**GEORGETOWN UNIVERSITY**

**Joseph and Rose Kennedy Institute of Ethics**

SUBJECT: Charles DeLisi

DATE: July 18, 1991

INTERVIEWER: Robert Cook-Deegan

*Q: This is an interview with Charles DeLisi in the Senate offices of Senator Domenici. I'm interviewing Charles DeLisi. [static]*

**DELISI**: A few years later, I had forgotten all about him. I got a paper to referee by him, and Mike Wallace and I wrote to him and said, "Why don't you move to NIH?" Because I was getting reinterested in molecular biology at the time. So he did. Then we developed an integrated database system, merging essentially three distinct databases, but merging them under one management system, namely the furnace relational database management system. And that consisted of Genbank, it consisted of the protein database, the theop database, and the structural database. And we still use that, with a variety of software packages for structural analysis, for looking for patterns and for their molecules.

And the neuroaesthesis advisor was Archie Wada; that's how I knew Wada.

*Q: Oh, I didn't know that.*

**DELISI:** Yes. And Manuro went back to Japan to become a professor at Kyoto. When I was at DOE, I guess it was in April '86, there must have been an article in *Nature* which he came across, and said that Wada wanted to talk to me. I was on my way to Japan at the time. So I guess that June I met with Wada in Tokyo, and he was at this point talking about building a robot that would, everybody knows, have a million bases a day. And that was going to happen in three years, certainly by 1989. And I invited him back to visit DOE, and then asked him to come over to NIH and introduced him to people there, and also invited Dave Kingsbury. So that's how the relationship with Wada started. Of course, the Japanese are just now, as you know, developing something, which really is behind schedule and 900,000-bases-a-day short.

*Q: Was that your first meeting with Wada?*

**DELISI:** No, I had met Wada before; we had spoken at conferences together. I had met him a couple of years earlier.

*Q: Because you were more or less in the same fields.*

**DELISI:** Originally, when I first moved out of physics, I moved into biophysical chemistry and I worked on structural transitions of nucleic acids, and that's exactly the sort of thing that Wada did, and it's the type of thing Manuro Kenedesa did, so we all had the same backgrounds. And I got interested in immunology in the seventies and forgot about molecular types of things, then became reinterested, so our paths reintersected then, in the eighties. And, remarkably enough, Wada and I both then became interested in sequencing the human genome, so we had a second convergence.

*Q: Did that come up at your first meeting in Japan, or had you had that idea yet?*

**DELISI:** Yes. Had I had that...? Oh, yes. No, this was after the Santa Fe workshop.

*Q: Charles, why don't you recount a little bit of your scientific background in the period up to when you became the director of OHER.*

**DELISI:** Oh, okay. I have a doctorate in physics. I did post-doctoral work in chemistry and biophysics at Yale. And there I did the structure of RNA. And I guess I did the first calculations of RNA secondary structure, back in the early seventies. I moved to Los Alamos in '72; that was my

first position. I was there from '72 to '75, working for George Bell. I was very much under George's influence. George was interested in cell biology, and I got interested in cell biology, especially immunology. Moved to NIH in '75, because that was the hotbed of immunology and that's what I was interested in.

*Q: You were at NCI?*

**DELISI:** I was at NCI. They formed a section for me, so I was chief of a section of theoretical immunology. As is typical in the case of bureaucracy, they only promote there when someone dies, and my lab chief died in 1981, and I became head of the laboratory of mathematical biology there then for two years. And left there in August '85 to head the DOE health and environmental research programs.

At this point you probably are in better touch, your memory is certainly better than mine with respect to the details of this project; you've been chronicling it. I have to think back now five years. At least I remember certain details that stand out, but there's a whole lot, I'm sure, that you know better than I do.

*Q: Actually the purpose of these interviews is largely to fill in the gaps. I mean, I can get the dates and the places and all that, but the things that are most useful*

*here will be your assessments of what was important, how things were connected to each other and all that.*

**DELISI:** You know, I think the idea of sequencing the genome must have been in the air, must have been around in the heads of certain scientists. Gilbert must have been thinking about things like that, maybe not particularly in a very visible way. I'm sure there were people at NIH. I was impressed, in 1980, when I looked again at molecular biology and saw what was happening.

See, when I was at post-doc., sequencing RNA (which was all you could sequence then directly) was a big deal. If you had a sequence two hundred long, it was very, very impressive, and you couldn't do DNA directly.

And then, of course, in between, was the Gilbert-Sanger. And, in 1980, when I looked at the explosion in sequences, it was obvious then that we were going to need computer methods to analyze sequences at any reasonable rate. Otherwise progress was going to be rate-limited by sequencing.

So I got interested (and Manuro then joined my lab particularly for this reason) in developing methods for picking out exon-intron boundaries.

I mean, the first question you have with a piece of nucleic DNA is: Where are the coding regions? And we were developing neural networks at the time. In fact, at the

time I was working on it in 1983, we had the most effective method available.

After you translate it and have a protein sequence, then the question is: What might the function of that protein be? Don't forget, we're thinking in terms of doing things sort of in real time, where we don't have the time in the laboratory to figure out what's going on.

Again, what struck me at the time was that we needed a method, what I wanted was a method that was going to be database-independent. I mean, the standard way of determining function now is by analogy with what's in a database. All right, now if you have to run a sequence against the whole database, and the database is exploding exponentially, you can project that you're quickly going to reach a time when you can run a Cray for a day and you're going to have real problems. Then the question is: Could we do something a lot better that would be more or less database-independent?

And in fact we did. We developed a method based upon discriminate analysis.

And the idea was very simple. You basically divide the database. You still have to have a database, of course, but the times of search become independent. Because what you do is, beforehand, you divide the known database into some number of functional categories depending on how much data you have and how fine you want the discrimination. You

might do a third of the categories, for example, toxins, ..., cytochromes and so on. And then you've got the sequences in each category, and you look for characteristics of a sequence in that category which are common and peculiar to that category. Now those characteristics of sequences are always going to be in multiple categories, but they might be predominant. The idea is to find characteristics which tend to be dominant for one category.

For example, for glogans, antitothicity. You know what an antitothic structure is, I mean, you look for 3.6 angstrom to turn antitothicity, which means you've got an antitothic altigilt. Well, that one characteristic is enough to filter out glogans from everything else with eighty-nine percent reliability. If you add on another couple of characteristics, you can filter out glogans with one hundred percent reliability.

So we then had sets of characteristics, a few characteristics for each category. And then we'd do this complicated discriminate analysis, which was based on a multivaried gausian distribution. And, at the time I stopped working on this, which was in the mid-eighties, we had about thirty categories, which represented about sixty percent of the database, that we could deal with reliabilities ranging from ninety to a hundred percent.

But the thing is, you do it instantly. I mean, because once you take a sequence, you allocate it, based upon what

its characteristics are. So it's totally, roughly, time-independent, not dependent at all on the size of the database.

Unfortunately the post-doc. who worked with me on that, Peter Kline, who was a Czechoslovakian refugee, in fact a defector in a sense, died very young, he had a tragic accident. And I never continued working on that. And Manuro probably is following up on that method. But it's what seems to me to be a very fundamental method, in the sense that it gets around the timesync that you're going to run into as the number of sequences grows.

So I was kind of primed. When I went to DOE, I was already interested in sequence analysis. I had done some work on it. I had a physics background, so I thought in terms of large projects. I was very interdisciplinary-oriented; I loved to see collaborations between mathematicians and biologists and physicists.

And so when I read the OTA report, it really resonated with me. And that was probably September '85, I guess, Dave Smith gave me not the report, but a copy of the report.

And, as I said, I think clearly the idea of sequencing the genome was discussed at Isolomar. It would surprise me greatly if there weren't a number of people in the community, both here and elsewhere, that hadn't thought about sequencing the entire genome. Not just Sinsheimer and Bill Decker, who came out with something six months later,

but the idea must have been prevalent. Ideas are never specific to a particular individual.

In any case, I happened to like it. And I called Mort Mendelssohn that very evening. Dave gave it to me sometime midday, and I read it, and that evening I called Mort and asked him what he thought. And he told me about the Sinsheimer workshop. And he said it was being discussed, but he didn't think that was the way to go. He thought mapping was a legitimate thing to do, but he thought sequencing the genome was crazy, more or less.

Now, you know, at the very beginning, when stories began breaking in *Nature* after the Santa Fe workshop, there was unfortunately a great misunderstanding, it seems to me.

Because, at least the way I proposed the project in my May '86 memo to Triblepeace, it was a two-phased project.

Phase one had these three components: mapping; the development of techniques, robotics and so on; and analysis, tools for analysis, including database analysis and structural analysis and whatnot.

The second phase was not well articulated. It was supposed to be, assuming the tools were developed, to go ahead and sequence the entire genome. And it wasn't going to cost three billion. I mean, I never thought of it in terms of starting a right-here-and-now...

In fact, it was a very telling remark made by Jim Decker, who was then Triblepeace's deputy, when he read the

article in *Nature* which said, "Three million dollars to sequence the genome," he said, "It's unfortunate that they said that, because of course that isn't the way we would go about sequencing the genome. What we would first do is develop technologies." And Decker, being a physicist and spending his days thinking about the SSC, knew that you don't just go out and do a big project, you lay the groundwork first.

So the thinking at DOE was you first develop the technologies, you see where you are after doing that, and then you go ahead and do it, and then it's much more cost effective.

And my interest in sequencing technologies was not to compete with Japan. That is, not to just take current technology, build a super giant robot, but to look for really innovative new methods that would bring the speeds up by about two, what is the value of two, you can bring the costs down by about two, what is the magnitude. And I thought if we could do that sometime over a five- to ten-year span, then sequencing the genome would be no big deal. We'd have the whole thing mapped, we'd split the costs over several agencies. And I think I mentioned this in my *American Scientist* article. So if everything was done correctly in phase one, phase two I thought was going to be rather easy. We'd learn a lot from it, but I didn't think

it was going to be a big deal; it wouldn't cause a lot of excitement.

I think the three million dollars was something that was maybe interesting to mention, because it caused a lot of public stir. But if you presented this as, well, in ten years from now each agency will spend three million on it, nobody would get hurt or particularly excited.

So I think it really stimulated a lot of debate. And that was good that it stimulated debate. We could have presented this in a way which wouldn't have stimulated debate at all, and I think debate is necessary.

I still, in fact, think there hasn't been enough debate. We held one public discussion in Massachusetts, back around six months ago. It was stimulated by someone who's with the World Health Organization who does volunteer work.

All technologies are accompanied by problems. I mean, the intention is always to serve society and to do something useful, but there are always going to be problems. And those things need to be thoroughly discussed and thoroughly aired, and the public needs to be informed about it, absolutely. So not only am I not afraid of public discussion, but I think public discussion is absolutely essential to moving any enterprise forward. I think people are very intelligent, and a mature, realistic public recognizes there are always difficulties. No matter what

you do there is going to be potential for negative side effects, for complexity, which there is certainly in this project. And I think it's important to discuss those openly and as thoroughly as possible. That may result in some minor setbacks along the way, but in the long run it will move much more smoothly.

*Q: You might even talk a little bit, it's a part that hasn't really been documented because there's no paperwork on it at DOE, you might even talk a little bit about what you had done before you left. Because that ball got dropped, actually, when you left.*

**DELISI**: Yeah, that was unfortunate. But Dave Smith could tell you. I mean, Dave and I and Ben Barnhart. I was very, very interested in seeing a certain percentage of money spent on ethical studies, ethical-legal, the whole schmeer. It looked like NIGMS wasn't going to do it; there was no genome office at NIH at the time. And we went over and spoke with people at Georgetown to get a sense of what their thinking was and what the real major problems were. It must have been around May or something like that. And the way I left it is, we were going to do that. Ben and Dave were going to move ahead with that.

Of course, I left DOE two months later, and I was distressed to learn, a couple of years later, that

apparently never happened. And I learned it because Bob Wood was properly raked over the coals during a congressional hearing because Jim Watson had the foresight and the sensitivity to go ahead and do it. So fortunately it got done.

And, you know, my feeling about it was... I really try very hard to adopt the attitude that who gets the credit is less important than whether something is getting done or not. And I think a whole lot more can get done if people stop worrying about who's getting credit and who isn't getting credit. I think we have to focus on the bottom line. And you know what you do, you feel comfortable with your own contributions, and I don't really think people need to go around waving flags about it... But I do think it's important that things are getting done, and I'm happy.

But I think it's unfortunate the way it happened at DOE, because they need not have been embarrassed about the whole thing. In fact, they could have...I think it's important for that agency, less so now, but when I was there, to take more of a lead if it was going to function as...if in fact the national labs and health and environment are going to realize their potential, then I think it was important that Jermantown and the central offices begin to develop a certain amount of stature and maturity. So I think that having been done that way was not in the best interests of the department or the laboratories.

*Q: You know, the other irony, of course, is that Watkins himself is very interested in this stuff.*

**DELISI**: That's right, Watkins is a very, very impressive person. I testified about a year and a half ago with him and Bromley. We held a series of meetings about... strategy. He is extremely sensitive to environmental issues and to all issues of public concern with the impact of new technologies.

...so he even ran counter to the way...well, actually the same was true of Solgado. Solgado would not tolerate any types... Solgado was very interested in cleaning up the plutonium production sites. He was aware of the problems. In fact, before I left, I spoke to him about putting more money into environmental research. Which he did; he recognized that it was inadequate. And he started a whole program on subsurface, which is continuing to this day. Not at the level that I think it ought to be at, but I think advocacy was lost in that area.

But there's a history of DOE concern. And what happened in the forties and what happened in the fifties, whatever the attitudes were then, those are not the attitudes certainly not now, and I don't think they were the attitudes when Mr. Solgado was the undersecretary either. I think the department has legitimate concerns. It's difficult... policy decisions to really make a big major

immediate impact on people who carry out the work. And of course, as you know, the Department of Energy has events, programs, responsibilities, and has research responsibilities.

The idea when I was there was that there was a separate assistant secretary for health, environment, and safety oversight. And they were supposed to provide oversight responsibilities for what was going on at the weapons facilities. And the person who was the head of that, I forgot her name, the assistant secretary, was very, very serious. I know, because inside the department it was creating very, very big problems with defense programs. I mean, she was a very, very strong and serious advocate of environmental safety, and it was causing lots of waves. Not quite as big as what the current secretary is causing, but there was a buildup of waves. We now have a tidal wave.

*Q: Charles, there are two things that you are almost uniquely positioned to be able to comment on, to fill in the gaps. One is the process of going from having this idea, in September or October or whatever it was of '85, and then getting the budget through the DOE hierarchy, and then OMB, and then the congressional stuff. So that's one thing. And then the other thing is the relationship to the initiative that came out of this office, Dominici's office. And the*

*degree to which they were interconnected, or whether they were independent.*

**DELISI:** Well, I spoke... I guess the first time I met Gilman it must have been '87 already. And I suppose probably in late '86 we began briefing congressional staff on this. It must have been probably the fall; I can't remember exactly. I mean, the first thing we did, it was obviously...my memo went to Triblepeace in May '86, I don't think I spoke to any congressional staff to tell them what the plan was, to brief Triblepeace, to charge HIRAC with developing a specific and detailed proposal. Because all my memo in '86 did was outline a broad project, a framework for the project. And then, with the department behind it, obviously I wasn't going to go to Congress without having...the Department of Energy didn't work that way, without having full departmental backing and without having OMB backing. So I spoke to Al probably in May, and Jim Decker.

Then, of course, articles were appearing in *Science* now. It was hard to avoid embarrassing situations. Because I think Judy Bostock, being the budget examiner, and Tom Palmieri, being her boss, probably first learned about it by reading a *Journal* article. And when I saw the article I immediately contacted her and said I wanted to come over and speak to her about what we had planned. And that happened

probably sometime June, July...remember, I have to think back five years now; you probably have the dates on this better than I do...that probably happened June, July of '86. Tom Palmieri was with her, and they were interested. I think what Tom liked about it, Tom was an engineer-physicist type and this was an engineering problem.

I mean, it was not presented as a scientific project. A lot of science is going to come out of this, obviously, but I always thought of it as a resource, as a set of tools that would be used to facilitate, to make doing science in this area much more efficient and effective. And, since it was that type of project, we were able to delineate specific targets and goals in specific years--this is what we needed and this is what we would accomplish. And OMB bought-off on things presented that way. They didn't buy-off very readily on vague give-us-the-money-and-let-us-do-what-we-want types of things.

*Q: What exactly came out of that? Was your focus up there trying to get this five-year budget agreement from Judy and Palmieri?*

**DELISI:** Yeah, I don't remember exactly. I briefed them on the general scope of the project, what we were trying to accomplish, roughly when we would be where with that project over the next five to seven years, hoping to have physical

maps, explaining how it tied in with what the labs were already doing.

I know Al Triblepeace, went he presented it to the secretary, presented it as a massive supercomputer project. Why should DOE get involved in it? Well, it's very heavily dependant upon computers, and DOE has the best computers in the world. I think basically that was Al's line.

But I think I tried to present to Judy and Tom the general scope of what it was and what we were trying to accomplish and when we were trying to accomplish it, and also indicated that I expected and hoped that it would strengthen our national competitiveness by stimulating... And that was one of the goals I had mentioned in the letter to Triblepeace when I reviewed what was discussed...when I... the Santa Fe workshop with what was discussed, one of those was in fact to strengthen economic competitiveness.

And that in fact is what I'm most distressed about. And I will mention this today at the workshop.

I think in many ways what's happened is spectacular. The amount of support that has been provided is very, very good. I think, as a nation, we're way out front in terms of the research. And that's typical of the United States--always way out in front in terms of research.

In terms of converting knowledge to products, I think we have a problem. And really my only concern now is that biotechnology in this country is going to go the way of the

electronics industry. And I'm going to say this today. I see no reason to think that anything other than that is going to happen.

I think, in terms of semiconductor manufacturing, for example, we're down to thirty percent of the world market now and continuing to decline. We once had practically a hundred percent of the photonics industry. The laser was invented here. The idea was conceived here. It was implemented here. Central to the photonics industry. The photonics industry now, as a fledgling industry, is a nine-billion-dollar-a-year industry Japan already dominates. Even the software industry in this country is beginning to feel problems of venture capital.

In fact, in biotech I think the problems are worse. I mean, there are three major problems that have to be confronted: one is liability; another is the regulatory agency; and the other is the price of capital. And there's a lot of discussion about this and a lot of talk, but I see no agenda for changes and nothing being implemented. And I see this thing leading inevitably, playing out to a very unfortunate... The Genome Project is a necessary condition, it is not a sufficient condition. And the way things are currently structured, I don't see a major impact on biotech unless there are some very fundamental policies put in place. That's what I'm concerned about.

*Q: Talk a little bit about what you were thinking of back in those days about what the commercial implications were going to be. What sorts of products were you thinking were going to flow out of this?*

**DELISI:** Oh, I think the thinking then was probably not very different from what it is now. I mean, what you see now is agreements between the labs in a particular company, or a transfer of one or another technologies--an enzyme assay or some particular instrument. And what we were concerned with then was that there were some tech transfer difficulties at the labs, which have since been sorted out, that arose because some labs were weapons labs and some labs were run by companies, like Martin Marietta. And those have been sorted out, and so there's a flow now with specific products, specific instances.

But what I'm talking about is much more. And what I've become concerned about much more recently I wasn't concerned about at the time. At the time, I saw no difficulties other than these little details. I really thought this was going to have a major impact on biotechnology. And I was not thinking more broadly. I mean, we're not talking about now with policies that are going to affect major, whole industries, not one little transfer of one piece of technology.

So we were thinking in terms of transferring instrumentation technologies, in terms of transferring particular types of assays to particular companies that would develop them and maybe sell them and whatnot. And that's useful to do, and I think it's important to do.

But I think the thinking is still there. I mean, that's what people are still thinking about. And I think the boat is being missed here. That's not going to make this country competitive with the Japanese. I mean, we are going to be in the same predicament we are currently in with electronics, and that we're probably going to head into in terms of... Fortunately we have some very talented people in the computer business that will hold their own for a while there. And there you're not faced with the same, you know, biotech, we've got these incredible regulatory problems that we don't have in the electronics industry, so it's not quite as serious.

But capital is a serious problem. You know, the whole problem of manufacturing. Last year, and I'll remind people of this, last year, you ask yourself what were the five companies that led in number of patents. Four of the five were Japanese. The four top ones, in fact, were Japanese. And these are U.S. patents I'm talking about, not world patents. And that's an indication of the sort of problem we have. And unless there are changes...

But I wasn't thinking about things quite that broadly at the time. And when I said we need to do this because the Japanese'll do it first if we don't do it, and this is going to be important to our competitiveness, I really naively believed that that's what we had to do--the Genome Project, sort out these little details of tech transfer at the labs, then we were going to be in great shape.

But unfortunately it's not quite that simple. And I think the people who are interested in the Genome Project... And I hope the senator will take a lead in setting the socio-economic agenda for change and for solving problems just the same way. And lay out a timetable--these are the problems, these are the options, and we're going to have this problem solved by then, and that problem solved by then, that's all.

I don't have the answers, obviously. All I can say is that my observation is there's a tremendous amount of talk, a lot of discussion. The vice president published something with the White House Council on Competitiveness. And it's kind of vague and general, and everybody talks about these things.

But we're definitely heading toward a problem in biotech, in my opinion. By the twenty-first century, "Made in Japan" will be the dominant household phrase in this country, and dominating will be the Japanese pharmaceutical industry.

*Q: Snapping back into history again, as you look back over the developments...*

**DELISI**: So we were briefing, I think your question is, we were briefing the Congress and the Senate, I think, starting late summer and heading through the fall of '86. And Domenici started to become interested.

*Q: At what point did the...you know...?*

**DELISI**: Dominici had held the hearing in May...it wasn't a hearing, it was a little meeting, in May of '87, where there's... [tape ended]

...and away from something that clearly, when the Cold War was over, was not going to be a growth industry anymore. And it's a big part of his state economy. So at some point those converged.

*Q: How did those come together? Was it when you came up here to brief them on the Genome Project?*

**DELISI**: Yes, and McConnell, who worked for Johnson & Johnson, I guess had become very interested, and I think McConnell probably spoke to Gilman before we did. And McConnell saw it as very important to the future of biotechnology, as we all did. I remember Gilman talking to

me about McConnell at the time, and he had McConnell down, he had Frederickson, I think he said he had me, McConnell, Frederickson, John Deutch at MIT, and so on. That was before the meeting that I had in mind; that hadn't all occurred.

*Q: So these two were essentially independent and then converged sometime in '87?*

**DELISI:** I think so. If the senator's objective is to get the labs to shift from the weapons industry, I don't think that's happening or will happen. I mean, all you have to do is read a mission statement, any mission statement that Los Alamos had, and weapons remain central. I'm sure the current directorate sees it, John Byrely in particular, sees it as central to the continuing mission of... Because there are energy laboratories. I'm not quite sure how that all fits in, nor do I know what the administration's thinking is, or what the secretary or deputy secretaries think about this whole thing. But there are weapons labs, and there are energy labs. So that's sort of already been scoped out. It seems to me unlikely that anyone would take the weapons lab and move it over into being an energy lab. So the central focus of Los Alamos and Livermore and the Pacific West has been weapons, though it may be that there'll be a need for more energy labs and a need for fewer weapons labs. Perhaps

that should change, and I think everybody hopes it will change. I don't know whether that's going to happen or not. And I don't see this project as playing a major role. And I think the amount of money coming into the labs is still very, very small compared to the laboratory budget, which is probably up around a billion. Los Alamos must be about a billion dollars by now. And Genome could be ten million dollars... So it's a minor per...dation on the laboratory. It'll need much more than the Genome Project to move this laboratory into something other than weapons.

*Q: One other thing that I'd like to hear your views on is also this transition period. You kind of left in the middle of it, but you were there for the early phase of the NIH-DOE wrangling, or whatever it was that you would characterize it as.*

**DELISI:** Well, I was interested from the very beginning... I mean, I've said this a number of times, having been at NIH, I felt I understood the place and identified with the goals of the NIH and recognized the importance of NIH to the research health mission of the country.

And I never saw the DOE as being *the* major player in this. I saw them as probably the most important player initially in getting this thing moving, since the department had the managerial experience to launch complex projects.

And NIH, sure. It wasn't so much the size of the project, that wasn't the reason I thought they couldn't do it initially, it was the interdisciplinarity of the project, the fact that mathematicians... And I know, it's unfortunate, but I know that almost all senior administrators at NIH do not have a sense of what computers or mathematics or physical sciences can do for the biomedical sciences. It's unfortunate, but it's true. So a combination of that and the interdisciplinary complexity convinced me that they weren't...

We invited Ruth Kirstein to the Santa Fe meeting. She neither attended nor sent anyone. And in fact I'm sure she would be the first to say that she saw DOE as being the predominant player in the early phases of this thing.

I spoke with Vince DeVita about it and he was very supportive, and he sent me a supportive note on it and he said he wanted to get involved in it. There were obviously some internal problems between him and Jim Wyngaarden. I suspect that he was knocked out of this, cancer was knocked out of this rather early on.

I got in touch with Don Frederickson, who was the director most of my time at NIH. He was then heading Howard Hughes. And I and Dave Smith and Mark Tinsky went over and spoke with him. That must have been probably around May '86. And he was very interested. And Don is a mover and shaker type and he was interested. I thought for a while

that Hughes was going to play a bigger role. They are playing a very useful role, but I thought they were going to play a bigger role than they wound up playing. And I'm not quite sure what went on behind the scenes there or whether Frederickson got the support he needed to really get Hughes involved in this.

And Deb Burger could tell you what she did. We went over and spoke to Agriculture, and she was exploring different agencies behind the scenes.

And I wrote a letter and sent it to a number of agencies, including EPA, in fact, and really got no positive responses on this whole thing.

So, as far as I was concerned, we were going to go this alone. And I charged HIRAC, and I was hoping NIH would do something.

And finally NIH did. Jim Wyngaarden, I think, probably from the beginning, was favorably disposed to a mapping project, but was cautious, as most people at NIH are. NIH, as you know because you've had so much experience there with them, is pulled is twenty different directions by a hundred different constituencies, or maybe it's a hundred directions by twenty constituencies, and so it's hard to do anything to move that place in any particular direction.

And Wyngaarden had an advisory committee meeting, I guess it must have been in the fall of '86, which he asked me to give a presentation at. Which I reluctantly did.

I was actually trying to stay more behind the scenes. I was not...my personality...I'm actually rather a shy person with..., and I was actually trying to keep behind the scenes on this thing. And in fact when Ruth asked me to...Ruth Kirstein was the one who asked me to talk at this, I was going to send Dave Smith, who I was sending to most of... I didn't go to the Santa Fe workshop for the same reason. I really wanted to...

The other reason I wanted to stay out of it early on is because I didn't want people saying positive things for the wrong reason. That is, I was a little bit concerned that if I went, for example, to Santa Fe, and if people really thought that there was going to be a flood of money, that the government was going to come through and put money into this, that it might influence their judgment. They might see an opportunity to get more money into the biomedical sciences, and I didn't want that to be the reason. I wanted the reason to be a real reason, that there was going to be real useful information coming out of this and it was really going to do something for us. So I didn't want that type of decision-making authority present at those early meetings that I was trying to stay out of.

Anyway, I did wind up going, at Ruth's urging. She said, "They want to hear from you, they don't want to hear from anyone else." And so I went and made a few remarks. And it was at that meeting, it was kind of interesting I

think, Dave Baltimore was very angry that the Department of Energy was involved in this, and asked me what right does DOE have being involved in this, and isn't it true that we have no peer review anyway? So you can judge the quality of this. I explained that we had almost a regulatory role in health safety issues, which stemmed from the AEC Act in the late forties, and the department for that reason had a health issue, and that we did have, in fact, a rather extensive peer review.

This whole peer review thing was a red herring, and I still see that going around. The fact is that the national labs are intramural, like DOE labs. They're analogous to the NIH intramural program except they're nationally distributed rather than at headquarters, and they're managed, and of course they're contracted out. But that is considered to be DOE intramural program. So if you're going to make a comparison between peer review, what you have to compare is how do we handle peer review at the labs and how does NIH handle peer review in an intramural program. And I am intimately familiar with both. I was in the NIH intramural program, and the NIH intramural peer review is terrible, and it is nothing like the extramural peer review which I now go through as an extramural scientist. It is much, much less rigorous, and in fact it is probably less comprehensive than the DOE intramural peer review. We, for example, evaluate the whole radiation program, cutting

across all labs. It would be similar to NIH reviewing its immunology programs, across all the institutes, to make sure they all make sense, to make sure they're reinforcing one another, to make sure there's no needless duplication, to make sure the money is spent efficiently. DOE does that; NIH doesn't do it.

The extramural proposals are handled more the way NSF handles their extramural proposals than the way NIH does. That is, by mail. But they are handled in an acceptable fashion, just the way NSF does. And I think in both cases it's less rigorous; that is, the extramural review at DOE and at NSF is less rigorous, and at most agencies, is less rigorous than the extramural review at NIH, where you have fifteen people meeting in a panel and getting together and really going over this quite critically, as opposed to sending out three to four to five letters and then having the program manager basically having a lot more say. The DOE and the NSF program managers have a lot more say about what gets funded at universities.

But the point is, there was nothing peculiar about the...when people think of DOE peer review, they think of the labs. And it's true, the labs are not handled the same way as the NIH extramural, nor is the NIH intramural handled the same way. So I think there's a lot of misunderstanding there.

In any case, apparently after that meeting (and I met with Wyngaarden afterwards), he felt he had the okay to go ahead with mapping. And I was particularly eager to see... We were interested, by the way, in linkage analysis, because we spoke, I spoke and Dave Smith, at a meeting of a bunch of us with collaborative, for example. Collaborative came in with a proposal. I mean, I heard at the time that people had submitted RFLP proposals, methodology proposals, to NIH and they got turned down flatly. And I thought that was important. And we were ready, in fact, to look at that very, very seriously. Collaborative did not come in to us with a proposal. If they had come in, and it was of high quality, which it probably would have been since... was there at the time, we would have looked upon it very, very sympathetically.

But that was another limitation of the NIH system, and another reason why I felt that we couldn't rely completely on NIH to move this thing forward. Because NIH did not look well upon methodology proposals even when they were experimental methodology proposals. If they were computer methodology proposals, you could forget it. So there were real deficiencies in the whole NIH system with respect to a project of this sort, aside from the political difficulties of moving something which really has a new sociological dimension. That is, a project of this magnitude which spans disciplines like this just isn't normally isn't done.

So there were problems at NIH, and I felt DOE did not have those problems and it was therefore ready to go along on this.

In any case, Jim Wyngaarden, after that meeting, was ready to move ahead with the mapping, apparently, and did. And then, of course, ultimately Jim Watson was hired. And I think, the way things are going now, it's excellent. I'm very much an outsider, looking at this from the outside and not tracking it very, very closely, but, as far as I can tell, there is an excellent cooperation between the two agencies, and there is a lot of communication at our regular meetings, and I think things couldn't have turned out better.

*Q: One other little piece that I actually don't have the whole history on, because there are no documents, again, this initial meeting with Wyn Frolich...*

**DELISI:** Who's Frolich?

*Q: Wyn Frolich was the guy from Hatch's staff.*

**DELISI:** Oh, yes.

*Q: And I know that you guys met with him. I'm trying to remember when you and I met, it must have been September or so of '87.*

**DELISI:** It was about the time that you and I first met. Was it that late?

*Q: You had already met with Wyn.*

**DELISI:** That's right.

*Q: Then I got this funny memo from Jack Gibbons telling me I should talk to you.*

**DELISI:** It was within a month or so, I'd say, we had that meeting. You mean September '86.

*Q: Yeah, '86, you're right, you're right.*

**DELISI:** It was roughly around the time when we first met. And Hatch, I guess, was concerned about the abortion issue. He saw three billion dollars moving into this, which conjured up notions of very rapid movement before anyone had a chance to think through the ethical issues involved in it. And I met with him and said we had only proposed...we had proposed ten million dollars at the time, or twelve million

dollars, and then he lost interest. He didn't feel that was big. In fact, I mean, if they were going to worry about that, then they had to worry about all of child health. So they were really worried about something very, very major.

As I say, I think all the ethical issues, whether it has to do with privacy, or whether it has to do with abortion issues or anything else, are all very serious issues, as far as I'm concerned. They all need to be taken seriously. They all need to be looked at. And if legislation is introduced, it needs to be introduced. But they need to be fought about. So I was happy to meet with him. I mean, they were going to hold the project up, and I'm glad they didn't, because I think a lot of these issues will be resolved.

And, in fact, in the case of abortions being performed for disease reasons, I think the only real way to prevent that is to move this project forward to the point where cures can be developed. I think right now the problem is that you can diagnose and you can't treat. And if you stop progress now, you'll always be in a position where you can diagnose and you can't treat. And what you want to do is to be able to move this thing forward to the point where you can treat, and then abortions, for that reason anyway, won't happen forever after. So you have the ethical implications definitely on the side, for that issue, of moving this

project forward. And it would the wrong thing to do, in fact, for that reason, to stop it.

*Q: One other thing that just struck me. That period, '86 to '87, there was a lot of confusion, and a lot of major personalities were involved in it, from your perspective. In my mind, it was that '86 to '88 window, while the NRC study and the OT studies were going on, there was an awful lot of other stuff that was going on. Who were, in your view, kind of the critical players, the folks who really made the big difference in the picture?*

**DELISI:** Oh, I think Walter Gilbert was easily the most important person in the scientific world. I think he was the most articulate. I mean, he took the extreme position in this project, and because he took the extreme position, and because he articulated it very clearly and very eloquently, he aroused a great deal of important controversy. And he was very logical in his positions; there was nothing flamboyant about it. And of course he was Walter Gilbert and had the ear of the community when he spoke. So I would say Walter Gilbert was easily the most... and, in my mind, really the only one that I thought counted in the outside world. In terms of us moving this thing forward, I don't think anybody else was particularly... I mean, a lot of other people came on the scene. But I think,

in terms of articulating this program before the community, and articulating the extreme view of it, which was necessary to present because it stimulated thought, I would say he stood out.

I really thought, by the way, most of the scientific community was just missing the boat. I mean, they were behind us. The vast majority of thinking in the scientific community was six months to a year behind our thinking at DOE. I mean, there was no question about it. When the National Academy first started meeting, they were discussing issues that we had thought about a year earlier. Other than a few key people like Gilbert, I don't see the scientific community as being the big driving force that could have stopped it if they had disagreed with it. But they weren't the motive.

I think that Sinsheimer's meeting... Sinsheimer had the meeting after Isolomar, so the idea was around. I think it was an important meeting, but it had no impact. I mean, there was no big discussion in the community, nothing in the press. In fact, Delveccho's article wasn't even mentioned in the Sinsheimer meeting.

*Q: He didn't know about it.*

**DELISI**: So Delveccho, in the early years, not very far away geographically, and he didn't know about it. So, other than

Sinsheimer wanted to do it, which shows a great deal of personal foresight, in terms of whether it had an impact or not, I don't think that had any impact.

*Q: If we're thinking of Walter Gilbert as the vector, that was what infected him. So, okay.*

**DELISI**: Well, I thought Sinsheimer, I asked, you know, I had a lot of respect for him as a scientist. Same thing with Delveccho. I invited them to be on our advisory committee, so both Sinsheimer and..., I wanted to make the connection there. Now Delveccho's article was directed toward cancer, and it may be another reason that DeVita was so sympathetic to this thing. But again there was no impact, because cancer didn't really get involved.

*Q: You know, there was one other question I wanted to ask you. There was also, in this NIH or DOE jockeying, one of the events in there...that I don't actually know the answer to this, so this is an open question. I guess I hope all of them have been.*

**DELISI**: I don't know the answer on that either.

*Q: Well, I was curious, when the HIRAC report came back to you in '87, what was done with that? Because basically it*

*recommended these...what I heard you saying earlier was you didn't see DOE as being the major lead agency. You, all along, thought that it was going to push the technologies and the computational biology part, and then NIH was going have to pick up some of the rest of it. Yet, from your committee, you got back a very big budget that went... I don't know if... What was done with that? What was your sense of how to handle that report when you got it back from HIRAC?*

**DELISI:** Well, I think a lot of what was going on... I think there was a lot of frustration building in the scientific community at NIH not moving forward with this. And, although I felt that they ought to, I was ready to move ahead. If there was going to be a vacuum, I felt strongly that this program needed to be done. And so did a number of people in the administration. I mean, it's a kind of peculiar situation, where people in the administration who are lifetime administrators, including OMB, had strong feelings about this program, and in the Congress, and the scientific community did not present a cohesive..., and the NIH, which was the lead agency in health and environment, was not really moving forward with it. So I was ready to take that very seriously however it came down. And those reports are used, in large part, so that the secretary and the secretary's science advisor, who was Al Triblepeace at

the time, understands that important scientists in the area have considered this very, very carefully, and he knows what their views are on that. So I think it was important documentation that we were doing the right thing. And it was very thoughtful; it obviously filled in a lot of gaps. Those HIRAC reports in general, I think, have not made the type of impact they ought to have made. There were a number of reports done before I got there; they helped me familiarize myself with the agency before I arrived at DOE. But whether they really made an impact, I don't know. I think this thing had an impact just because of personal presentations. And certainly, if the HIRAC advisory committee said don't do it, we wouldn't have been able to do it. I mean, it would have been very difficult to do. But they said do it, so that was another positive factor in this whole thing.

*Q: How did you use that document? Do you use it then mainly as an internal planning document?*

**DELISI**: Yes, that's the main reason. Well, the other reason I wanted to do it is because I wanted to get leaders in the scientific community, in the molecular biology community, plugged into the Department of Energy. I mean, the Department of Energy... When I arrived at OHER, I mean, a couple of months ago, Leslie Roach wrote a beautiful

article about Dave Gallis. And, you know, that organization was unknown when I arrived here. I mean, it was literally unknown, totally invisible. The community was not well connected to the biological community. That's why this seems so strange to everybody--where did this place come from? And I thought it was very important that the leading scientists in molecular genetics become aware of what OHER was, what its mission was, what they were trying to do. And that was part of the other reason for putting together an advisory...was basically obviously to provide advice, but also so that the leaders became familiar with our operation. And, while they were advising it, they had to become familiar with it in order to advise us.

*Q: One final question, because we're both getting tired. This whole process was, when you conceived of it in the pre-Christmas days of '85...one of the things I noticed when I was reading through the memos, there is a lot of focus on the substance of the science and the technology. And there was some glimmering that there might be controversy down the line. What's your feeling about...one way to phrase the question, Are there things you would have done differently? But there's a separate question that I actually really wanted to get at, which is: From your perspective, having headed a program like this and having gotten on the map,*

*what were the personal issues that came up in connection with this? And how was it to deal in the fishbowl?*

**DELISI:** Well, let me say one thing, because I looked over some of that correspondence, too, and it's clear to me that Dave Smith was much more sensitive to potential controversy than I was.

And the reason for that, as you stop to look at our background, I mean, I was a scientist, a research scientist for my whole career. Other than minor administrative types that, you know, running an intramural laboratory, NIH is... people, and a two-million-dollar budget is no big deal when you're operating in a specialized area. So it's quite possible that had I been in the federal bureaucracy for... and....that sort of person, I would have been much more concerned about... I mean, I can understand about people at NIH being cautious about moving forward on this.

Dave was sensitive to the fact that this was going to cause a lot of controversy. And I felt that this, at least in my mind, was well enough justified that I'd be able to respond effectively to that controversy. But I was thinking in a very rational way about that, and I really was not taking into account human emotions. And there's a tremendous amount of..., and Dave was.

I don't know if that answers your question. Was there another dimension to your question?

*Q: Well, part of that is to what degree was this a conscious choice to wade into controversy, to steer into the storm?*

**DELISI:** Well, as I said, I basically felt that whatever the controversy was, I had sound, rational responses to any issues that could be raised, and that I was going to get advice from the scientific community--I obviously was not an expert in molecular genetics and molecular biology--and I felt I could meet any challenges very rationally. But what I neglected, as a naive scientist, were the emotional and political aspects of this. So that I went into it in a rational way, basically. I knew I was probably going to be reminded by Dave, if I didn't know myself, that we were getting into a quagmire, but I felt strongly enough about rationality prevailing in the end that it didn't deter me.

*Q: And the second, kind of a corollary, question related to that is what's your sense of the degree to which the controversy...this was a very public, you know, I think, after AIDS, this was probably the most discussed topic in biology for a two- or three-year period. What's your sense about whether that was productive, unproductive, in what ways, this, the very public part of the genome debate?*

**DELISI:** Among the scientific community, or the population in general?

*Q: In general. I mean, is it good for science, is it bad for science? Is it good for the Genome Project, bad for it?*

**DELISI:** Absolutely good for science. And absolutely good for the public. You know, I've said before, I think very strongly that all new technologies--and we're developing new technologies--have very complex ramifications. There's no simple ramification of any important technology.

And I believe that it's very important--not everybody probably agrees with it--but I believe that it's very important for public discussion. Not everybody agrees because public discussion inevitably exposes in broad daylight all the defects of any technology, all the evil things that come with any new technology.

You know, basically I think I'm very rational person, and I still believe, in the end, new technology... I guess I'm optimistic basically. I'm optimistic enough to believe that people are intelligent enough to control technologies so that they're used for the benefit of the human race. I ultimately believe that over the long run that will always happen.

I'm just not a pessimist, and therefore I believe that open discussion is very important. I think closed sorts of

decisions are the worst things that can happen. Because if anything undermines public confidence, it's when things aren't discussed, and then all the negative possible impacts leak out to the public through the news. That could really have devastating effects. But I think openness--openness of information, openness of discussion--is always the way to go, on anything.

You know, I was once asked, in talking about U.S. competitiveness and all the knowledge that we're producing, it's quite possible that Europeans or Japanese will put it to much better use in terms of product development than we will, for reasons I mentioned before, and should we be restricting access to it?

And the answer is: absolutely not. That's not the way to solve the problem. It's our problem; it's not their problem. And we have to put in place much broader policies, and not just for this specific instance, that are going to allow us to produce useful products from the knowledge we generate.

So I'm unequivocally and irrevocably committed to open conversation, regardless of short term obstacles that it puts in the way.

*Q: Is there anything that you would like to add that I haven't covered?*

**DELISI**: I'll probably think of things, but no.

*Q: Well, if so, just send them to me.*

**DELISI**: Well, good, that gives me... That's great.

*Q: Well, thank you very much, Charles.*

**DELISI**: Thank you.