A conversation with Harold Varmus

For the first of our series Conversations with Giants in Medicine, we spoke with Harold Varmus, who has been the director of the National Cancer Institute since July 2010 (Figure 1). He has previously served as director of the National Institutes of Health (1993–1999) and as president of the Memorial Sloan-Kettering Cancer Center (2000–2010). Among his many awards, Varmus was awarded the 1989 Nobel Prize in Physiology or Medicine together with J. Michael Bishop in recognition of their discovery of the cellular origin of retroviral oncogenes. The full interview can be seen on the *JCI* website, http://www.jci.org/kiosk/cgm.

JCI: Can you speak about your beginnings in science?

Varmus: I was brought up in a health-oriented household — my father was a general practitioner, my mother was a psychiatric social worker. There was anticipation that a nice Jewish boy from Long Island would end up being a physician; but once I got to college I suddenly discovered a much wider world. I ended up being an English major, writing a thesis on Charles Dickens, running the school paper, getting a C in organic chemistry, and deciding after a prolonged period of ambiguity to go to graduate school in English literature. During that year I decided I would reapply to medical school; I went to Columbia's College of Physicians and Surgeons and loved it. I went there thinking that somebody who liked words and books and was interested in the workings of the mind would be a psychiatrist. But then I became interested in internal medicine because of its narrative aspects — the medical history and the detection part of it, figuring out what's wrong with somebody. I'd never done any science, and that is a key element in the story. However, I didn't have many choices as a draft-eligible MD in the late '60s who was fiercely opposed to the Vietnam War — for me it was Canada or the public health service. Fortunately, despite not having any research credentials, I was matched with a laboratory at the NIH.

JCI: That was Ira Pastan's lab?

Varmus: It was. He was working on release of thyroxin from the thyroid — it seemed like the kind of problem I could work on with my medical training and limited background in science. But before I arrived at the NIH, Ira had developed a new interest in learning how cyclic AMP might work to regulate genes in bacteria. As soon as I got to the NIH, I began to learn about the tools of molecular biology, developed my first assay, and was really excited. I learned the power of having instruments to measure things and how exciting it is to be able to tell your colleague at the next bench that you had a result. And suddenly I was hooked on science, at the age of 28.

JCI: So you trace your interest in laboratory science to that time?

Varmus: Absolutely. I began thinking, "This is fun and exciting." But at the same time I realized that I didn't have enough grounding in bacterial genetics. Moreover, I wanted to make some use of my medical training and my inherent interest in medical problems. So I began to look for an area of research that was closer to my medical background. In those days the NIH was endowed with many wonderful courses, and from them I learned about cancer biology and how frustrating it had been to understand how a normal cell becomes a cancer cell. I also found a unique tool: tumor viruses. These viruses could cause cancer in animals, and they were remarkably appealing to me. Cells are complex — they have tens of thousands of genes; but tumor viruses have only a few genes, and they are competent to change the behavior of a normal animal cell. If these simple agents can make complex cells behave like cancer cells, then we could do something to try to understand how cancer arises — what do those viral genes do, what are they, where do they come from?

JCI: You moved on to study cancer biology in California.

Varmus: There was a choice to make after the NIH. I wasn't crazy about Washington. I'd just got married, and Connie and I wanted to go to California for various reasons. So I began shopping around for a place to work, and for something to do. I knew I was interested in tumor viruses. Completely unannounced, I just walked into a lab I had heard about at UCSF and introduced myself to the faculty there. One of them was Mike Bishop. It quickly became very clear that Mike and I had a very similar perspective. Once I joined the group a year later, Mike and I and our colleagues studied how retroviruses grow and how they cause cancer — this class of tumor viruses has proven to be an incredibly potent source of knowledge about how human cancer arises. Retroviruses lead us to a set of cellular genes (proto-oncogenes, the precursors of viral oncogenes) that proved to be crucial. Look at the advances that have occurred therapeutically in the last few years: most of them are the result of understanding mutations in the cellular genes that are precursors to the retroviral cancer genes.

JCI: When you transitioned from UCSF back to the NIH, how were you able to make the decision to leave such exciting research?

Varmus: After arriving at UCSF and becoming part of this team and having a very long-term partnership with Mike Bishop and others, I lived in a kind of scientific nirvana for over twenty years. There were a lot of reasons to stay there forever, but I had what I guess you could call a midlife crisis. Mike and I had just won a Nobel Prize. I hesitate to self-advertise, but this event did have a very significant role in my life. Until then, I was a respected scientist but not someone you would necessarily turn to for a verdict on some social or political issue. Afterwards, I didn't think I had the knowledge or the right to speak out on politics in general, but I did think that I knew enough to talk about the politics of science, what the results of governmental decisions would be on training and funding of scientists, the integrity of science, and the way in which the government supports science financially. So I began talking about these things publicly and got quite interested in how the issues were worked out. In early 1993, just after Bill Clinton became president, the directorship of the NIH became available, and I thought, why not at least have a look? I threw my hat in the ring, was interviewed, got along well with Donna Shalala, the secretary of the Department of Health and Human Services, and the job was mine.

JCI: While there you oversaw a legendary doubling of the budget. What made you want to leave after 6 years?

Varmus: It wasn't a matter of saying I didn't like the NIH anymore; the issue was how long I could be an effective leader. Anybody who's been in a leadership position knows that after six to eight years you are likely to have done most of the things you wanted to do. I realized I liked running

Figure 1
Ushma Neill interviewing Harold Varmus on February 17, 2012. Image credit: Karen Guth.

institutions, but I also knew I wanted to be in New York. Then an opportunity came along at Memorial Sloan-Kettering, where I could be the leader of the institution and continue to do research.

JCI: So then what precipitated the desire to go back into a more governmental directorship [the National Cancer Institute in 2010]?

Varmus: Well, I wasn't looking for a government job. After seven or eight years at Sloan-Kettering, I knew that I had gotten done the big things that I wanted to do — enlarge the research community and improve it; reorganize the scientific enterprise by bringing clinicians and basic scientists together; and create some new kinds of training programs, including our own graduate school in cancer biology. So I had done a lot of the things I'd sought to achieve there, and I knew I was beginning to show less originality in the way I thought about the next phase of life for Sloan-Kettering. I began to think about other possibilities. At the same time I was quite active politically — I had supported Barack Obama early on and was interested in helping by serving his administration. I accepted his invitation to cochair his Council of Advisors on Science and Technology, and I was part of the transition team, helping the administration find candidates to run various agencies, including the National Cancer Institute. At one point a former student of mine looked at me and said, "Why don't you do it?" Because it is a particularly exciting time in cancer research, I thought it would be important to oversee how we give out money for doing this kind of work, how we assemble teams for new initiatives, and how we inspire people to do work that moves quickly, even if the budgetary outlook in a recession is not good.

JCI: So in terms of the somewhat bleak current financial picture, what is your advice to trainees — what initiatives are you pushing the most at the NCI? Where are the most opportunities?

Varmus: I think your question is multilayered: because there is a financial shortfall, the success rate for grantees is relatively low, and that is discouraging. But that in some ways is independent of another issue: what are the biggest opportunities for doing exciting science? In every domain of NCI- or NIH-sponsored research, the competition is severe. Overall at the NIH last year the success rate for a grant applicant was about 17% [and at] the NCI was about 14%. We ensure that new investigators have at least as good a success rate as senior people, but it's still tough. While things may be a bit tougher at the NCI than elsewhere, we think that the scientific opportunities are still remarkably exciting.

I would highlight a few things that are especially attractive. For the first time we are painting a clear picture of what is going on in a cancer cell — by sequencing genomes, looking at chromosomal rearrangements, studying gene expression patterns, looking at DNA methylation, looking at the expression of microRNAs, and looking for potential biomarkers to detect and monitor disease. All these things are being done in a very rapid, high-throughput scale in a way that presents exciting experimental opportunities. The new information is just that — information, not understanding. If a gene is mutated in several cancers, it doesn't mean that it is making contributions to all of those cancers, and it doesn't tell you what kind of contribution that genes might be making. So there are tremendous opportunities for new functional studies and opportunities for translating science into clinical benefits in therapeutics and diagnostics There's a lot of reason for someone who is interested in cancer research to be extremely excited about getting into this field, even though the chances of succeeding to obtain support from the NIH are definitely less than they used to be or ought to be.

JCI: What made you decide in 2009 it was time to write a memoir?

Varmus: It began as an obligation, not as a decision, when I was invited in 2004 to give a series of three lectures sponsored by W.W. Norton publishers at the New York Public Library. I very much enjoyed giving the lectures — one on becoming a scientist, one on being a scientist, one on being a political scientist. In the fine print, the contract said Norton expects you to publish these lectures. I decided to take the opportunity to write something bigger by exploring each of the three topics in greater depth than was possible in three one-hour lectures. For example, I was able to write much more in detail about my experience as NIH director and about three or four things that I really care about: global health, science publishing, and stem cell and embryo research.

JCI: What would you have done if you were not a scientist?

Varmus: One option was journalism, which I entertained for a while when I was running the Amherst College newspaper. The second possibility would be a professor of English literature; after all, I was on my way there as a graduate student. I wish I had more talent as a musician or an athlete, so that I could have entertained the idea of careers in those areas.

Ushma S. Neill