Pyrenees, in Vichy-controlled France. The Vichy French, who collaborated with the Germans, sent the ethnic Germans back to Germany and kept the Jews interned. The internment camps had no food or sanitation. Many prisoners died, most from typhoid or starvation.

About ten months later, those of us with US visas were allowed to go to another camp, near Marseilles, where there was an American consulate. My visa had expired, but I pleaded for its renewal. It was ultimately granted, and in June 1941, ten days before my 18th birthday, I left France legally, crossed Spain into Portugal, and sailed from Lisbon to America. Ten days later and I wouldn't have made it, because Franco did not allow males 18 or older to pass through Spain. A few months later, the Vichy French turned over all their internment camps to the Gestapo.

In August 1941, I arrived in America and joined my father in Chicago. Two years later, we learned that my mother and brother and sister had also survived. With the help of Belgian friends, they had crossed illegally into neutral Switzerland, where they were allowed to live unharmed until the end of the war. My family reunited in Chicago in early 1946.

In Chicago in 1942, I was 18 years old and hadn't finished high school. Fortunately, there was an arrangement by which you could take examinations on material you knew. I'd not had any formal school since the months in Brussels, but in the internment camps there were informal classes, since among the internees were many professors and teachers. We didn't have books, but

Figure 1

Gretel and Arno Motulsky in Chicago, 1945. Gretel and I met in night school in Chicago in 1943. I became a US citizen, joined the army, was sent to Yale to complete my premed courses, and then returned to Chicago for medical school at the University of Illinois. We were married in 1945.

we had our brains. So I learned quite a lot, and with the special exam system in Chicago received my high school certificate. This arrangement still exists and now is called the GED. I am its greatest fan.

With my high school certification, I could attend college on evenings and Saturday afternoons while working during the week. I attended Central YMCA College, which later became Roosevelt University, in downtown Chicago and took biology, chemistry, and trigonometry. I met Gretel Stern in an English course, where she was a better student than I, because she had survived the war in England and America after leaving Germany in 1938 on the Kindertransport. We were married a few years later, in 1945 (**Figure 1**). But meanwhile, in 1943, I applied for medical school and was accepted at the University of Illinois in Chicago. At the same time, I became a US citizen, joined the army, and was assigned to a specialized program for rapid training of young physicians. The army sent me to Yale to finish my premedical courses. Yale was fantastic! I walked into Sterling Library, looked up and around, and thought I'd died and gone to heaven.

The next year at Yale was a tremendous experience. I took genetics with Donald Poulson and was hooked forever. I finished the premed courses at Yale at the end of 1943, and in the three months before medical school started back in Chicago, was assigned as an orderly to an army hospital near Boston. In April 1944, I began medical school at the University of Illinois as a soldier, private first class. I was released from the army in 1946 at the end of the war, finished medical school in 1947, and took a residency in internal medicine and a fellowship in hematology at Michael Reese Hospital in Chicago.

HEREDITARY HEMOGLOBIN DISORDERS

My fellowship mentor was the dynamic biochemist and hematologist Karl Singer, who was interested in sickle cell anemia (40–42). Dr. Singer asked me to compare hemoglobin from patients with sickle cell anemia to hemoglobin from unaffected individuals by injecting the hemoglobins into rabbits, making antibodies, and showing that there was a difference between anti-sickle-hemoglobin antibodies and anti-normal-hemoglobin antibodies. Unfortunately, I couldn't get any decent antibodies to make the appropriate comparisons. But in science, when ideas are in the air, critical discoveries happen fast. In July 1949, Jim Neel proposed that a mutation made hemoglobin abnormal so that under conditions of low oxygen pressure it took on the sickled form, that sickle trait carriers had both normal and abnormal hemoglobins, and that sickle cell anemia patients were homozygous for the mutation, and so had only abnormal hemoglobin (33). In November 1949, Linus Pauling showed a difference in electrophoretic mobility between adult hemoglobin and sickle hemoglobin, naming sickle cell anemia the first "molecular disease" (34). It was a beautiful story.

World events soon intervened again. In 1951, at the time of the Korean War, I went back into the army. All of us who had the benefit of medical education under army auspices were expected to serve again. I was given a very good assignment in a general hospital doing internal medicine and then, after six or seven months, got orders to go to Walter Reed Hospital in Washington, DC. A research unit in hematology was being set up, directed by William Crosby, an excellent hematologist (2). In the lab next to me was a chemist by the name of E.L. Durrum, who had worked out a straightforward method of paper electrophoresis of serum proteins. I was very interested in electrophoresis of hemoglobin. I thought it would be terrific to adapt this simple method to hemoglobin. It worked beautifully (27)!

At Walter Reed, we studied hemolytic anemias that might explain problems encountered by our soldiers. One of these was a red cell abnormality known as hereditary elliptocytosis. It was interesting and puzzling: Some people with the condition had hemolytic anemia that destroyed their red cells, while others had red cells with morphologic abnormalities but with a normal cell life span. The disease was genetically heterogeneous, with two varieties at least (28). We studied other hemolytic anemias, in particular hereditary nonspherocytic anemias, that proved to be enzyme deficiencies of the red cell (25, 49). Singer had encouraged me to think about biochemical mechanisms, and here were genetic diseases, for which mechanisms could be studied to the direct benefit of patients.

In 1953, I was discharged again from the army, this time for good. I'd been offered a postdoctoral fellowship in hematology at Harvard with William Castle, and would have liked to have taken it. But with so many people coming out of the military at the same time, there was a backlog of candidates, and I would have had to wait for an opening in the lab. So when I was offered an instructor's position at a new medical school at the University of Washington in Seattle, Gretel and I decided we should take it, even though Seattle seemed a very long way away (**Figure 2**).

A DIVISION OF MEDICAL GENETICS

In the early 1950s, medical genetics was not yet taught to medical students. I was hired to teach internal medicine and specialized courses in hematology. So at UW, I used some of my hematology lectures to teach bootleg medical genetics (**Figure 3**). I made up a syllabus based on little vignettes, case descriptions for which genetics could solve the case. Word got around. After a couple of years, the chair of medicine, Robert Williams, suggested that I start a Division of Medical Genetics, similar to the Divisions of Cardiology, Hematology, and Endocrinology. Initially I was a little skeptical: There weren't any models. Interestingly, Victor McKusick and I learned later that we

Figure 2

The Motulsky family in Washington State, 1954. When Gretel and I were offered the opportunity to move to Seattle, it seemed very far away to two young people from Europe who had never been west of Chicago. But coming here was absolutely the right decision for all of us. Judy and Harvey are with Gretel and me on this hike; Arlene was born a year later.

were thinking the same thing at the same time. The Divisions of Medical Genetics at Johns Hopkins and UW ultimately opened in the same year, 1957.

Before starting a Division of Medical Genetics, I needed to learn what was possible. Jim Neel's department at Michigan was the most exciting human genetics program in the country. Jim was a geneticist with tremendous breadth and depth in the field who had gone to medical school after completing his PhD (39). He realized that the province of medical genetics extended all the way from physiology to populations and embraced areas, like statistical genetics, outside his immediate expertise. He became my mentor and role model, although he was only seven years older than me. In order to bring Jim's broad perspective to Seattle, I needed to know more about mathematical genetics. So I spent eight months in the human genetics unit of Lionel Penrose at University College London (10). Penrose's department was the best in human genetics in Europe, including, in addition to Penrose himself, J.B.S. Haldane, C.A.B. Smith, and several others. People were very critical and helped me recognize excellent work.

The final encouragement for starting a Division of Medical Genetics came from the First International Congress of Human Genetics, in 1956 in Copenhagen. The event was very exciting, because there had never before been such a meeting. I met geneticists from everywhere, most importantly Stan Gartler, a geneticist with his PhD from UC Berkeley who was working at Columbia University in New York on biochemical variation in humans (**Figure 4**). I asked him to join the new division in Seattle and, to my delight, he accepted, beginning lovely work on X chromosome inactivation (15). We felt that our unit should include scientists with a variety of interests that could be brought to bear on problems in genetics. No one can be an expert in everything, and we needed colleagues in biochemistry and statistics and later in molecular biology

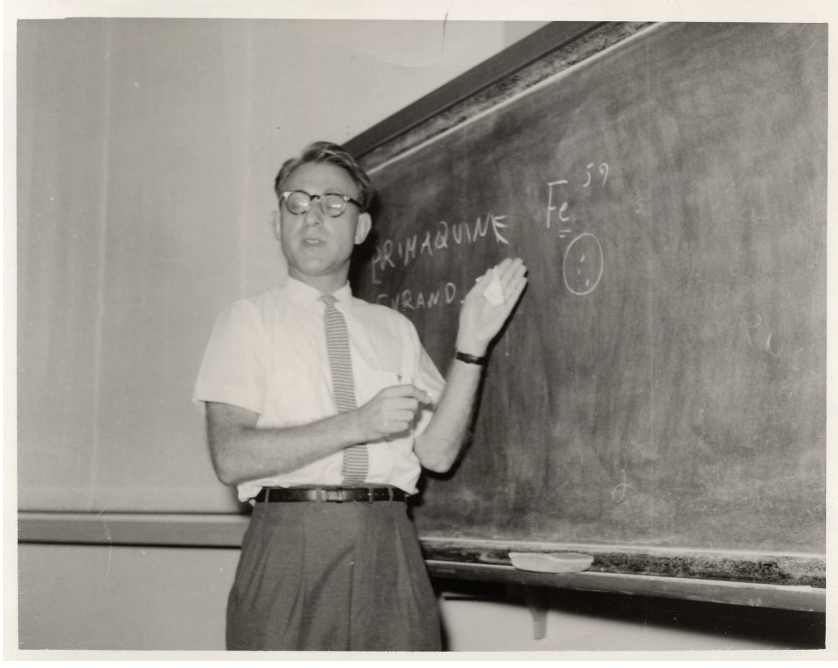

Figure 3

Teaching bootleg genetics. In 1953, I was hired by the new medical school at the University of Washington to teach internal medicine and hematology. I used some of my hematology lectures to teach genetics. A couple of years later, the chair of medicine, Robert Williams, asked me to create a Division of Medical Genetics. I opened the division in 1957.

and genomics to carry out the research that would be useful to our patients. In order to specialize in medical genetics in those days, you had to be a little adventurous. It was exciting to inspire adventurous people further (**Figure 5**).

DEER MICE AND BONE MARROW TRANSPLANTATION

Working in the Pacific Northwest, I soon learned about some deer mice that had a lot to teach us about human disease (1, 13, 26). Knowing my interest in hereditary hemolytic anemias, Ralph Huestis, a geneticist at the University of Oregon, told me about mice that were severely jaundiced at birth (12). These deer mice had hereditary spherocytosis. Their red cells were globular, and their physical condition was very similar to hereditary spherocytosis in human patients. Mice and humans had an apparently identical disease, except that the human disease was autosomal dominant and the deer mouse disease was autosomal recessive. The disease in mice was easily cured. The globular red cells got stuck in the spleen. If the spleens of the spherocytic mice were removed, the life span of their red cells became normal. So we asked another question. I knew that if red cells from a human hereditary spherocytosis patient were put in an incubator, they would break up and hemolyse. In fact, a simple test for the human disease was to put red cells at 37°C. I wondered how a very warm environment might affect deer mice with spherocytosis. We put one group of spherocytosis mice at an ambient temperature of 35°C (95°F) and another group of spherocytosis mice at 4°C (40°F). The mice at 35°C developed severe hemolysis, and most died within two weeks.

Figure 4

Stan Gartler, PhD. Stan and I met in 1956 at the First International Congress of Human Genetics in Copenhagen. He agreed to move from New York to Seattle to join our new Division of Medical Genetics. This made two of us on the division's faculty.

Figure 5

A clinical conference in the Division of Medical Genetics, 1962. The division grew rapidly to include many colleagues and fellows. Working directly with patients was stimulating and satisfying for the fellows and for me.

The mice at 4°C were fine. Spherocytosis was temperature sensitive: benign in a cool environment but lethal in a hot environment. It was a natural example of gene-environment interaction.

The next question was how to treat hereditary spherocytosis in these mice. Could we treat mice by bone marrow transplant, replacing the abnormal erythroid precursor cells with normal precursor cells? We injected newborn mice with normal erythroid precursor cells (23). These animals were a natural population, rather than inbred in a lab, and so varied from one another genetically. Therefore we treated newborn mice with newborn marrow in order to minimize graft rejection. Later we did the same thing with adult mice, irradiating them first to knock out the mechanism of rejection (48). Prior to that time, bone marrow transplantation had been tried only in inbred mice. Our deer mice were a model for how to treat bone marrow disease by transplantation, and this was the first application of marrow transplantation for hereditary red cell disease. About this time, Don Thomas, who eventually was awarded the Nobel Prize for his work on bone marrow transplantation, had started working on dogs. Years later, Don ultimately succeeded with a human protocol that is used widely now to treat aplastic anemia and leukemias and to enable high-dose chemotherapy. In his first paper on successful bone marrow transplantation in human patients, he kindly gave us credit for our work (50).

PHARMACOGENETICS: G6PD DEFICIENCY, DRUG RESPONSE, AND MALARIA

At the same time, I became interested in what we now call pharmacogenetics—that is, differential reaction to drugs among people based on their genotypes (17, 21). At the Copenhagen meeting, a paper was presented on pseudocholinesterase deficiency in prolonged apnea. During surgery, the drug suxamethonium relaxes the muscles. In almost everyone, suxamethonium is destroyed rapidly by the enzyme pseudocholinesterase, and its use is benign. But in people with an abnormal, mutant pseudocholinesterase, suxamethonium is not broken down, and patients require artificial respiration. The condition was genetic. I was intrigued with the interaction of enzymes, genetics, drug reactions, and disease and compiled a review of the then-known examples (16).

At the time, the best-understood example of this interaction was the relationship between G6PD (glucose-6-phosphate dehydrogenase) deficiency and primaquine sensitivity. G6PD deficiency is common among populations in subtropical and tropical regions. The G6PD gene is X linked, so males have either a normal or abnormal type of enzyme, not both, but females can be heterozygotes. The condition was recognized during the Korean War because G6PD-deficient males were sensitive to a variety of drugs. The antimalarial drug primaquine, for example, destroyed their red blood cells. About 10% of African American men as well as many men with origins in the Mediterranean region and India were G6PD deficient. Why was this trait so common in some populations and completely absent elsewhere? The distribution in men from tropical and subtropical areas of the world suggested that the trait was selected for, that it gave some protection against some serious problem in tropical environments. There was a clue from sickle cell trait, which was also common in African populations. There was a very strong suspicion that malaria was the selective factor leading to the persistence of sickle cell mutations, in that sickle cell trait carriers were less likely to die from falciparum malaria. I thought the same might be true for G6PD deficiency, and so visited populations in Africa living in areas of high malaria frequency and others living in areas of low malaria frequency. We evaluated G6PD genotypes and malarial infections of people throughout the region. There was a correlation between the frequency of falciparum malaria and the frequency of G6PD deficiency in populations and between milder malarial infection and the presence of G6PD deficiency in individuals (24, 30).

Figure 6

George Stamatoyannopoulos, MD. George and I met in the early 1960s while studying the genetics of hemoglobin disorders in Mediterranean populations. He joined our Division of Medical Genetics in 1964 and was my successor as division head in 1989.

Marcello Siniscalco invited me to join him in Sardinia to test the same hypothesis with respect to thalassemia. In Sardinia, malaria was common in the valleys and rare in the mountains, where there were no transmitting mosquitos. As we expected, the frequency of beta-thalassemia alleles in Sardinia was inversely correlated with elevation (43). Sickle trait, G6PD deficiency, and the thalassemias all appeared to be evolutionary responses to malaria.

Studying hemoglobin disorders in the Mediterranean basin soon led me to cross paths with George Stamatoyannopoulos, a brilliant young physician from Athens who was interested in the genetics of G6PD deficiency, thalassemia, and sickle cell anemia (**Figure 6**). In 1964, George joined us in Seattle and became one of my closest friends and collaborators (29, 44–47, 52). Twenty-five years later, in 1989, he succeeded me as head of the Division of Medical Genetics.

LIPID DISORDERS, CORONARY DISEASE, AND FAMILIAL HYPERCHOLESTEROLEMIA

During the 1960s, it became increasingly clear that elevated lipids are important risk factors for coronary heart disease. So I wondered: Among patients with coronary heart disease, how many have lipid disorders, and what genetic mechanisms are involved? I had this problem in mind, but didn't have the right person to work on it until the early 1970s, when Joe Goldstein arrived for a genetics fellowship (**Figure 7**). Joe set up a study in 11 hospitals in Seattle, enrolling patients who had a myocardial infarct (MI) and measuring their cholesterol and triglyceride levels three

Figure 7

Joe Goldstein, MD. In 1971, Joe came to the University of Washington for a fellowship in medical genetics. While here, he began the studies of familial hyperlipidemias that led him and Mike Brown to discover the role of the LDL receptor in hypercholesterolemia, and later to the development of statins as treatment for elevated lipids regardless of cause.

months after their attacks (8). Then he selected patients with the highest cholesterol levels or highest triglyceride levels or both, and enrolled their family members and measured their lipids as well. About 5% of the MI patients had very high cholesterol levels that segregated in their families in a clear genetic way. We named this condition familial hypercholesterolemia (38). Other MI patients had extremely high levels specifically of triglycerides that also segregated in their families (6). And yet another 12% of MI patients had elevated levels of both cholesterol and triglycerides, both segregating in their families. We named this condition familial combined hyperlipidemia (9).

This work set the stage for understanding the mechanism of familial hypercholesterolemia. Joe soon moved to Dallas to continue the work with Mike Brown at UT Southwestern. They studied first the hypercholesterolemia families with the most extreme phenotypes: the likely homozygotes for the still-hypothetical gene that underlay this condition. Only one in a million people in the population had such extremely high cholesterol levels. It was smart to study these extreme families first, because they were the most informative, with all three hypothetical genotypes present. Brown and Goldstein's studies led to the identification of the LDL (low-density lipoprotein) receptor and its mutations, to the development of statins, and eventually to the Nobel Prize (reviewed in 7).

Brown and Goldstein's work is the most elegant example I know of how genetics can work. Their work progressed from identification of a very rare phenotype, to identification of the responsible gene, to the development of a drug to treat the phenotype. Statins are now among the most widely used drugs in the world. Very few people are homozygotes for familial hypercholesterolemia. Statin

drugs are used to treat people with cholesterol elevation for any reason, genetic or otherwise. 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 is a beautiful, cohesive story, and it took a long time—more than 20 years (20).

COLOR VISION AS A MODEL FOR PERCEPTION

Ever since I was a teenager, I had been interested in neuroscience, psychiatry, and the brain, but by the 1980s, I still wasn't working directly in that field. Then a colleague told me about a large family with inheritance of several different kinds of color vision (4). Jeremy Nathans at Stanford had just shown that red-green color vision was controlled by a complex locus, with one gene for red pigment and one, two, three, or four genes for green pigment (32). Because the genes are so similar, abnormal recombination and rearrangements are common, leading either to deletions or to fusion genes that include only some of the pigment genes, so that much of the locus is not expressed. Samir Deeb, a biochemical and molecular geneticist, had just joined us in Seattle. Together we worked with psychophysiologists who measured perception and color matching while we measured genotypes. We studied both color vision defects and normal polymorphic variation in these genes (3, 5, 11, 14). Our most intriguing observation was a serine-alanine polymorphism in the red pigment gene, with a distribution of about 60:40 in European populations. The polymorphism was completely benign, but the "serine people" and "alanine people" gave different responses to color-matching tests: Their perceptions of red were different (37).

I think this observation gives us a window into perception more generally. It may be that our worlds differ because our brains perceive certain features of the environment differently. The general question of differences in perception is very difficult. Unlike the linear systems we deal with as geneticists, the biology underlying perception is multidimensional. We don't yet know how it works.

GENETICS OF POPULATIONS AND RACES

Years ago I read studies of the history, archaeology, and anthropology of the ancient Etruscans. It occurred to me that the Jews, particularly the Ashkenazi Jews, would also be an excellent population to study with this integrated approach. In 1961, after the Second International Congress of Human Genetics in Rome, an ancillary meeting was held in Jerusalem. Geneticists who studied variation in blood groups, enzymes, and protein markers met with people who knew about Jewish history and culture. The British geneticist J.B.S. Haldane was the chair, and he was terrific. I've been fascinated by this field ever since (18, 19, 22, 35).

In general, populations from anywhere in the world can now be distinguished from each other by allele frequencies, and the more markers and people are tested, the more one can learn about the origins of populations (36). Any discussion of population origins raises the question of whether the term "race" is meaningful in genetics. I am uncomfortable with the term, because of the horrible misdeeds that have been done in its name. On the other hand, it can be a way to identify ancestry from one of the five broad continental groups. I wish there was another term that did the same. Ancestry does matter to medicine, in two quite different ways. In the context of medical treatment, it is important to know a patient's ethnic background for nongenetic reasons, to understand contributions of culture, diet, lifestyle, and discrimination. With respect to genetic ancestry, race is less important than a patient's genotype at any specific alleles that influence sensitivity to disease or to a drug.

MENTORING

I believe that my most important contribution to medical genetics has been mentoring hundreds of fellows and students over the past 50 years, and I was delighted when my way of mentoring became a model for the field (31). Part of mentoring, including reaching young scientists I don't know personally, has been writing textbooks that present our field in all its complexity and elegance. Between 1979 and 2010, Friedrich Vogel and I wrote four editions of *Human Genetics: Problems and Approaches* (51). The text has appeared in English, German, Italian, Russian, Japanese, and Chinese. We present genetics as a series of problems for readers to think about, applying approaches from medicine, biochemistry, statistics, and most recently genomics to their solution. In advising young fellows how to select a research problem, whether by example from the text or from clinical work or from an experimental observation, my theme is that a good problem pushes knowledge ahead. It does not just add another brick to the edifice. In practical terms, it's probably a good idea to have several projects in play at the same time. The most fun are Sunday morning projects, to work on when no one else is around. Sunday morning projects are less likely to work, but ultimately a few may really change the field.

What will be good problems for the next generation of geneticists? With the completion of the Human Genome Project, we now have the table of genes, just like the table of elements. We can answer genetics questions much more rapidly than in the past, but the fundamental questions themselves have not changed. I think the next great challenge will be to understand how gene products interact with each other and with nongenetic factors. Genetics is linear, but these problems have more dimensions.

REFLECTIONS

I was only able to do all that I did because Gretel took care of everything: our home, our children, and me. And she made it look easy. She was amazing. I was incredibly lucky to have found, early in my life, a partner of such intelligence, humor, and spirit (**Figure 8**). If, in 1953, we had gone to Harvard rather than coming to Seattle, I would have become a respectable hematologist, but I wouldn't have been able to give bootleg lectures in medical genetics. I'm very glad that I came to a new institution that gave a young person tremendous opportunities to put new ideas into practice.

Figure 8

Gretel and Arno Motulsky, 1990. I was only able to do everything I did because Gretel took care of everything else.

Throughout my career, I have very much enjoyed the practice of medicine. Until I was 70 years old, I was an attending physician in general internal medicine. The human contact, to be able to help people, is enormously rewarding. And I always learned something. I was stimulated to ask new questions by seeing things that I hadn't previously thought about. And with respect to medical genetics in particular, I know of no other field in science and medicine that is as fascinating. Medical genetics is closer to science than most specialties in medicine. It reveals exciting new biological phenomena. It has social implications and historical implications and ethical implications. I cannot imagine having done anything more exciting for the past 70 years.

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LITERATURE CITED

1. Anderson R, Huestis RR, Motulsky AG. 1960. Hereditary spherocytosis in the deer mouse: its similarity to the human disease. *Blood* 15:491–504
2. Crosby WH. 1950. Hereditary nonspherocytic hemolytic anemia. *Blood* 5:233–53
3. Deeb SS, Lindsey DT, Hibiya Y, Sanocki E, Winderickx J, et al. 1992. Genotype-phenotype relationships in human red/green color vision defects: molecular and psychophysical studies. *Am. J. Hum. Genet.* 51:687–700
4. Drummond-Borg M, Deeb SS, Motulsky AG. 1988. Molecular basis of abnormal red-green color vision: a family with three types of color vision defects. *Am. J. Hum. Genet.* 43:675–83
5. Drummond-Borg M, Deeb SS, Motulsky AG. 1989. Molecular patterns of X chromosome-linked color vision genes among 134 men of European ancestry. *PNAS* 86:983–87
6. Goldstein JL, Albers JJ, Schrott HG, Hazzard WR, Bierman EL, Motulsky AG. 1974. Plasma lipid levels and coronary heart disease in relatives of newborns with normal and elevated cord blood lipids. *Am. J. Hum. Genet.* 26:727–35
7. Goldstein JL, Brown MS. 2009. The LDL receptor. *Arterioscler. Thromb. Vasc. Biol.* 29:431–38
8. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. 1973. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J. Clin. Investig.* 52:1533–43
9. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. 1973. Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder. *J. Clin. Investig.* 52:1544–68
10. Harris H. 1973. Lionel Sharples Penrose. *Biogr. Mem. Fellows R. Soc.* 19:521–61
11. Hayashi T, Motulsky AG, Deeb SS. 1999. Position of a 'green-red' hybrid gene in the visual pigment array determines colour-vision phenotype. *Nat. Genet.* 22:90–93
12. Huestis RR, Anderson R. 1954. Inherited jaundice in *Peromyscus*. *Science* 120:852–53
13. Huestis RR, Anderson R, Motulsky AG. 1956. Hereditary spherocytosis in peromyscus. I. Genetic studies. *J. Hered.* 47:225–28
14. Jørgensen AL, Deeb SS, Motulsky AG. 1990. Molecular genetics of X chromosome-linked color vision among populations of African and Japanese descent: high frequency of a shortened red pigment gene among Afro-Americans. *PNAS* 87:6512–16

15. Linder D, Gartler SM. 1965. Glucose-6-phosphate dehydrogenase mosaicism: utilization as a cell marker in the study of leiomyomas. *Science* 150:67–69
16. Motulsky AG. 1957. Drug reactions, enzymes and biochemical genetics. *JAMA* 165:835–37
17. Motulsky AG. 1964. Pharmacogenetics. *Prog. Med. Genet.* 3:49–74
18. Motulsky AG. 1979. Possible selective effects of urbanization on Ashkenazi Jewish populations. In *Genetic Diseases Among Ashkenazi Jews*, ed. RM Goodman, AG Motulsky, pp. 301–12. New York: Raven
19. Motulsky AG. 1980. Ashkenazi Jewish gene pools: admixture, drift and selection. In *Population Structure and Genetic Disorders*, ed. AW Eriksson, H Forsius, HR Nevanlinna, PL Workman, RK Norio, pp. 353–65. London: Academic
20. Motulsky AG. 1986. The 1985 Nobel Prize in physiology or medicine. *Science* 231:126–29
21. Motulsky AG. 1991. Pharmacogenetics and ecogenetics in 1991. *Pharmacogenetics* 1:2–3
22. Motulsky AG. 1995. Jewish diseases and origins. *Nat. Genet.* 9:99–101
23. Motulsky AG, Anderson R, Sparkes RS, Huestis RH. 1962. Marrow transplantation in newborn mice with hereditary spherocytosis: a model system. *Trans. Assoc. Am. Phys.* 75:64–71
24. Motulsky AG, Campbell-Kraut JM. 1960. Population genetics of glucose-6-phosphate dehydrogenase deficiency of the red cell. In *Proceedings of the Conference on Genetic Polymorphisms and Geographic Variations in Disease*, ed. BS Blumberg, pp. 159–81. New York: Grune & Stratton
25. Motulsky AG, Crosby WH, Rappoport H. 1954. Hereditary nonspherocytic hemolytic disease: a study of a singular familial hemolytic syndrome. *Blood* 9:749–72
26. Motulsky AG, Huestis RR, Anderson R. 1956. Hereditary spherocytosis in mouse and man. *Acta Genet.* 6:240–45
27. Motulsky AG, Paul MH, Durrum EL. 1954. Paper electrophoresis of abnormal hemoglobins and its clinical applications: a simple semiquantitative method for the study of the hereditary hemoglobinopathies. *Blood* 9:897–910
28. Motulsky AG, Singer K, Crosby WH, Smith V. 1954. The life span of the elliptocyte: hereditary elliptocytosis and its relationship to other familial hemolytic diseases. *Blood* 9:57–72
29. Motulsky AG, Stamatoyannopoulos G. 1966. Clinical implications of G6PD deficiency. *Ann. Intern. Med.* 65:1329–34
30. Motulsky AG, Vandepitte J, Fraser GR. 1966. Population genetics in the Congo. I. Glucose-6-phosphate dehydrogenase deficiency, hemoglobin S and malaria. *Am. J. Hum. Genet.* 18:514–37
31. Nakamura J, Shernoff DJ, Hooker CH. 2009. *Good Mentoring: Fostering Excellent Practice in Higher Education.* New York: Jossey-Bass
32. Nathans J, Piantanida TP, Eddy RL, Shows TB, Hogness DS. 1986. Molecular genetics of inherited variation in human color vision. *Science* 232:203–10
33. Neel JV. 1949. The inheritance of sickle cell anemia. *Science* 110:64–66
34. Pauling L, Itano HA, Singer SJ, Wells IC. 1949. Sickle cell anemia, a molecular disease. *Science* 110:543–48
35. Pierce SB, Spurrell CH, Mandell JB, Lee MK, Michael SZ, et al. 2011. Garrod's fourth inborn error of metabolism solved by the identification of mutations causing pentosuria. *PNAS* 108:18313–17
36. Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, et al. 2002. Genetic structure of human populations. *Science* 298:2381–85
37. Sanocki E, Lindsey DT, Winderickx J, Teller DY, Deeb SS, Motulsky AG. 1993. Serine/alanine amino acid polymorphism of the L and M cone pigments: effects on Rayleigh matches among deuteranopes protanopes and color normal observers. *Vis. Res.* 33:2139–52
38. Schrott HG, Goldstein JL, Hazzard WR, Goodwin MM, Motulsky AG. 1973. Familial hypercholesterolemia in a large kindred: evidence for a monogenic mechanism. *Ann. Intern. Med.* 76:711–20
39. Schull WJ. 2002. James Van Gundia Neel. *Biogr. Mem. Natl. Acad. Sci.* 81:214–33
40. Singer K, Motulsky AG. 1949. The developing (Coombs) test in spherocytic hemolytic anemias: its significance for the pathophysiology of spherocytosis and splenic hemolysis. *J. Lab. Clin. Med.* 34:768–83
41. Singer K, Motulsky AG, Shanberge JN. 1950. Thrombotic thrombocytopenic purpura. II. Studies on the hemolytic syndrome in this disease. *Blood* 5:434–48
42. Singer K, Motulsky AG, Wile SA. 1950. Aplastic crisis in sickle cell anemia: a study of its mechanism and its relationship to other types of hemolytic crises. *J. Lab. Clin. Med.* 35:721–36

43. Siniscalco M, Bernini L, Latte B, Motulsky AG. 1961. Favism and thalassaemia in Sardinia and their relationship to malaria. *Nature* 190:1179–80
44. Stamatoyannopoulos G, Fraser GR, Motulsky AG, Fessas P, Akrivakis A, Papayannopoulou T. 1966. On the familial predisposition to favism. *Am. J. Hum. Genet.* 18:253–63
45. Stamatoyannopoulos G, Panayotopoulos A, Motulsky AG. 1966. The distribution of glucose-6-phosphate dehydrogenase deficiency in Greece. *Am. J. Hum. Genet.* 18:296–308
46. Stamatoyannopoulos G, Papayannopoulou T, Bakopoulos C, Motulsky AG. 1966. Methemoglobin reduction and the inactive X-hypothesis. *Am. J. Hum. Genet.* 18:417–23
47. Stamatoyannopoulos G, Yoshida A, Bacopoulos C, Motulsky AG. 1967. Athens variant of glucose-6-phosphate dehydrogenase. *Science* 157:831–33
48. Steinmuller D, Motulsky AG. 1967. Treatment of hereditary spherocytosis in peromyscus by radiation and allogeneic bone marrow transplantation. *Blood* 29:320–30
49. Terry DW, Motulsky AG, Rath CE. 1954. Homozygous hemoglobin C: a new hereditary hemolytic disease. *N. Engl. J. Med.* 251:364–73
50. Thomas ED, Lochte HL Jr., Lu WC, Ferrebee JW. 1957. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. *N. Engl. J. Med.* 257:491–96
51. Vogel F, Motulsky AG. 2010. *Human Genetics: Problems and Approaches*. Berlin: Springer-Verlag. 4th ed.
52. Yoshida A, Stamatoyannopoulos G, Motulsky AG. 1967. Negro variant of glucose-6-phosphate dehydrogenase (A^-) in man. *Science* 155:97–99