

Harold Varmus, MD and J. Michael Bishop, MD

rs. Harold Varmus and J. Michael Bishop are two of our institution's brightest stars. They have worked closely together for the past two decades, sharing a devotion to teaching and research. Happily, they now share the Nobel Prize for medicine.

By way of introduction, they have supplied us with the following biographical material.

J. Michael Bishop, MD was born and raised in rural Pennsylvania. He attended Gettysburg College, graduating as valedictorian. He earned an MD at Harvard University and obtained his first research experience by taking the unorthodox approach of ignoring the formal fourth-year curriculum. Ironically, his interest in research was first awakened by the hope of becoming a teacher. The example of his most respected faculty soon taught Bishop that teaching and scholarly investigation are companion and inseparable vocations. Independent reading had piqued his interest in the burgeoning field of molecular biology. Casting about for new departures in this field, he chose the use of animal viruses to study genetic processes in higher organisms.

Two years of training in internal medicine at Massachusetts General Hospital left Bishop uncertain of his future in clinical medicine, so he entered enthusiastically into the unique Research Associates Program at the National Institutes of Health. He then joined the faculty at the University of California and began his work on RNA tumor viruses, which has since remained an unforgiving preoccupation.

Harold Varmus, MD was born on the south shore of Long Island. He attended public schools in Freeport, New York, before entering Amherst College in the fall of 1957, intending to prepare for medical school. The intensity and pleasure of academic life challenged Varmus' presumptions about his future as a physician, and his course of study drifted from science to philosophy and finally to English literature. Following graduation from Amherst, a Woodrow

by Michael Drake, MD '75 and Robert Schindler, MD '67

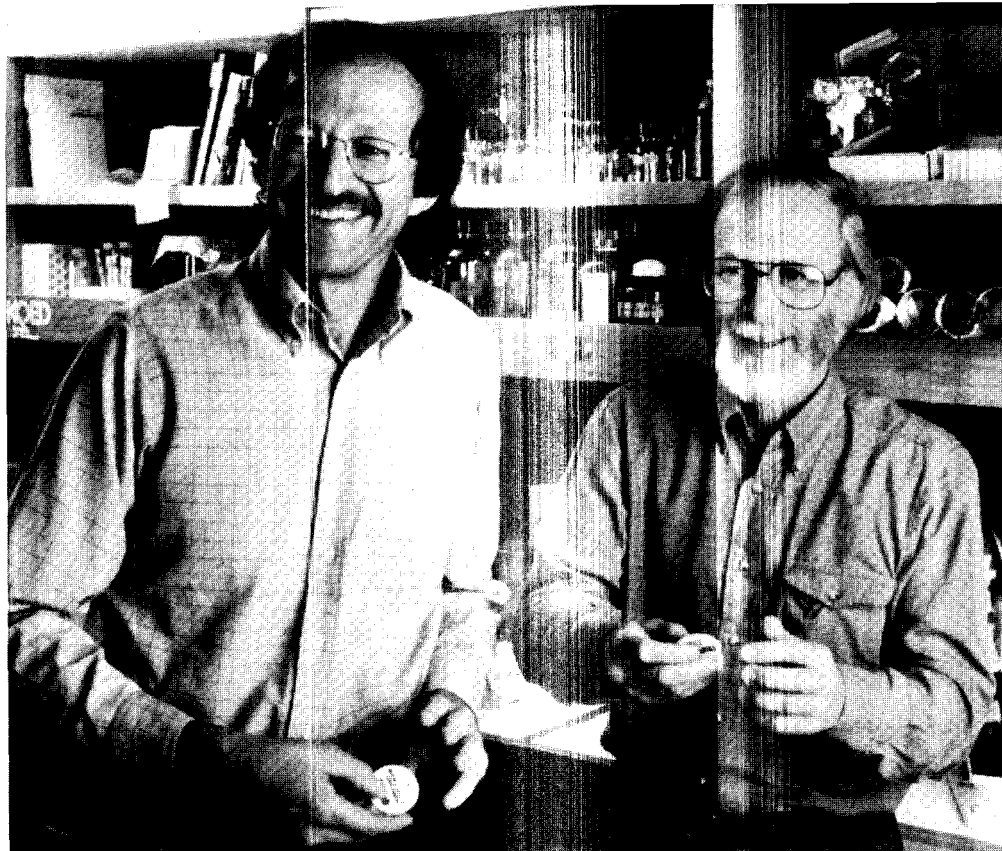
Wilson fellowship enabled him to pursue his interest in literary scholarship by beginning graduate studies at Harvard University. Within a year, he again felt the lure of medicine and entered Columbia College of Physicians and Surgeons.

In preparation for a career in academic medicine, he worked as a medical house officer at Columbia-Presbyterian Hospital from 1966 to 1968, and then joined Ira Pastan's laboratory at the National Institutes of Health as a clinical associate. He joined J. Michael Bishop, MD as a postdoctoral fellow at UCSF in 1970, was appointed lecturer shortly thereafter, and in 1972 became a regular member of the faculty in the Department of Microbiology and Immunology.

This past January, Drs. Robert Schindler and Michael Drake interviewed Drs. Bishop and Varmus in the Ernest Jawetz Library, Department of Microbiology at the University of California San Francisco. Excerpts from that interview follow.

I'm interested in what brought each of you to UCSF. Mike, you arrived first. I understand that Leon Levintow, chairman of Microbiology and Immunology, was involved in your coming here. How did that happen?

Dr. Bishop: When I went to the NIH looking for a postdoctoral slot, Leon was one of the staff who interviewed me. I was particularly interested in animal viruses, and he was the person from that orbit who interviewed me and subsequently offered me postdoctoral training. He was my postdoctoral supervisor. He skipped town after a year to come here, and I spent a year at NIH working more or less on my own, corresponding with him. Later, Ernest Jawetz offered me a job here. I went off to Germany to think about it and eventually decided to take this job. When I arrived here my lab was essentially joined to Leon's. When I wasn't at the bench, we spent a great deal of the working day talking about everything. The administration didn't know who I was or anything about me, and I think Leon had a great deal to do



Harold Varmus, MD and J. Michael Bishop, MD

with convincing them when I was young and unknown that I was worth supporting. Also, he was very encouraging about the idea of joining up with Warren Levinson to study retroviruses.

Warren and I essentially powwowed together, each of us making our own contribution, and my responsibility was to get the molecular biology going any way we could. Leon really fostered that collaboration and fostered my interest in RNA tumor viruses.

Harold, what attracted you to the group?

Dr. Varmus: I came on rather different terms. I had been at the NIH, learning to do science after clinical training, and had learned enough to know that I was attracted to the tools of molecular biology. As a result of some courses taken at the NIH, I became very interested in tumor viruses and was looking around for a place to learn the lore as a postdoctoral fellow. At that point, I had never heard of Bishop or Levintow or Levinson. The people I'd heard of were people like Harry Rubin at UC Berkeley and Renato Dulbecco at Cal Tech. Rubin asked me to come chat with him and

he mentioned that there was a group just starting to work on tumor viruses at the University of California San Francisco. I knew about Moffitt Hospital, as a place where one could go without suffering a loss of reputation as a clinician, but I didn't know anything about the science that was being done here. The truth

***There's been a
"sea change"***

... It's been amazing

was there wasn't an awful lot to talk about at that point. Anyway, I came over one day to meet Leon and Mike and was told they were having lunch in the Golden Gate Room, which seemed to me to be a wonderful place to be having lunch — until I had a look at it! That led to conversations with Mike and Leon. Mike obviously had a lot of energy and Leon had a fatherly attitude and a strong history in biochemistry.

Mike, when did you make the decision that you wanted to be a laboratory scientist as opposed to a clinician?

Dr. Bishop: I had no idea what I wanted to do when I entered medical school. I wasn't even sure I wanted to be a doctor. But I was interested in human biology and medical school was the obvious place to study that. I received my degree in chemistry, but I took the minimum to get the major. It was not a real chemistry major. I spent most of my time dallying with other things. Academic things, you name it, I tried it!

Harold, you majored in the humanities, right?

Dr. Varmus: I did. But I had a certain amount of science to take. At Amherst in those days there was quite a large segment of required core curriculum. I had assumed that I'd be like my father, a doctor, and take a pre-medical course. But I hadn't been there long before I started dabbling in lots of things — philosophy, physics, and other things — pretty superficially in the first couple of years. But then I developed a true love of literature and majored in it. I went to graduate school for a year before realizing that I liked science too much and

was too interested in contemporary things to spend my life studying 17th century prose.

Mike, what impressed you about Harold in the beginning?

Dr. Bishop: To a nominal supervisor, the quality most important is independence. Harold was independent from the moment he arrived. We kicked around ideas about what he might do. He chose what he wanted to do and ran with it. I don't think we ever really had a supervisory relationship. We very quickly fell into a co-equal relationship. Most of our collaboration consisted of advising others together. That was very intensive. We met regularly with all the students and postdocs who were under our joint supervision and would discuss what they were going to do. It was never really a mentor kind of relationship.

Dr. Varmus: I don't think we should undervalue that because certainly at the very beginning I needed advice about working with the system.

Dr. Bishop: Yes, but that was available in the lab.

Dr. Varmus: Sure it was, but there were moments of advice that I can still recall. I suppose that the advice I got could have come from a lot of sources, but because I value Mike's judgement, the advice that came from him I took more seriously.

Harold, when you came here what drew you to Mike, was there something about his science?

Was there something about the questions he was asking?

Dr. Varmus: I think it had more to do with commonality of language. I had been shopping very briefly in the tumor virus field. I had done a fair amount of reading at NIH, and I was finding people still mired in the old school of phenomonology, attempting to put a virus into an animal to see what kind of tumor the animal gets. I wasn't interested in that. I had grown up in the previous couple of years in an atmosphere where the questions were being asked at a more molecular level. I hadn't been here more than 5 minutes before Mike and I were talking about making specific hybridization probes. We were on the same wavelength in a way that hadn't been the case with other people I had been speaking with about postdoctoral work.

When did you realize that you had made a discovery? That you had proved a theory?

Dr. Bishop: The work in the first paper made it reasonably clear. From that moment on we could argue that if what we had found in the cell was indeed a reasonable facsimile of the oncogene in the virus, most likely the gene had moved from the cell to the virus rather than vice versa. This was the first purchase on anything resembling a pre-cancer gene, if you will, in cells. It was a way station and I'm sure we thought we discovered something important, in the sense that the simple hybridization curves weren't lying. Exactly what it meant and how the rest of it would work out keeps you going.

Dr. Varmus: We knew, obviously, that it was important. It was a long



King Carl Gustaf of Sweden presenting the Nobel Prize to J. Michael Bishop, MD

time before I realized how important everyone else thought it was.

Dr. Bishop: Right, for me, too. People within the field, of course, recognized it. You could tell from the flood of people beginning to do the same kind of experiments, that's a sure sign that you're on to something. Bees know where nectar is.

I'm interested in something Mike said earlier. You were talking about UCSF as a place for science and how it was in the late 1960s when you arrived. How has the milieu changed in the last 20 years? How would you compare it then with now?

Dr. Bishop: To use a phrase, there's been a "sea change". Where did that term come from?

Dr. Varmus: From "The Tempest."

Dr. Bishop: There's been a sea change, it's amazing. When I came here there were about three people on campus who were in any way, shape, or form on my wavelength scientifically. Herb Boyer was here, and he and I spent many nights together in the cold room. He taught me how to run columns and I kept his morale up. I didn't teach him anything! There was Warren Levinson, there was Leon Levintow, and there were one or two folks in the biochemistry department who have long since departed, who at least had an inkling of where I was trying to take animal virus problems. There were one or two folks around who weren't molecularly oriented. The biochemistry department had been decimated by a seven-year vacancy in the chair. There was nothing going on.

Getting Bill Rutter to be chairman of biochemistry was the first important step. On the other hand, I still look back with some nostalgia at the fact that I was completely on my own and free to think about whatever I wanted and to find my own pace. I didn't have all these incredibly accomplished peers in my immediate presence to cause me anxiety. I had my own standards. So I've nostalgic recollections of that,



King Carl Gustaf of Sweden presenting the Nobel Prize to Harold E. Varmus, MD

but I would still say that if you had a choice you should choose an environment that's rich rather than one that's poor, as this one was when I came here.

Dr. Varmus: Things had obviously improved quite a bit, even between Mike's arrival and mine three years later, because Bill Rutter and Gordon Tompkins had both added a tremendous amount to the atmosphere. Gordon, although not chairman of the department, was incredibly influential at attracting young scientists, many of whom are still here, like Keith Yamamoto. Even though the faculty definitely was stronger by 1980 or so, something happened around 1980 that made this place much more popular. Part of that was increased attention to our graduate programs and to the MD-PhD program. So that at this point, a day like today, for example, is filled with a morning meeting with graduate students, MD-PhD students, PIBS Journal Club in the afternoon, and seminars. I don't know how we got any bench work done in the 1970s.

Do you feel pressure living as a role model now for young scientists coming in or doesn't it ever come up?

Dr. Varmus: I feel a little more cautious about making a joke because I don't want to be taken as treating someone lightly. I am aware of the possibility that they would take my comments with undue seriousness.

How about you Mike?

Dr. Bishop: I would agree with Harold. You're always a role model from the first time you stand up in front of a classroom. We haven't been in this exalted state very long. Maybe we're going to learn something we don't know yet!