2015 Association of American Physicians George M. Kober Medal

Introduction of Francis S. Collins

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Francis Sellers Collins was born in Staunton, Virginia, on April 14, 1950, with his family pedigree shown in Figure 1A. His parents, Margaret and Fletcher, met as graduate students at Yale — his mother in English and his father in drama. They settled in Staunton, Virginia, in 1946, where Fletcher taught theater at Mary Baldwin College and Margaret wrote plays. They spent the rest of their very full lives in Staunton, both living to the age of 98 and married for 73 years. Fletcher and Margaret's home was a center for music and theater culture in Staunton, including serving as the site for their Annual Twelfth Night Music party, which was attended by major folk music figures each year and in which Francis would also reliably participate. Francis is the youngest of four brothers (Figure 1B) and was home-schooled until he was 10. He then attended Robert E. Lee High School, graduating at the age of 16 (Figure 2) and moving on to the University of Virginia, where he graduated in 1970 with a BS in Chemistry. Figure 3 shows Francis with his college band, the last known picture of him without a mustache.

His college research resulted in his first published scientific papers (1), and like his parents, Francis next moved on to graduate work at Yale, earning his PhD in Physical Chemistry in 1974. Despite two more papers on his CV, unravelling the mysteries behind the "vibrationally inelastic scattering of $H^+ + H_2$" (2), after considerable soul searching, Francis ultimately decided to switch to Medicine. He earned his MD from the University of North Carolina in 1977, followed by Internal Medicine internship, residency, and chief residency, all at UNC. For the final phase of his training, Francis headed back to Yale as a genetics fellow from 1981–1984.

As a postdoctoral fellow with Sherm Weissman, Francis made his first major contributions to the field of Medical Genetics, unravelling the molecular basis for the nondeletion forms of hereditary persistence of fetal hemoglobin, showing that these puzzling disorders were due to regulatory point mutations upstream of the fetal globin genes (3). However, the major scientific innovation of his postdoctoral work, which launched the next phase of Francis' career, was the clever idea that he and his colleagues referred to as chromosome jumping (4). At that time, figuring out how to get from one place in the genome to the next was a difficult challenge, limited to an approach called chromosome "walking," in which the sequences at the end of one phage or cosmid clone led to the next clone, which led to the next, typically in steps of a few thousand base pairs at a time. Francis came up with the idea of making large circles of DNA that would bring together pieces that were actually quite far apart in the genome. Now, instead of walking in small steps, going quickly from the end of one of these large circles to the other would jump over large distances in the genome. As we'll discuss, this innova-

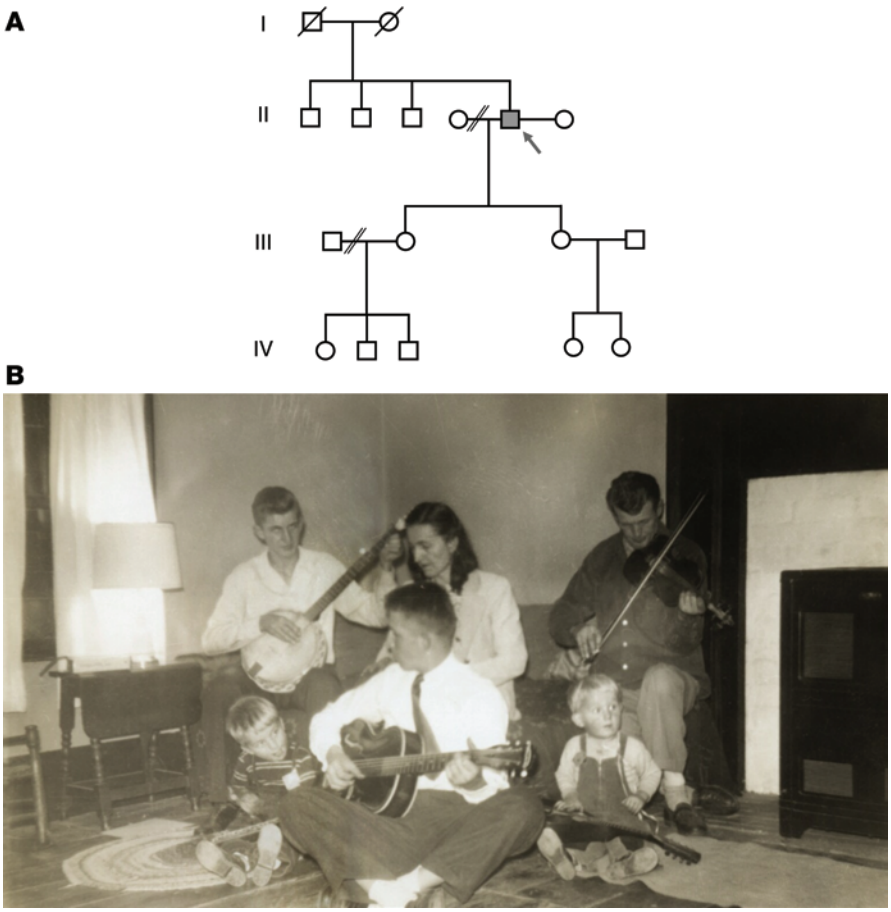

Figure 1. Francis' origins. A four-generation pedigree is shown in (**A**), with the proband, indicated by the arrow and shaded in gray. (**B**) The family at their early home in Staunton, Pennyroyal Farm. Francis' mother, Margaret, is in the back, and his father, Fletcher Jr., is playing the fiddle. Brother Brandon plays the banjo, and brother Kit plays the guitar. Fletcher III is on the left, and Francis, the youngest of the four boys, is on the right.

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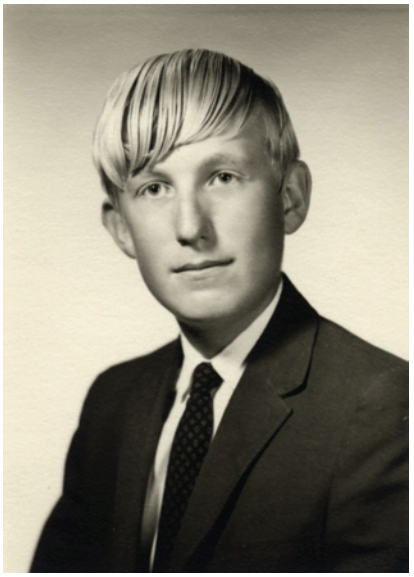

Figure 2. Francis' High School graduation picture (age 16).

Figure 3. Francis (far right) with his college band.

tive technique came in quite handy for Francis' later "gene hunting."

Francis moved to the University of Michigan in 1984. He and the author, shown together in Figure 4 in the traditional photo at the 1985 Human Genetics Gordon Conference, met when the latter joined the Michigan faculty in 1985 and have remained the closest of friends since that time. They were part of a group of young faculty who were recruited by Bill Kelley into the Howard Hughes Medical Institute at Michigan, all of whom are still very grateful to Bill for the profound influence he had on all their careers. A few of these individuals, including last year's Kober medalist, Betsy Nabel, are shown in Figure 5, at a party celebrating Bill's receipt of the Kober Medal in 2005.

Figure 4. Francis and the author at the 1985 Human Genetics Gordon Research Conference, along with several luminaries of the ASCI/AAP.

In his new lab at Michigan, Francis took on what was a very daunting problem at the time: finding the gene responsible for a genetic disease by purely genetic means. His first target was the gene for cystic fibrosis (CF), to which he applied his novel jumping technique, along with other methods. The success of this team (5–7), a close collaboration between Lap-Chee Tsui's group in Toronto and Francis' lab at Michigan (shown in Figure 6), was a landmark achievement for the field of Human Genetics, and the overall approach this work pioneered was referred to by Francis and others as positional cloning, and likened by Francis to "finding a needle in a haystack" (Figure 7). How fitting that, at this year's ASCI/AAP meeting — along with the presentation of the Kober Medal to Francis — the remarkable progress in the treatment of CF was reviewed, including the recent introduction of new FDA-approved treatments into the clinic, based on the understanding of the CF gene and how it works, made possible by the discovery of the CF gene over 25 years ago.

The next big success of the positional cloning approach was Neurofibromatosis type 1, a classic autosomal dominant disease (8), followed by the identification of a long-elusive target, the Huntington Disease gene, by a large collaborative team

Figure 5. Bill Kelley (2nd from the right front), along with some of his "recruits" to Michigan, at a party celebrating Bill's receipt of the Kober Medal in 2005. From the left: Jeff Leiden, Betsy Nabel (2014 Kober Medal recipient), David Ginsburg, and Gary Nabel. On the far right, David Fox. Francis is in the back.

including Francis' lab (9). These were incredibly exciting and triumphant days, with the discovery of genes about which nothing was previously known bringing the opportunity to study the underlying biology of the corresponding disease. In the following years, Francis' lab contributed to the identification of a number of other Mendelian disease genes, including Alagille Syndrome (10), MEN1 (11), Ataxia Telangiectasia (12), Familial Mediterranean fever (13), BRCA1 (14), and familial prostate cancer (15).

In 1993, Francis was recruited to the NIH by Bernadine Healy to succeed Jim Watson as the second Director of the Human Genome Project and as the first Director of what was to become the National Human Genome Research Institute (NHGRI). The Genome Project was a new kind of science that had not been seen previously in biology. This was a huge, collaborative undertaking more familiar to the field of physics, in which many, many people work together toward a major scientific goal. A small group of the leading figures are shown in Figure 8, though Francis was the face and major voice of the Genome Project, as well as a key intellectual force in guiding this program to its successful completion. Though a draft was announced in the White House on June 26, 2000, and an initial analysis was published on February 15, 2001 (Figure 9), the final polishing work of the Human Genome Project continues to this day. Francis was a steadfast defender of the idea that this information belonged in the public domain, and he deserves much of the credit for all of the data resulting from this project continuing to be freely available to all scientists around the world — and everyone else, for that matter. Remarkable advances in sequencing technology, catalyzed by the genome project,

Figure 6. The Collins lab at the University of Michigan, 1989.

Figure 7. "Positional cloning," as depicted by Francis in 1988.

have resulted in a startlingly rapid drop in the cost of sequencing from approximately 400 million dollars for the original human genome sequence to about $1,000 today. These advances have had an astounding impact on the field of human genetics and medicine in general. When Francis and the author were medical students, there was one group of human disease for which the responsible gene was known: the hemoglobinopathies (thalassemia and sickle cell anemia, due to mutations in the hemoglobin genes). By the time Francis and his team found the CF gene in 1989, there were still only a handful of human diseases for which the underlying gene was known. Today, that figure is over 6,000.

Despite the enormous demands of his leadership position in science and his key role in guiding national policy, Francis continues to this day to run a highly productive lab. In 2003, his group identified the gene responsible for Hutchinson-Gilford progeria (16), a particularly difficult challenge, since this disorder is typically sporadic in appearance due to new mutations in the affected individuals. Over the past 15 years, the Collins lab has focused on complex diseases, most notably type 2 diabetes, in close collaboration with Mike Boehnke and others. Like the genome project, this program is enormously collaborative and has required collaboration between many groups working closely together (17).

Francis has continued to catalyze a number of other large-scale collaborative projects that have greatly benefited the entire scientific community, including the HapMap Project and ENCODE. He also played a major role in making sure that attention was paid to the key ethical, legal, and social issues introduced

Figure 8. International leadership of the Human Genome Project, at a meeting at Cold Spring Harbor, New York.

Figure 9. The cover of Nature, February 15, 2001 (left); President Clinton with Francis at the June 26, 2000, announcement of the completion of the draft of the human genome (top right); the cover of Time magazine, July 3, 2000 (lower right).

by these rapid advances in the science of genetics, including passage of the Genetic Nondiscrimination Act (GINA), a key protection for patients and now a part of the practice of clinical genetics (Figure 10). In 2009, Francis was picked by President Obama to serve as the new NIH Director, and he has moved on to an even more prominent leadership role as the key spokesman for United States biomedical research.

Unlike most academicians and scientists, Francis is very open and public about his thoughts and feelings on the big and, some would say, unknowable questions. In this author's view, Francis deserves extraordinary respect for his integrity, bravery, and openness in talking about his faith. Though a few scientists expressed the surprising and disappointing view that religious belief should disqualify someone as NIH director, Francis weathered this undemocratic criticism with incredible grace and integrity. He has written three books dealing with the issue of reconciling faith and science, including "The Language of God" (>10 weeks on the New York Times bestseller list).

Francis' role as NIH Director requires frequent trips to testify before Congress, where he advocates for legislation such as GINA, and defends and tries to expand the NIH budget. He regularly guides distinguished visitors on tours of the NIH, enhancing their interest and excitement about science, and consults with the president and others in the administration about scientific initiatives. The entire biomedical enterprise owes Francis a tremendous debt of gratitude as its primary advocate for the importance of biomedical research and the very core values of the ASCI and AAP. It's hard to imagine anyone who could have better carried out this role, particularly at these difficult times. Though Francis' job requires considerable personal sacrifice, he has also gotten to meet a lot of famous people and likely holds the record for the scientist with the most appearances on The Colbert Report.

To very briefly summarize the rest of his CV, Francis' honors are far too numerous to count but include, in addition to the ASCI and AAP, election to the Institute of Medicine, the American Academy of Arts and Sciences, and the National Academy of Sciences. He is the recipient of the ASCI Stanley J. Korsmeyer Award, the William Allan Award from the American Society of Human Genetics, 14 honorary doctorates, the Gairdner Foundation International Award, the Albany Prize, the Presidential Medal of Freedom, and the National Medal of Science. His bibliography includes over 500 peer-reviewed papers, remarkably with more than 200 as 1st or senior author.

With all of these accomplishments, the obvious question that comes to mind is, "Does this guy ever do anything other than work?" Well, he does — from working as a volunteer physician in a hospital in Nigeria along with his daughter, Margaret, when she was a medical student, as well as traveling to exotic places oversees, from a motorcycle tour in the south of France to an African safari. Music has always been a major part of Francis' life, and when he's

Figure 10. 2008 Capitol Hill press conference (with Senator Ted Kennedy and four members of the House of Representatives) on the afternoon that GINA passed the House (upper panel); signing ceremony for GINA at the White House (lower panel).

not working, music is one of the ways he spends a lot of his time — from his college band to the annual Twelfth Night event at his parents' home in Staunton, playing with celebrities, and playing with bands of his lab mates and others at the NIH, to music nights at Diane and Francis' home in Bethesda.

Finally, somehow, with all the things that he does, Francis still finds the time, and makes it a priority, to be a wonderful husband, father, grandfather, and friend. His wife and best friend, Diane, plays a central role in Francis' work, life, and play. He's a great father to his daughters, Margaret and Liz, and a doting grandfather to his five grandchildren (Figure 11). As his friend, the author is profoundly grateful for the fond memories of the many special times they and their families have spent together over the past 30 years.

Figure 11. Francis and his family at NIH, just after the White House Award ceremony for the National Medal of Science, October, 2009. Daughter Margaret Collins, MD (back right); daughter Liz Fraker, MSW (back, 2nd from left); wife Diane Baker, MS (lower left); with all five grandchildren and their fathers.

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