

Interview with Dr. James Wyngaarden (JW)
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JM: The information I am about to give you and your response will now be recorded. My name is Jennifer Midura and I am a student at Duke University. I am in a course on the history of genomics that includes oral history. One goal is to produce a written transcript of interviews with important figures in genomics. Some of the interviews may be archived or made public through a website. I selected you as the person I would like to interview. The interview should last about 45 minutes. Your participation in this interview is strictly voluntary, and you may withdraw at any time. You do not have to answer every question asked. The information that you provide will be “on the record” and may be attributed to you. This interview is being recorded and I will take written notes during the interview. The interviews that are posted publicly will be archived as a history resource. If you prefer that the interview be used only for the course and not made public, please indicate this. One risk of this study is that you may disclose information that later could be requested for legal proceedings. Or you may say something that embarrasses you or offends someone else when they read it on a public website. The benefit of participating in this study is ensuring that your side of the story is properly portrayed in the history of genomics. Dr. Wyngaarden, do you agree to the interview?

JW: Yes, no problem.

JM: All right. So, how was the human genome project initially conceived? Considering the technological limitations at the time, why and how was this going to be accomplished instead of at any other time?

JW: Shortly after I became the director, I became aware that a number of groups were beginning to look at this issue. One was the Howard Hughes Medical Institute. Dr. Ruth Kirschstein, the director of the National Institute of General Medical Sciences (NIGMS), was attending their conferences and reporting to me. NIGMS is the NIH institute from which most of the scientists at Duke, for example, would have gotten their grants in biochemistry, physiology and so forth. NIGMS supports basic science work without a specific medical application. Some disease-oriented Institutes at NIH were starting limited sequencing projects. They were small in scale, targeting specific genes of medical interest but without any plan to conduct a massive organized sequencing program. Also, at least one outside scientist of note was promoting the idea of a sequencing program, namely Dr. Robert Sinsheimer in California who talked with me about this at a reception at the Italian embassy at one time. However, within NIH there was no organized program to do the whole genome.

Actually, as your question implies, there were serious technical limitations to doing it. For example, you would have to have overlapping stretches of DNA to sequence so that you could overlay them and eventually get a complete sequence. To do that you'd have to isolate small segments of human DNA and then multiply these segments in some vehicle. At the time, the *E. coli* vehicle was being used and it would have taken at least 60,000 different cultures to

accommodate the entire human genome. That would have been a daunting task. Nevertheless, the idea of doing it moved forward in confidence that there would be a way to solve these problems.

About this time I was in London at a meeting of the European Medical Research Council, to which the NIH director is always invited as an observer. At the reception the first evening someone came up to me and asked what I thought of the announcement by the U.S. Department of Energy (DOE) that they had funds to sequence the human genome at an estimated cost of 2 billion dollars.

As soon as I heard that, I knew we had to decide, were we going to play in this game or not? You asked, in one of the questions on your list, why we would want to do it. Well, one of the great values of knowing the sequence of the human genome would be in its medical applications, and although DOE had a great interest in health issues related to the environment, it's not fundamentally a disease oriented institute, so I knew if gene sequencing was to be done and we didn't participate actively we would have missed the boat on one of the great projects of our age. So, my instant reaction was, "Not on my watch will it be done by DOE alone."

DOE has a different style of doing things. They tend to deal with big projects. NIH historically has been a champion of the small scientists, doing small projects in small laboratories. An organized program in gene sequencing would be a major departure from anything the NIH had done until then.

One of your questions also relates to why there was internal opposition to such a project? Well, each one of these individual institutes jealously protected its own territory, and many were in the process of sequencing genes of interest to them, but this was a hit and miss project. There was nothing organized about it, no idea of starting at one end and ending up at the other end of the human genome, so we were not likely to get to the goal of this project by this random approach. I didn't think we'd ever get it done that way. Also, a large, organized project was perceived as a serious budgetary challenge to those directors, that would be competitive with funds for their historic programs. In truth, I think that was more knee-jerk protectionism than scientific logic because there was plenty for everybody to do. Another point was, they were concerned about the NIH getting involved in big, massively organized science projects. That approach would be a departure from the historic style under which individual scientists apply for research grants to do projects with limited, well defined goals in their own laboratories. It was my view that we could do both, and that we would undertake the sequencing project with new money.

When it became clear that we were going to have to make a decision whether or not to do it, I did two things that I felt were necessary to obtain broad support within the biomedical research community to undertake this project. First, through the Secretary's office we requested the U. S. National Academy of Sciences to study the project and give its opinion as to whether it was a viable project to do at this time. The Academy committee was chaired by Bruce Alberts, who later became President of the Academy. There were many notable geneticists were on the committee, including Jim Watson. And they did recommend the project. They were somewhat divided between the NIH and the DOE as to which should become the lead institute, recognizing

that it was historically the kind of project that DOE was accustomed to doing and that it was new territory for NIH. Some favored DOE and thought they would be better managers of a project of large size. Others saw immediately that the relationship to health was going to drive this project, knowing that the Congress was more likely to support this work with large sums of money if it could defend the project on the basis of potential benefits to the health of the American people. I thought we could make a case for the benefit of genome knowledge through the health route much better than DOE could. But we still needed broad support within the scientific community, and some high profile biological scientists were strongly opposed to the sequencing idea.

I thought the way to address that issue was to have an NIH sponsored conference bringing in leading biological scientists, including in particular some of the more vocal dissenters. One of the most vocal and most prominent was David Baltimore so we asked David to chair the conference for us. And when he chaired it and heard the merits of it from scientists he greatly respected, he became persuaded that the reasons for the opposition from many scientists were unfounded, this was going to be additive and not competitive with the other things we were doing, and the NIH had a much greater capacity to generate the funds than the DOE did. So the results of that conference reinforced the academy report and gave us courage to go ahead. It gave me what I needed to deal with the other directors.

It wasn't quite as easy as it sounds because the NIH isn't an autocratic institute. It's not an army where the general speaks and everyone falls in line, not at all. But these two committee reports gave me a great deal of purchase with the individual institute directors at NIH. Ruth Kirschstein was in favor of it but she was the only one. At the end of that second committee meeting, when it was clear to all participants that I wanted to do it, a small group told me that they thought it might be possible to get Jim Watson to direct it. And I had known Jim Watson for some time. In fact, I knew him well enough to know his assets, which were enormous, and his liabilities, which were also considerable. You asked about his outspokenness. He's known as Honest Jim because he says whatever is on his mind and it doesn't matter whom he hurts by it. He doesn't mean it viciously, it's just that he's so frank, so honest, that he'll say what's on his mind no matter if the person is going to explode at hearing it and sometimes people do. And I've had him yell at me and an hour later it's all over. I had no problem with that characteristic of Jim's. I thought it would be wonderful if Jim would agree to direct the project, for several reasons. His stature would give it the kind of prominence that would be useful. I thought it would give me much more leverage internally to have someone like Jim directing it, rather than a less prominent person.

All of this was taking place in about the fourth or fifth year of my tenure at NIH. I would not have known how to negotiate this process the first day I arrived. Steering this process first through the Academy and then through our committee, and only after that going to Congress for the necessary funding, was a process that gave it legitimacy far beyond what a simple budget request would have achieved. All requests go through the Office of Management and Budget, and they can delete anything they don't like. But they are usually very supportive if they understand the proposal and it has broad support from prestigious bodies.

This particular year, after our budget hearings had ended, Congress came back and said that they were able to free up some supplementary funds and asked me to provide an amended budgetary request for an additional billion dollars in one hundred million dollar increments. In order to avoid any internal revolt, I used the first 4 one hundred million dollar increments to fill gaps within the budgets of the internal institutes. Then, in the fifth increment I requested something like 50 million dollars to launch the human genome project. The committee reduced this request to 30 and after some rescissions we obtained something like 26 million dollars, but at least we were launched.

I then turned around and asked Jim Watson to direct the project. He was then the director of the Cold Spring Harbor Laboratory. He wasn't willing to give that up, so I worked out an arrangement for him to serve at NIH part time. We made a lot of special concessions for him. He could do a lot of this work from Cold Spring Harbor and be in Bethesda an average of 2 or 3 days a week. Initially, some of that time would be spent negotiating with the DOE, some of it would be with Congress, or consulting with other scientists, but it wouldn't all necessarily be on the premises. And there were review procedures to go through that anyone coming into the government must satisfy, including a financial review to make sure you don't own stock that is in conflict with governmental activities. Later when he got into problems with my successor as Director, Bernadine Healy, she latched onto the fact that he had some pharmaceutical stock and tried to make the case that the Human Genome Project would create drug opportunities from which pharmaceutical companies might benefit, and that this situation created a conflict of interest for Jim. She couldn't handle Jim, and forced his resignation. But that was long after I had left government service

JM: I imagine it was probably difficult because that was right when AIDS/HIV was starting to become a big deal. Did that make things difficult?

JW: No, by that time, HIV had been on our agenda for some time. That was an interesting matter too. Congress was giving us everything we asked for in HIV research but the OMB and White House were not reacting at all. The White House didn't acknowledge that HIV existed until Rock Hudson flew to Paris for treatment and embarrassed the White House. At that point the administration came out and backed our research and our budgets. But we were operating with their full knowledge, there was nothing hidden about what we were doing, it was in the public domain, but without any comment whatever from the administration until the Hudson event. From Congress, yes, but not from the administration.

JM: So that didn't...

JW: It didn't conflict. We were getting everything we requested for HIV and we were getting support for the genome project. Let me make one background point—the NIH budget doubled in my first five and a half or six years there, driven primarily by these two factors, the HIV and human genome projects. But behind that was the momentum of funding the NIH and the fact that the previous five or six years in the Carter administration had been one of the worst periods of inflation in our nation's history. We were just emerging from that period of double digit inflation and Congress realized that the NIH, as many other institutes, had suffered from that

huge inflation and they were in a mind to repair the budget and finally had some additional money to do it. And so through no particular doing of my own, I came in as Director at a time when the budget was set to take off and it was driven by those two events, by HIV and the genome project.

JM: How did you react when James Watson announced the ELSI program?

JW: Oh, I was standing right next to him when he announced this at his initial press conference, and he hadn't told me a word about this! I thought it was an absolutely brilliant stroke. I knew Jim well enough not to be too surprised, even though he hadn't discussed that idea with anyone. And the press just ate it up. They thought it was marvelous, as did I, to devote 3% of the Genome budget to study the ethical, legal and social aspects of human genome research. It was brilliant in the extreme and utterly novel. It immediately created the single largest budget in the world for ethical studies. It eclipsed all of the components of all the other institutes that were doing ethical work.

JM: What do you think what would have happened if he hadn't done that?

JW: The ELSI part of it? It's hard to know. We still would have done the science, but it might have had a different reception

JM: What do you think the major repercussions would be now? I can think of a lot.

JW: Well, I'm not sure if you can surmise that. Maybe it would not have received such enthusiastic support in some circles. I don't think it would have been opposed, but it was very well received by the press and the public.

JM: Were there any people behind the scenes that were upset by it?

JW: No.

JM: Let's see. Some people say that securing the budget for the human genome project was your biggest contribution. Others say it was appointing James Watson. What do you think of the two, or is there something unrelated entirely?

JW: Well it's not an either/or. You could take the point that without the budget you would have nothing, no way to do this project, no way to consider bringing in Jim Watson. So in a sense of what's primary and what's secondary, the budget would have had to come first.

JM: How did you originally get involved in genetics?

JW: I don't consider myself a geneticist. I was interested in the interface between chemistry and medicine. This is probably more history than you want to know but, I came along during the Second World War. I was in a navy-sponsored training program for most of my college years. This was long before we had the atom bomb and we were totally unprepared for the war. We had

something like the 13th largest army in the world, right after Romania's, when the war broke out. We had a one ocean navy, most of which was sunk in the Pacific.

And so the planners made arrangements and created the mindset of a very long war, concentrated in Europe first, while we would probably be unable to hold the Japanese back from controlling the entire Pacific, maybe even losing Hawaii, and then having to reclaim these islands one at a time. This was before the atom bomb was even on the horizon. And so the government created training programs to provide a continuous supply of officers.

I was in the naval officer training program in college on the way to midshipman school when they announced 3 additional programs: one in medicine, one in dentistry, and one in engineering. I had applied for the medical program and heard nothing. I was actually in midshipman school for one day when my orders arrived transferring me to the medical program. So I was on my way to medical school. But in college, I had enjoyed chemistry, particularly organic chemistry so much, that I had wavered whether I wanted to go into chemistry or medicine. And then in medical school, I had particularly enjoyed biochemistry. But what attracted me as I got into the clinical years were the diseases which exhibited deranged biochemistry. And I saw a field that could combine chemistry and medicine.

The war suddenly ended, I finished medical school, and pursued a medical residency at the Massachusetts General Hospital. Then we got into the Korean War, and those of us who were in government-sponsored training programs in World War II were recalled. One of the alternatives was the U.S. Public Health Service, at the National Institutes of Health, which was just then opening. The director of one of the institutes, Jim Shannon, came to Boston looking for some young physicians with scientific interests, and because the facilities in Bethesda were delayed a bit, I had a year after finishing my clinical training to spend totally immersed in biochemical research in New York. Then I went to Bethesda. I had gotten started on some work on purine metabolism in New York which I was very much interested in and was able to continue in Bethesda. I came to Duke in 1956, about the time when genetically controlled regulatory mechanisms of biosynthetic pathways were being elucidated in bacteria. I was particularly interested in systems in which end products of a biosynthetic pathway inhibited the first committed reaction that led to that end product, in a sort of a servo or feed-back mechanism. I undertook the study of regulatory mechanism affecting the pathway of purine production, stimulated by my interest in gout and uric acid.

Our work progressed pretty well, and quite a few fellows came to work with me on this and related projects. In the process I taught myself considerable enzymology. We became known as the purine capital of the world! I was also interested in inborn errors of metabolism, genetically determined diseases that exhibited biochemical defects. Together with a friend from Boston and another from Bethesda we produced a book entitled *The Metabolic Basis of Inherited Disease*, in which well qualified authors wrote about a collection of diseases that were genetically determined and about which quite a lot was known concerning their deranged biochemistry that could usually be attributed to a specific missing or damaged gene. That book hit the market at just the right time; it was one of the best-selling specialty medical textbooks in the country and in the world for a number of years. And that's what got me into genetics, but it

came through the medical side—medical diseases that were genetically determined. I never was really a geneticist in that I studied the genetics of those diseases. Others did that. I studied the metabolic derangements of certain diseases, the biochemical side of it. People give me far more credit for genetics than I deserve. I've done nothing important in genetics itself

JM: Could you describe how you were appointed NIH director? Were you ever asked about your party affiliation or who you voted for? Do you think this is different from how Harold Varmus or Elias Zerhouni were vetted in the Clinton and Bush administrations respectively?

JW: Well, you've got three different examples and I'm well acquainted with all of those. When the NIH directorship is vacant, it's really up to the Secretary of the Department of Health and Human Services to appoint the successor, the new director. Secretaries have approached this opportunity in various ways at various times. In my particular case, the Secretary asked the Assistant Secretary of Health to organize a committee to find a director, and this man had come just a year before from the University of Oklahoma; his name was Ed Brandt. He approached this assignment more like an academic search than had ever been done before. He asked two other people in the department to serve on this committee with him, and they wrote to probably every dean of a medical school or graduate school, and chairs of major departments; I got a letter asking for nominations. I sent in five names not including my own. Then I heard no more, until one day I got a phone call from Ed Brandt, saying they were getting down to a small number of names and they were now inquiring about degree of interest. I said I was flattered to get the phone call but I was pretty happy with what I was doing, I had no reason to want to leave Duke. We chatted a little bit; I had met him once or twice. He said, "Will you think about it for a little while and let me call you in a week or ten days?"

So I thought about it some and I realized I had been doing what I was doing seventeen years as chairman, and I kind of jokingly said that when I started as chairman the most exciting day was July 1, when the new interns arrived, and the day I now dreaded most was July 1, when the new interns arrived. But I also thought that if I was ever going to do something different, this would be a very interesting thing to do. It would be a very major change. I was able to consider that because my kids were pretty well through college at that time. I think my son was still in engineering school. So expenses were not so much of an issue, although the salary was considerably less than here [at Duke]. When he called the next time, I said I had thought about it a little bit and was a little more open to the idea than the first time he called, although I hadn't really decided that I wanted to be considered. He said, "Will you at least send me a C.V.?" So I did.

I didn't realize that by doing that I had formally applied for the position. Under government regulations, for anything lower than a cabinet position you have to formally apply. It's a way of keeping these positions open to everybody. I didn't hear anything for a while. Then I got another call asking that I come for interviews, including meeting with people at the White House. Meanwhile the *New York Times* was picking up rumors, and they published a list of six or eight names. I was among them, but there were a number of other people on their list that were not correct. It was not a very accurate list.

In the end there were two candidates; one from inside and myself. We were interviewed at the White House and they eventually offered me the job. I'm a registered Democrat in North Carolina but, to be candid about that, I was a Republican all my life until coming down here when I discovered that after the primaries, the election was over. Everything was decided in the primaries except for the governor's race or something like that. All the local positions: the school board, the sheriff, everything; there weren't any Republicans except an occasional strange person. So I transferred to the Democratic party so I could vote in the primaries and have a vote that meant something. Once you get to the post-primary, the general election, it's open—you can vote for anybody. So it makes no difference how you're registered in my view; I still have never voted a straight party ticket in any case that I can recall, so I left it that way. A few people at the White House asked me about my registration (never whom I voted for!) A man named Pendleton James was the Personnel Officer for the President, and it didn't worry him a bit. It worried one woman in the organization but she didn't prevail. On the other hand, the fact that I was a registered Democrat and the Democrats had control of Congress, made my confirmation hearing easy. Ted Kennedy was the chairman of the committee. I didn't know him before, but I got to know him very well during those years and was at his house a time or two. But the Congress considered me a Democrat, and it was a predominantly Democratic Congress. I had it both ways.

JM: I know that Craig Venter was working when you were NIH director but you had left by the time the EST controversy came about. If you had been working there at the time the EST controversy came about, how would you have handled it since it eventually led to Venter leaving?

JW: Well it was a highly technical issue and I'll have to confess I knew the controversy; I heard both sides; and I would not have been able to decide. It sounded that Craig's approach was succeeding, and his technology sounded like a very logical way to go. His opponents contended it was so selective that it would miss important fragments and I thought they were logical too. In the end, I think it was a tempest in a teapot, and as usual, personalities counted for more than anything else. Craig Venter and Jim Watson were just oil and water [laughs].

JM: Why did you leave NIH?

JW: Well it's a political appointment; a presidential appointment and each new president wants to put in his own team. I was a Reagan appointee; I stayed there through the entire Reagan tenure, and when a president comes to the end of his tenure every presidential appointee automatically sends in a formal, one-sentence, "I hereby resign my position as ----." There are times when the new president will reappointment somebody but, in this case, George Bush had certain obligations that he picked up during his campaign, and he appointed somebody else as director of NIH and asked me to come to the White House, so I went to the White House Science Office as Associate Director for life Sciences, a position in which I oversaw all biological and health related research in the U.S. government.

JM: What about HUGO? I know you were involved in that.

JW: I was. That turned out to be not to be a very effective organization. I discovered when I was in that position that what it primarily needed was funds. It got a nice launching sum grant from the Howard Hughes Medical Institute and I raised a little bit of money during that year, went to a lot of meetings and so forth, but halfway through that year I was asked by the Committee Chairman of the National Academy of Sciences of which I had been a member for years if I would consider running for the Foreign Secretary position. And I thought that was a much better use of my time so I dropped out of HUGO and did that. I was elected to that, did that for four years.

JM: Have you been pleased with the results of the Human Genome Project?

JW: Oh, it's exceeded my expectations. Back to that statement I made earlier that at its onset, one would have required sixty thousand clones given the length of the DNA fragment you could deal with in *E. coli*? Well, during that first year of the project when we were primarily supporting methodological work, Maynard Olsen at Washington University in St. Louis developed the YAC—yeast artificial chromosome method—which immediately reduced the required number of clones from 60,000 to 6,000 because you could now deal with ten times the length of a DNA strand. So there was one major advance, and then mechanical sequencing devices came along, and so on. We never would have guessed at the outset that this could be essentially done in a half a dozen years.

JM: What do you think of where they're going now with it?

JW: Well, you know I don't stay in day-by-day contact with this. I just read *Science* magazine and occasionally to talk to people. It's been a beautiful job to sequence the entire genome and to be able to extend this to model genomes all over the place. It's lab science at a dizzying rate. One never would have predicted that that would have gone so fast or so well.

JM: Do you think that having Celera come in and try to sequence the human genome helped it in the end?

JW: Oh, unquestionably. Competition is always good.

JM: Because I know a lot of people that were involved, because it is a government project, were upset when they started treading on the toes of that...

JW: Well Francis Collins has done a fantastic job at the NIH as well, and Collins and Craig don't get along any better than Jim Watson and Craig did. They're both brilliant people, and I think in the end it was good for the field to have these two people going at it from different approaches.

JM: What do you wish people would ask you about the genome project, or do you have anything else you would want to comment on?

JW: You've asked most of the questions.

JM: There's nothing no one's ever asked that you've always wished you been asked about?

JW: I can't think of anything that's been omitted. My role was not in the technical side of it, it was in the enabling side of it. I like to think it was an informed decision based on my prior experiences, appreciation of the medical as well as the scientific value of knowing sequences. I think the NIH would have been severely diminished had we not done this. Somebody was going to do it, and this way NIH gets credit for a great deal of it. Not all, because Venter and the private sector deserve a lot of credit also. But the focus is where it should be, and it is in knowing the genome for the benefits that this may confer upon health and industry. I think the NIH was the best-positioned institute to do that.

JM: Thank you very much. I really appreciate your time.

JW: You're quite welcome.