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Ruth Williams

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Francis Collins

Manning the Helm with Optimism

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Francis Sellers Collins, who was sworn in as the 16th Director of the National Institutes of Health (NIH) on Monday August 17, 2009, is well acquainted with big projects, big budgets, and big politics. He had previously served as director of the National Human Genome Research Institute (NHGRI) from 1993 to 2008, during which he oversaw the US publically financed arm of the Human Genome Project.[1–4]

Collins was already a world-renowned geneticist and master gene hunter when he was asked to lead the Human Genome Project. As a postdoctoral Fellow in Human Genetics at Yale University, he had developed a technique called chromosome jumping, which allowed gene hunters to jump over large sections of chromosomes to reach the location of disease genes.[5] Later, at the University of Michigan, where he became Professor of Internal Medicine and Human Genetics, he used these and other tools to track down the genes for cystic fibrosis,[6,7] Huntington disease,[8] neurofibromatosis,[9] and the M4 subtype of acute myeloid leukemia.[10] He also helped identify numerous other disease genes and their mutations—work that continues at his laboratory at the NHGRI.

The first rough draft of the human genome sequence was announced by Collins and J. Craig Venter on June 26, 2000, and just 3 years later, the final version was completed.[3,4] The project had been finished ahead of schedule and under budget—words that should be music to any politician's ear. As an unquestionably first-class scientist and leader, it was not surprising to many that Collins should be picked to head the NIH.

Collins, who grew up on a farm in Virginia and was homeschooled until the 6th grade, has reached the loftiest possible heights of academia. However, at 60 years of age, Collins remains an ebullient optimist and told *Circulation Research* that he likes to think the best of his career is yet to come.

Figure 1. Francis Collins.

When Did You Become Interested in Science?

One of my earliest inspirations was my 10th grade chemistry teacher, John House, who emphasized the power of the human mind to find answers to scientific questions. On the first day of class, Mr. House told us we were going to do an experiment. He then gave us a box that was painted black and had an object inside. Our task? To map out all the various approaches we could use to identify the object without opening the box.

My initial reaction was, "What a dumb idea!" But then I started trying to come up with a list of experiments one could do to discover the object's identity. And I got caught up in solving the problem. It was the first time somebody had challenged me to think in that way. I knew something was different here.

There were many other experiments after that. Mr. House really knew how to spur a young person's interest in the exploration of the unknown. The excitement of scientific discovery grabbed me, and it's never let me go.

You Chose to Study Chemistry. What Prompted Your Eventual Move to Medicine?

In high school, I didn't like the life sciences at all. Our biology class was focused on memorization; a typical assignment was learning the parts of the crayfish. What's more, there didn't seem to be any overarching principles or organization. Consequently, I decided that I had no interest in biology, medicine, or any aspects of science that dealt with this messy thing called life. Instead, I gravitated toward physics and chemistry, sciences in which things seemed to be wonderfully logical.

While working toward my PhD in physical chemistry at Yale, I realized that I'd made a bit of a mistake: biology might be more organized than I thought. The revelation came during a biochemistry course that sparked my interest in DNA and RNA, which are the molecules that contain the instructions that make each type of organism unique. Based

The opinions expressed in this Profile in Cardiovascular Science are not necessarily those of the editors or of the American Heart Association. E-mail ruth.williams@absw.org.uk

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on what could be learned by studying these molecules and their remarkably logical code, it was clear to me that a revolution was coming in biomedical research, and I wanted to be part of it.

So, I shifted gears and enrolled in medical school at the University of North Carolina at Chapel Hill, where I earned an MD in 1977.

What Happened Next?

After a residency and chief residency in internal medicine, I returned to Yale for a postdoctoral fellowship in human genetics. There, I developed an approach called chromosome jumping to cross large strands of DNA to identify genes responsible for inherited disorders. I applied this approach at the University of Michigan and then at the National Institutes of Health to discover a number of long-sought genes, including those for cystic fibrosis, neurofibromatosis, Huntington disease, and Hutchinson-Gilford progeria.

Subsequently, I was asked to lead the Human Genome Project, the monumental effort to determine the sequence of the 3 billion nucleotides, or letters, in the human DNA instruction manual. For me as a physician, the great appeal of sequencing our genome was the opportunity it offered to tackle some of medicine's biggest questions. Today, as I look across all fields of biomedical research, it is clear that genomics is helping to answer many of those questions.

What Has Been Your Personal Favorite Moment of Your Career?

Since I'm always looking toward the future, I'd like to think the best is yet to come. However, any list of my most gratifying moments in science would have to include the successful completion of the Human Genome Project, which we finished in April 2003, nearly 2 years ahead of schedule and under budget.

Once we fully understand this vast and complex DNA instruction manual, it will be the most powerful textbook of medicine ever. Virtually every human disease has some basis in our DNA. Until recently, physicians were able to take genes into consideration only in cases of relatively rare diseases with very simple inheritance patterns caused by a change in a single gene.

Thanks to the sequencing of the human genome, we have much more powerful tools to study the role that genetic factors play in more complex conditions, including various types of cardiovascular disease, lipid disorders, obesity, and hypertension.

Our next big goal is to cut the cost of sequencing an entire human genome to $1000 or less. This advance should enable each person's genome to be sequenced as a routine part of health care, ushering in the era of personalized medicine.

Have There Been Any Low Points in Your Career?

Searching for the causes of human diseases has always been right at the edge of the possible. Beginning with the search for the cystic fibrosis gene in the late 1980s and extending right up to the present efforts of my lab to understand hereditary factors in type 2 diabetes, there are always disappointments in research, moments where you thought you had the answer, only to see it slip through your fingers. That's the nature of science—but the death of a great hypothesis, torpedoed by a stubborn experimental result, is still a bit hard to take.

How Important Do You Think Hard Work Is Compared With Other Scientific Attributes?

Perseverance is essential in science. It is what keeps brilliant minds going when, despite their most creative thoughts and sharpest reasoning, their research hits an unexpected speed bump or maybe even runs smack into a brick wall. So, I'd say a remarkable capacity for hard work, especially hard work of one's own choosing, is among the attributes of most great scientists.

What Advice Would You Give to Young Scientists?

Work on really important problems, and seek out great mentors. Furthermore, be aware that science does not operate in a vacuum. Part of your job is to get the word out to the rest of the world about the ways in which your research may help to improve health, ease suffering, and reduce disability. You can do this in many different ways: talking to students, doing interviews with local media, giving policy makers a tour of your lab, or meeting with groups of patients or health professionals.

What Are Your Own Strengths, and Weaknesses?

I'm an irrepressible optimist, and, depending on whom you ask, that's either my greatest strength or my greatest weakness. I've often urged my scientific colleagues to set audacious goals with ambitious timelines for large-scale science endeavors, such as the Human Genome Project, even when skeptics deemed those goals difficult or downright impossible to achieve. But I have the utmost confidence in the ability of researchers from many diverse disciplines and many different parts of the world to rise to the challenge, and to work together for the common good.

Our ability to unravel nature's mysteries and solve medicine's toughest puzzles hinges on assembling teams that meld biologic know-how with expertise in clinical research, pharmacology, chemistry, epidemiology, statistics, computer science, and many other fields.

Admittedly, some observers find my optimistic views of the future of biomedical research a bit much. They fear that my seemingly boundless enthusiasm might give rise to unrealistic expectations. But I think the public is pretty good at understanding that science is likely to deliver sooner on some promises of hope than on others. So, rather than apologizing for my optimism, I prefer to work as hard as I can to turn today's bright vision into tomorrow's reality.

References

1. The Human Genome. *Nature*. 2001;409:745–964.
2. The Human Genome. *Science*. 2001;291:1145–1434.
3. Double helix at 50. *Nature*. 2003;422:787–929.
4. Building on the DNA revolution. *Science*. 2003;300:197–376.
5. Collins FS, Drumm ML, Cole JL, Lockwood WK, Vande Woude GF, Iannuzzi MC. Construction of a general human chromosome jumping library, with application to cystic fibrosis. *Science*. 1987;235:1046–1049.
6. Rommens JM, Iannuzzi MC, Kerem B, Drumm JL, Melmer G, Dean M, Rozmahel R, Cole JL, Kennedy D, Hidaka N, Zsiga M, Buchwald M, Riordan JR, Tsui LC, Collins FS. Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science*. 1989;245:1059–1065.
7. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, Zielenski J, Lok S, Plavic N, Chou JL, Drumm ML, Iannuzzi MC, Collins FS, Tsui LC. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science*. 1989;245:1066–1073.
8. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993;72:971–983.
9. Wallace MR, Marchuk DA, Andersen LB, Letcher R, Odeh HM, Saulino AM, Fountain JW, Brereton A, Nicholson J, Mitchell AL, Collins FS. Type 1 neurofibromatosis gene: identification of a large transcript disrupted in three NF1 patients. *Science*. 1990;249:181–186.
10. Liu P, Tarlé SA, Hajra A, Claxton DF, Marlton P, Freedman M, Siciliano MJ, Collins FS. Fusion between transcription factor CBF beta/PEBP2 beta and a myosin heavy chain in acute myeloid leukemia. *Science*. 1993;261:1041–1044.