GENOME INTERVIEW TRANSCRIPTION: Eric Lander, 12/17/90

SUBJECT: Eric Lander, Whitehead Institute, interview at Salk Institute, 7:30 P.M., December 17, 1990.

INTERVIEWER: Robert Cook-Deegan

TAPE NOTES: Interview begins at start of tape side A.
Interview stops about 2/3 through tape side A, and resumes at the beginning of tape side B.
Interview ends about 2/3 through tape side B.

MISC NOTES: Proper names, acronyms, and unclear phrases are placed in parentheses, ending with a question mark, e.g. (Markowski?). Uncompleted sentences or pauses are marked with an ellipsis (..).

*** START OF INTERVIEW

COOK-DEEGAN: This is an interview with Eric Lander, it's 7:30 PM at the Salk Institute on December 17th, 1990. Basically I wanted to ask this series of questions, and other things which might come up. First of all, one of the things that's most interesting to me, and you're one of the few people, as I had explained before, who is relatively young, most of the interviews in this series are going to be with people like Jim (Watson) and Wally (Gilbert), people who were in decision-making positions of great power, and swept things along behind them. You are a representative of kind of the next level of..

LANDER: The people who are going to be around with the promissory notes that Jim puts out, when they come due!

COOK-DEEGAN: .. I mean, the programs that are going to be the genome project as it actually comes to be. So I'm interested from your perspective, what, reflecting on this five-year debate about the genome project, what's happened to the definition, what is the genome project now, what did it used to be, from your own perspective..

LANDER: Should I just start in at random? .. The problem with even giving histories that go back five years is that they change as they change as they gestate in your mind. So I have to go back to remember what it was at the beginning, and to be sure that I'm not remembering things in some framework I've constructed later, I'll try to do the best I can. Do you actually have a tape of the Cold Spring Harbor '86 debate?

COOK-DEEGAN: Yes.

LANDER: And does that have an audience comments and things like that? I'd be interested to actually go back and to remember exactly what I said at that, I have a recollection of what I said, but it'd be very interesting to know if there's any resemblance..

COOK-DEEGAN: Oh, you were at that.

LANDER: Yes, not only was I at that, but I was the first young person who had spoken out in that debate, at least that's my strong recollection. I mean, I know I spoke at that, I think.. I'll reconstruct it as best I can. Cold Spring Harbor '86 holds a very special meaning for me, because it was the first talk I had given in biology. I had never given a talk before in biology at all. I had been doing molecular biology and genetics for four or five years up to that point, but moonlighting from my position at the Harvard Business School, still doing a little mathematics, mostly doing drosophila genetics for a couple of years, then went and I spent a year at MIT doing (c. elegans?) genetics, that's where I met (Botslein?), which would have been in March of '85.

And we started talking about human genetics, we got into a long argument in the hall over human genetics, (Botslein?) made some wonderfully "Botstonian" pronouncement about, "it would be absolutely impossible to map a disease caused by more than one gene". And this was the first time I met (Botslein?), walking back from a seminar, MIT's main seminar room, 10-250. And it was a department seminar, and (Barbara Meyer?) introduced me to (Botlein?). I had been working in (Bob Horvitz's?), (Barbara Meyer?) was also in (worms?), she and I had talked a lot, and she was a good friend of (Botslein's?), and as we were walking back she said "this is someone you should meet". And we started talking, right away, instead of the usual pleasantries, (Botslein?) said, "aw, you're a mathematician! Well, there are all these problems a mathematician should think about in genetics". And I deeply resented this, because I had been working extremely hard to not

be seen as just the mathematician, for God's sakes, I spent four or five years at the bench, doing nothing related to mathematics. And here I felt (Botslein?) had immediately called me a mathematician.
But, in any case, he immediately launched into this whole business of genetic mapping in humans, because (David, i.e. Botslein?) had been desperately looking for some mathematical person to talk to. He had beaten down the doors of various mathematicians over the years, and none of them knew enough genetics to know what this man was raving about. And so, David launched into these "Botstonian" pronouncements, as I say, about what you couldn't do. And, I, having overcome at some point in life my natural shyness, said "B.S.", and we got into a long knock-down drag-out argument in the hall about what you could and couldn't map. And it was wonderful; we had a wonderful time enjoying each other's company, arguing about these things. And we spent the next couple of weeks intensively working together, talking together about what you might and might not be able to do with human genetics.

And, David was scheduled to give the plenary lecture at the human gene mapping conference in Helsinki, and he discarded everything he was going to talk about, and instead talked about what we had done in that last couple of months. Which was good, because David didn't have anything else to talk about at that point, he wasn't really working on human genome sorts of things. That was my first exposure to the human genome project, was an exposure through (Botslein?). And it was a very formative exposure, because to David, David of course saw the map as a whole, and thought as a.. (east?) geneticist. The same way that I thought as a fly and a worm geneticist, because that was what little training I had. Namely, that.. of course you map the whole genome, you always check the whole genome, who in the world would think of doing anything else. And I found it very amusing that people in human genetics would spend so long studying whether it maps on chromosome three, as if it were a big deal, you of course map out the whole genome.
And so, we always had a "whole-genome" notion as a starting point, and the question was, what was different about humans, rather than experimental organisms, but it was never an assumption that you wouldn't work with the whole map.

So we talked for a bit, and then I found in December of that year, I remember distinctly getting a letter in the mail from Jim Watson, inviting me to speak at the Cold Spring Harbor symposium in '86, and I was thrilled to bits, because Jim was firmly ensconced in my hagiography at that point. And, I was just thrilled to go do that, and I had never given a talk in biology. So, I went to the Cold Spring Harbor meeting in June of '86, and fortuitously, was scheduled to give one of the very first talks, I spoke third on the first morning of Cold Spring Harbor, right before the break, and laid out strategies for dissecting complex diseases, blah blah blah. I won't go into being, being terrified of that, actually writing notes, one of the few times in my life I've actually written notes for a talk.

But, be that as it may, it was my first exposure to a lot of these issues. And, when the debate came, later in the meeting, with (Paul Berg?) and (Wally Gilbert?) etc., it was very, it was a striking thing, to see this debate going on in public. I had not thought a lot about, I had heard little bits about it, but I'd not.. (Botslein?) had talked a bit. And when I heard essentially the Wally Gilbert position being laid out, "we're ready to start now, let's just start sequencing", very business-like position, I was really taken aback, because I didn't see how in the world we were going to start yet.

And, I made, it was probably for me, this is much too personal but what the hell, probably for me a very fateful decision, which was, I remember very early in the public debate, I decided I was going to here, really overcome my shyness and say something. And, I was relatively early in the thing, I think the first young person who stood up and said, "I'm worried about the way you're saying things", that, I remember saying something like, "to know that protein, you know, 6792, is homologous to a protein kinase, but it's not so interesting to know that protein 6792 is homologous to protein 3972. The only way we'll know the former and not the latter is if we make sure that we have a tremendous amount of work going on on function. And we've got to be very careful to not drive out people from the major, important thing, that I thought a balance was necessary, but that this sounded crazy, going overboard, toward the factory notion" that Wally was pressing. I remember (Botslein?) having made the major case for this, but (Botslein?) made it in the usual "Botstonian" fashion, very bombastically, and the Lewis, and the Clark, and the everything.

COOK-DEEGAN: (Don't go forward unless all flags are flying?)

LANDER: Yes, yes, exactly, it was the whole thing. And I remember, and you've got the tape, so you'll go back and find out, but I remember I spoke twice in the debate, laying out a very firm but very moderate position, that the only value of this was as an amplifier of function, an amplifier of experiments. And that, as that, it would be a good thing for me to be really careful not to shift the priorities to biology. It was a

little.. audacious to worry, to talk about the priorities of biology, because I was barely in biology, but what the hell.

And I distinctly remembered, because (Maxine Singer?) came over, who I hadn't known before, and said "I really liked what you said". Maxine and I spent that evening talking, it was the lobster dinner that night, because she had also spoken out in this debate, and it has been a mutual article of community between us that both wade in on virtually the same themes at that Cold Spring Harbor debate. That ended up being an important thing, because then I got calls from Science. And the very first Science article, I got called on for, what the hell did I know about these things, but I got called, and again spoke out on basically the same theme, of, that the strength of biology was diversity, you'll go back to the tapes, but it's coming back to me, I spoke out against "ossifying technology", that I thought the real risk of what (Wally?) was talking about was we would ossify technology, and in fact, (such total irrelevance?), a terrible thing to do in biology, that we had to let hundreds of flowers bloom. And that, the best ideas were yet to come, etc. etc.

And, I guess I said much the same thing to Science, and ended up sort of, even that first article, somewhere around the first page. And because of that, I got invited to then come to something that Howard Hughes sponsored on the genome project. And as one thing leads to another, you open your mouth, you get sucked into things, and I got sucked into genome policy, very much from having opened my mouth at Cold Spring Harbor in '86 twice, just having made two lengthy comments in that debate, famous debate, very interesting debate.

You remember the (Cary Mullis?) comments?

COOK-DEEGAN: I didn't know Cary at the time that I listened to that tape, so, I've undoubtedly heard his..

LANDER: It was the (G to W).

COOK-DEEGAN: Oh, I didn't know you did that..

LANDER: It was Cary, that's (Cary Mullis?). It was comic relief in the middle of a very heavy debate. Cary Mullis stood up and said,

COOK-DEEGAN: Jim, you need a letter, right..

LANDER: Right, "letter for Jim", and he was concerned about the typographical mutation and things, it's Cary Mullis. And (D.O.?), sitting next to (David Page?) and we were in stitches about this, we meant to have a shirt made, with a "G" in the front with a slash on it, and a "W" on the back. That's Cary Mullis, and it was also a very useful leavening of the discussion as well. It was completely out of left field, everybody thought he was out of his mind, until he worked into it, and we realized it was a full standup comedy routine, and we needed it at that point, because tensions were actually quite high.

So, initially I saw this debate in terms of, "let's get the factory in place immediately, let's not pussyfoot around", and all this namby-pamby whatever, we can do it, was the Wally Gilbert position. Very much the chairman of Biogen, very much the go-get-'em executive. (Bob Steinhar?) I respected a lot, going on, although I thought less than clear, there was no doubt where he was coming from, but as often happens with David's arguments, his instincts are superb, and the logic is sometimes hard for mortals to follow clearly, but his instincts are great. And I thought they were dead on, (Baltimore?) of course had the same set of instincts, and these were people I knew well, and I had a, you know, very different perspective on biology, but I shared the same thing, the power of the individual in biology, and the unexpected nature of twists and turns of its history, made a project like this absolutely insane, the way it was being described.

By contrast, and again I spoke out on it, in fact I think I said explicitly, that my estimation was that if we started today, '86, if we started today, '86, that we would complete the human genome by the year 2000. I thought that if we started in 1990, we would complete the human genome by the year 2000, and if we started in 1995, we would complete the human genome by the year 2000! And what we really needed to do is put money into technology, because we would be able to so much further accelerate by at least a level of magnitude or two the technology. And that, we'd get to the finishing line at roughly the same point, if we used today's technology and limped along, vs. if we invested in technology, and I thought the only sensible thing to do was to invest in technology.

I was not yet thinking about using this as a vehicle for mapping at the time, because the mapping effort in fact, was proceeding apace with (Collaborative and Ray White?), and it seemed to be making progress. It would be an interesting question as to whether or not

that actually might not have been a better thing, going back to that for a minute. But I remember pushing very hard that the technology was where we really needed to invest, and it was insane to set up the factory. And that was my end take on it, it's coming back to me, I actually very much remember the comments now, it was "ossify" and it was these deadlines that we would meet no matter what, and that's where we ought to put our money. You'll check the tape, and see how much of this is correct, but this is quite clear.

But I staked out, in my mind, this very strong position then, I actually still believe that position, but what's interesting is how the project's changed since. I remember, really the violent discussions with David, mostly with (Botslein?), little with (Baltimore?) who is of course much more controlled in the way he discussed, very much with David; about the oppressive nature of what (Molly?) was proposing, the insanity of it.

Then I remember the National Academy committee meeting being constituted, David being on it. And, David fulminating about what to do, and.. I got invited again, I suspect through (Botslein's?) auspices, but maybe not, to speak to the Academy committee on its first meeting, and I did, and I spoke on sequence matching and things like that, I think a relatively unmemorable talk, but sort of, I pointed out how little we knew about understanding DNA sequencing and urged very strongly that whatever they did, they ought to be calling for research in understanding DNA sequencing.
I remember distinctly I alienated the hell out of (Russ Doolittle?), who was appalled, because (Russ Doolittle?) felt he knew everything about sequence matching, and that people should simply send in the sequences and he'd match them, and he was going to put out a green sheet of all human genome sequences. And I think he was deeply insulted that some young turk was saying how little we knew about sequence matching, and (Russ Doolittle?) and I have never been friends since, this first time I'd met him. Again, that's not extremely relevant, but I do remember distinctly at that meeting and in conversations with David later, as he began to make such a big fuss over mapping.

Now, to me, I only get it indirectly, mostly through (Botslein?) here, but the fateful turn of events, when people, when particularly it seemed to me like (Botslein?) was pushing so very hard on the map, because he had the sense, by this point we really did have a sense, it was '87, that collaborative wasn't going to finish the whole thing, that collaborative could get so far, but it wasn't going to be it, we were going to have to go very much further, and it was clear that the collaborative didn't know what it was doing, and didn't have a business reason to sustain this. David was very concerned about the continuation of the mappings, we'd published these methods, but what were you going to do with the completion of the map, and we were sort of standing there waiting for people to start doing it. And the map wasn't coming, and it wasn't coming, and we knew so clearly what you could do, all the powerful methods you'd have, and yet the tools weren't there. And much the same thing was becoming clear in physical mapping as well, that it was just a killer.

I'm going to go back, I remember distinctly in '85, going to Helsinki, and finding out much to my shock, that although I'd been talking to (Botslein?) for four months about the whole genome, the whole genome; we got to Helsinki, everybody save only a handful were thinking about this little region or that little region, and I felt like this was amazingly Luddite, everyone had this notion that there was no way you could take on the whole genome, you could only work at most on a whole chromosome. And with a certain young arrogance, I thought "this is all going to be swept away". This is this "can't possibly" thing, these people don't see the future.

Again, I'm not sure why I had any business doing that, because I had so little perspective on the field, but I just was shocked to see so many people, the whole deans of the field, so caught up in psychology, which seemed to me a dying business. And so caught up in the Balkanization of the genomes into the little domains to which people belong. And being told point-blank on a bus in Helsinki during one of the tours by somebody, "oh, this whole genome business is pie-in-the-sky. It's just not practical to do that".

I feel sort of the same way right now about physical mapping, whether or not we have maybe made too much a big deal about physical mapping the chromosome, and I deeply worry whether (NCHR?) hasn't ossified in fact a certain point of view, by declaring that physical mapping has to be done chromosome by chromosome. And even inadvertently, we haven't given full flower to what probably should happen, which is techniques for mapping entire genomes, physical mapping entire genomes, which people think is somewhat audacious, but I just remember so well in Helsinki that everyone thought mapping the whole genome genetically was audacious. Which I'll note simply for the record, our genome center is devoted to mapping the whole mouse genome, contrary to what the DOE put in its little flyer, our grant is to create a complete physical map of all the chromosomes, it's not to do chromosome by chromosome. Because it's very much informed by that notion that if the technology gets any good, then we can do a whole genome, and if the technology doesn't get good enough to do a whole genome, then there's no point, because the point is to push

the technology to the point where it's easy to do a whole genome, it's not just to accomplish the whole genome as a trophy to put up on the wall, it's to make it trivial to make a whole genome, and if you haven't won that, then you really haven't won the battle.

But I get ahead of myself. So I remember the concern that, who's going to do the map, and getting only scattered bits of the story from (Botslein?) about the trouble he had in funding the map in the first place, and getting turned down by NIH, I remember talking to (Mel Simon?) who tried to get the mouse mapped early, and he was getting turned down by NIH. Everybody's saying it was either completely impractical or not really very valuable.

And again, it was a question of human geneticists having not the slightest clue of what genetics was all about. The perfect example of course were reverse genetics. Human geneticists are so confused about genetics, that after years of being able to do nothing but biochemistry, identify a protein that was wrong in a disease, and then by virtue of the protein get the gene, when for the first time, they can actually get a gene by genetic mapping, by position, by what (Sturteyvant?) laid out in 1911, by what had been used in drosophila to clone genes; they called it reverse genetics! For the first time they could do genetics, and they called it reverse genetics! It ungenerously suggested somebody had their head on backwards, and yet an entire field had its head on backwards. And I still think that's the case largely in human genetics, that the field has yet to come to grips with the fact that it's doing genetics, just like in drosophila, just like in flies and worms, and yeast. And that we're still in this cottage industry, people colonizing little regions, etc.

The real impact of the human genome project is that we're going to sweep away all that, so that we do in fact do genetics, like we do in any other organism. And I bet that 95% of human geneticists have no idea what that means right now. And it's not like a grandiose thing. It's not like the book of life, it's just, it will be no big deal to map something to a region and clone it, like it isn't in drosophila. But it means that you start thinking as a geneticist, which is not what people for the most part, though there are many exceptions, but as a field, I'm always struck by having made a very brief transition of about a week, from working on (c. elegans?) to thinking about human problems.

So my real detailed knowledge of the shift is very indirect, the shift from the factory a la Wally, to the physical, to the genetic maps, it's quite indirect, it's very much through (Botslein?), who simply expressed over and over the concern that these things wouldn't be done, and these were the things that really mattered, what we really needed to do was to do genetics, and we would tell ourselves in lengthy discussions back and forth, because David and I just spent a tremendous amount of time together during those years, during the years '85 through '88, before he went off to California, we spent a lot of time just talking, that they just didn't understand that the sequence just wasn't going to tell them where cystic fibrosis was. And the sequence wasn't going to tell them what the basis of, you know, alcoholism might be, and things like that. That in fact, the genetic and physical maps were much more informative than sequence was, and there was actually a much more desperate need, and we could see it happening.

David pushed very hard to have it happen, and again, here you'd have to go back to the tapes, I think I made the model organism point at the Cold Spring harbor debate as well, but I don't recall it, there I may be crossing history..

COOK-DEEGAN: Yes, I don't remember where it came from..

LANDER: I think I made the model organism point as well, that for God's sakes we hadn't mapped, we hadn't sequenced the genomes of lower organisms, what in the world do we think we're doing about model organisms, we should build up the evolutionary ladder. I think I made that point, I do remember now another point comes back to me from Cold Spring Harbor '86, about spending huge amounts of money to get sequence when it was premature. I remember distinctly saying, "one could have envisaged a genome project in the early 70's, to get the complete genetic sequence of (lambda?), and one could have done it by (n-degradation?). You could have prepared a huge amount of (lambda-DNA?), and by (n-degradation?), one at a time, read off the sequence. You could have justified a three-billion dollar crash program, to read the complete sequence of a genome. And this would have been insanity. This was part of my general argument, that if we started five years later, at the sequencing..

Anyway, there was a whole combination of those things, a clear feeling that the whole project was just.. insane thing about sequencing right now, and the concomitant feeling that people were missing what they could do to turn humans into genetics. And (Botslein?) fought that battle, as best I remember, on the committee. Although I think he had support

from others. I think in fact, this is very indirect, but from the many discussions I had with him, it was a sop, it originally started as a sop to him and a few others, that, "yes, of course making genetic and physical maps, the cost of these is small compared to the magic three billion dollars", and if that's all it took to buy (Botslein?), that was easy. And since (Botslein?) was A-number-one major critic, if you can buy your major critic for 10% of the cost of the project, no big deal. So I don't think people fully appreciated what they were getting into there. That in fact, they were talking about doing bigger scale, with higher throughput, work than they had ever dealt with before. Because only (Botslein?) and (Henry White?) and those around them had experience with what it meant to do a large project like this. And (Helen?, Don S. Keller?), basically those few groups, no one else had the slightest conception of organizing a large enterprise and all the complexities around it.

With due respect, Wally didn't. Because the other involvement I'd had was through Wally, who I had come to know as well. And, Wally asked me to be on the scientific advisory board of (GenomeCorp?), which I said I would do. So I spent many a lunch with Wally at (Roca Restaurant?) in Harvard Square, going over the financials, the mythical financials, for (GenomeCorp?). And of course I was a professor at the business school, so I had some actual knowledge of how to read financials, and a thing about a business, and so for a number of reasons, both because Wally recognized it would be good to talk to me about databases and analysis and things like this, because I had some business experience, you know, he would inflict on me each version of the business plan. Which was a rapidly changing, fast moving target. The business plan just went bing, but you should get for your archives, the collected business plans of the erstwhile (GenomeCorp?). For awhile, he was going to support the genome by first getting (cosmids?) covering the whole genome, and selling them for $50K apiece, and various other things like this. But he did actually have three meetings if I remember correctly, of the (S.A.B.? Strategic Advisory Board?) of (GenomeCorp?), on which I served, unpaid. And, it sort of died of its own weight, it was wonderful, I was grateful, I had no objection to serving on the (S.A.B.?) of this, because, for God's sakes, if he was going to privately sequence the whole genome, I had no objection to this. I thought that was great, it didn't conflict with my notions of balancing the rest of the biology. And it was quite fun, and so I thought, why not.

But it was clear that there was simply no economics, Wally wasn't going to patent the genome, those were big misconceptions, Wally understood full well he couldn't patent the genome. Wally knew that at best he could copyright data, as in a news service or something like that, or a map: you can copyright your map of Boston, you can't copyright the street plan of Boston. He knew that distinction, but he expected, like CompuServe or something, he'd make his money on line access. But you go through the economics of spending 3 billion dollars for 15 years before you get your revenues, and you do the discounted present value of money 15 years out, and you've got to have a lot of users dialing up an awful lot to cover your upfront costs. And that's where these desperate plans to sell cosmids and things like that came in. And the thing never made economic sense, it was just crazy. There was just no way to do it economically.

And then there was the time of discussing "first looks for drug companies", early looks, six-month advance window looks, to pay for it, and that again didn't make a lot of sense.

So, with Wally off the committee, doing genome, the major driving force behind the factory, the importance of just getting on with it, no nonsense, at least to those of us on the outside, just sort of evaporated. And the (Botstonian?) argument about maps, and why maps matter more than anything, and really the yeast geneticist coming through, recognizing that these were the tools of honest doing genetics, came through, and they bought them off, or maybe they understood, and of course (Maynard?) was also crucial in that. (Maynard?) coming on the committee in place of Wally I think was a dramatically important event, because (Maynard?) and (Botslein?) had very similar views of what really mattered, in doing honest genetics and finding genes.

So, next I knew, it was all in place, I wasn't very close to the workings of the committee, and by no means did I articulate clearly a vision of genetic and physical map as being touchstones, cornerstones of this enterprise, but it made a hell of a lot more sense. When we started talking with (Hulian?) about the way everything else in biology had been done, namely, up the evolutionary ladder, starting with the smallest organisms and working up and learning our ways, starting making genetic and physical maps of the model systems, and then with sequences of those, percolating those technologies up to more complex systems, it had the ring of sense in it. And, at that point, I began to publicly defend the new genome project, as opposed to the old genome project, because it made a great deal of sense. We'd learn small, where we stood a chance to proliferate technologies, evaluate them, see which ones work, and we would then apply them in manageable doses, and we would apply them to systems in which we could do experiments and tests.

And, that also shared this very strong vision of what maps were good for, which we still haven't fully achieved, we still don't know what maps are good for in the full sense. When it becomes trivial to do it, I digress here, but when it becomes trivial to get markers across an entire region and do linkage disequilibrium studies, up and down a region, and automatically trace the history of that chromosome region, and pinpoint diseases that way, then we'll what maps are really about. And that they represent a tremendous treasure trove of history, that the people who say "well we only need five (centum?) of organ maps, or two (centum?) of worms", they don't know what they're talking about. We need one tenth of a (centum?) organ maps, we need to be able to apply them very rapidly in an automated fashion, because the history is there. The only change we have of studying these meioses in a non-experimental system is to make use of the meioses God gave us through history. And those meioses are very powerful, but you've got to be able to make up for lack of crosses in the lab, with density of markers, and this was the point to the Cold Spring Harbor '86 talk, and the point to the Cold Spring Harbor '86 paper. That you could make up for the inability to manipulate the human experimentally with better and better maps, down to a tenth of a (centum?) of resolution.

And so I of course bought it very strongly and began to shift from being very cautious, as in this '88 article you've got here from American Pharmacy, where I'm saying things like "pouring money into the project before basic technology's in place isn't warranted, but only diverts money from mainstream research biology", to feeling that "well if in fact one was provided"....

*** INTERVIEW STOPS 2/3 THROUGH SIDE A.
*** TURN TAPE OVER AND REWIND TO BEGINNING OF SIDE B.
*** INTERVIEW RESUMES AT BEGINNING OF SIDE B.

LANDER: OK, so, reporters who would, you know, have their usual suspects to call on, by then I was a usual suspect, would call me up as being on record as a critic of the human genome project. And I would make clear that I was critic of one human genome project, and in favor of another completely different human genome project, and one had to distinguish between the two genome projects being talked about. And, even Whitehead had an I.A.P. debate..

COOK-DEEGAN: What's I.A.P..

LANDER: I.A.P. is a period at MIT during January, between terms, inter-activities period, whatever it's called, and during I.A.P. there are all sorts of public lectures and events. We had a debate between Wally Gilbert and David Baltimore of the human genome project, and I was the moderate, the middle ground. And, they both spoke, and I synthesized, or vice versa, or something like that.
COOK-DEEGAN: (Was it on tape?)

LANDER: I doubt it, I doubt it. But I tried to, in fact I went first, and I tried to lay out what the genome project was about, what the issues were, the stages of human genetics, and Wally spoke, David spoke, and we all got up there and did a panel discussion. With me in between David Baltimore on one side and Wally Gilbert on the other side, trying to make sense! And again, I was being my usual rabidly moderate self, trying to say "there's a middle ground here". But it was a fascinating experience, because I was a young untenured person, just hanging out as a fellow at the Whitehead Institute, still employed at the Harvard Business School.

So, anyway, I kept trying to point out to reporters, to no particular use, and no particular success, that there were two completely separate human genome projects. And then it became clear, with the Reston meeting, in January '88..

COOK-DEEGAN: February actually, February to March, it was the 29th actually..

LANDER: Is that right, I thought it was January to February, you could be right, whatever.

COOK-DEEGAN: The NRC report came out in February 11th..

LANDER: I'm pleased I got the year right! In early '88, whenever it was: I'd been asked to co-chair the committee on informatics, for the ad hoc committee, and by the time of the Reston report and that discussion, I was now strongly in favor, because all of the sensible things, all the things that I think I said in Cold Spring Harbor, that made the genome project completely fly in the face of sensible biological wisdom, were now in place. Namely, that we were going to do it incrementally, we were going to proliferate technologies, and push technology development, we're not going to ossify around anything, we're going to start with model systems and work up; all those things were there, and they were exactly the things I had attacked early on, as being contrary to the way we do

biology. And, so I at that point essentially signed on completely to the fact that this now made a great deal of sense, and became a strong supporter, while remaining, while attempting to remain a critic of the early vision.

And, that's simply lost on reporters, reporters have never managed to distinguish that the human genome project, they say the critics, some reporters say that the critics caved in on the human genome project, or that the critics were won over, it's not true. The critics took over the project. The critics of the human genome project won. And the human genome project that exists today is in fact the vision of the critics, is not the vision of the people who proposed it. That vision was gutted and replaced by something of a piece with the rest of biological history and the rest of molecular biological science, in this century. I think it's a marvelous thing that they kept the name while they eviscerated the organism. And they put in an entirely new set of guts, and yet still said, it's still a human genome project, still "the" human genome project. And it was debated at Reston, of course, about calling it the "complex genome project" or things like this, and now people stuck to "we've got to call it the human genome project or Congress won't understand". The name was kept, even though the internals were totally different. And I think it's a marvelous piece of sleight-of-hand, because it was accomplished without people really noticing.

And of course it's come back to haunt the project. It's come back to haunt the project terribly, because it was accomplished so slickly, that many people in biology didn't know it had happened, the goals had been totally changed, and only the name was saved to protect the innocents. And.. but it was a good move, and it worked, and as it became clear, and here I mean at Reston in particular it became clear when we started talking money, how much money it was going to take, to make a good genetic map and make a good physical map, and to develop sequencing technology. And as it emerged clearly from the discussion at Reston, nobody wanted to do sequencing right away. We at most wanted to do sequencing technology, which was again the position I had felt strongly about at Cold Spring Harbor.

It was clear that we aren't going to be building Wally's factory any time soon, it was completely taken over, and that the economics alone was causing this to be a technology project for genetics, and an infrastructure-building project for, really, applying genetics. And I thought this was wonderful, because it was true that this was an infrastructure that was a bit too complex for any one lab to do it at this point. So, following Reston, I thought that the whole thing made a lot of sense, and had completely shifted, and I guess I at that point was part of the floating genome cocktail party that went around to infinitely many genome meetings, and it began to get out of hand. There were meetings that discussed the human genome project everywhere, there was a meeting here at the Salk, that discussed the human genome project, and I was invited as a discussant to this thing. Any number of these meetings.

And there were relatively few people who were knowledgeable and willing to talk out about it, so that the same ones of us kept getting invited to the damn things! To no particular good if you ask me! And so it went, on and on.

COOK-DEEGAN: What's your sense of what the goals are?

LANDER: Now?

COOK-DEEGAN: Yeah, what are the..

LANDER: The goals now, alright. Well, I'm not sure my genome project is necessarily Jim Watson's genome project, necessarily. My sense of the honest-to-God goals of the genome project are a couple. One is to put in place a real, usable genetic and physical map of the human genome, and of the mouse genome. But I emphasize "usable" more than most people probably will. I think the genome project will be a failure if we put in place a map that doesn't allow us to map a family for the entire genome, within a week, on average. Our goal is to able to score crosses, and that means we've got to have a set of markers that cover the genome consistently so that when you're done using them you can score the whole genome. And you can use them quickly, so that, you know, I'd be willing to score 40 families in 20 weeks for the whole genome, I think it would be useful if you could do that. Until we get to that point, we haven't achieved the goal of the human genome project, which is, in some very economic sense, to push us down the learning curve.
I think every organism, in almost every (trade?) of molecular biology is going down some sort of learning curve, that's taken us from barely being able to do something, to being able to do it like falling off a log. And that's what the genome project is about, is pushing this down a learning curve in mammalian genetics, which may be a particularly thorny one. Simply because of scale, and all sorts of things. It's a learning curve, that just like every other learning curve, we're not going to able to get down, without new tools.

In this case these tools may be for the first time, automation. Not sure that that's the case, but I wouldn't be shocked if in fact this represents the real introduction into the molecular biology lab as a standard thing. Every one of my students now needs a (PCR?) machine. I basically have one (PCR?) machine per person in the lab. I just bought my second (BioMac?) and it seems very likely I'll have a third (BioMac?) workstation by the middle of this year. It's not inconceivable that we'll end up having one (BioMac?) for every two to three students. And I'm watching the way it's transforming my lab. So it's coming down a learning curve, both for genetic and for physical mapping, I should say for physical as well, and all that.

Secondarily, it's the infrastructure itself, it's actually having the clones. But, I'd hope that we'd achieve the goals of the human genome project in such a way that if, for example, somebody God forbid threw out the physical map, we could regenerate it in 4 months for the genome. And I don't just mean by having (SDS? STS?) sequences stored, but just to take four months to get all the clones back and order them. That would be an achievement. I mean, we could also go do the cow if we wanted to or any other genome like that. And then it becomes trivial to do the genetics of higher organisms. Those are the real goals to me.

The truth is, everything else is icing. My guess is.. I'll go a little further. Another goal I have is, I'd like to see sequencing technology get considerably easier, and I think we're all agreed on that, it's got to get at least an order of magnitude easier, and there's easily an order of magnitude to be had in it. I don't know that we'll ever be able to do all the genome. We may, I'm just agnostic on that question, but were we to declare that at this decade, that we had achieved those initial goals, that we had sped up sequencing by a factor of 10, but that we didn't see how to do a whole genome, and declared victory and pulled out, I would think it would be a fabulous success. We would have so transformed what it means to do mammalian genetics, that it would be irrelevant whether we get the whole sequence or not.

On the other hand, I'd like to be optimistic, and imagine we can get a whole sequence, and make that a trivial thing too, to have a complete sequence. Because coming as a mathematician, I know what we could do with all that data. I think it would again transform biology in another way, if we could start with sequence, I don't have to ramble on with that, but I feel strongly we could. I don't know, I'm more uncertain, about whether we'll achieve that. Simply because I recognize how many orders of magnitude we have, and I recognize that there are very few technologies in this world that have consistently achieved order-of-magnitude achievements in three consecutive decades. Microelectronics is cited as a classic example, but it ain't easy to find others. Very few examples of such technologies. Whether or not we can be clever enough, I don't know.

Now the thing about microelectronics that I always come back to as an example, is that each generation of lithography of chips, each new generation of finer and finer features of chips, has cost more and more in research and development to put in place. It takes increasing returns of research to be able to achieve these goals. And I suspect it's going to be the same thing with sequencing, the question is, how much more is it going to cost, with each new generation of sequencing? My guess is that a zillion (ABI?) sequencers working their tails off isn't going to do us the human genome project. It's not the graceful human genome project I want to see, the small science human genome project that I'd like to see. And I don't think it's going to even be practical, I think we're going to need completely new technology, and that's a big gamble, we don't know whether that's going to happen or not.

To me, those are the goals. I never know with Jim, whether his adherence to the article of faith that we'll sequence the whole human genome project, is a deeply held belief or is a public position he has to take. I publicly won't go as far as I'm going here, in questioning how far we can go, because it's probably very important to have unbounded optimism at the beginning to see how far it goes. Nothing like pessimism to achieve that you actually won't achieve the goal. I feel I'm being ridiculously optimistic enough about the physical and genetic mapping that I can afford to remain cautious about the sequenced map, just to maintain some balance of reality in my life.

But to me those are the goals, and I think to the young people doing the project, those are the goals, to the (Glen Evanses and the Francis Collinses?), that's the goal. The goal is to transform the way we do mammalian genetics, and everything else is icing on it, we'd like to push hard for it, but we're realistic. That that transformation alone would be so momentous, we'd be willing to settle for a little while.

COOK-DEEGAN: You've gone over our first seven questions actually..

LANDER: In a terrible ramble all over the place..

COOK-DEEGAN: This is wonderful. There's one other set of topics I'd like to cover, and it's in fact related to today's meeting. You have given several talks that I've heard where you've kind of danced this line..

LANDER: My rabidly moderate position, yes!

COOK-DEEGAN: The genetic determination as opposed to these kind of equally orthodox, anti-deterministic views. (It's) been part of the 1970's and 1980's. What's your sense of where that's going, and how to handle that, not necessarily as a public policy matter but as in fact, as a, what's going to happen to people who are trying to do work in the genome project as you are. We could start actually by asking, I proposed in what I said today, there are two interpretations of why it was done. One, the preemptive strike view, and the other being, this is actually something that is welling up in the scientific community, and in how the scientific community interacts with the general public. You do a lot of public speaking, what's your consensus?

LANDER: I think it's some of both in there. I must say, I didn't hear Jim talk about this before it was brought to him. I've got to imagine, to some extent, the ethics program as publicly declared, with 3 to 5% of the budget going to it as preemptive strike, that said, the concern about ethics was clearly there, everybody's worried about it. I wrote about ethics in '87, and it appeared in (a prints?) in my weekly article, before there was any genome project or any ethics, because it was so obvious, the screening for Huntington's disease raised all these questions. And to me that was the obvious case, and in a funny sense, (Nancy Wexler?) as a symbol made it so much more palpable for us, because we knew somebody who was making a decision, who was making a decision not to know. And that brought on..

COOK-DEEGAN: (How did you know Nancy?)

LANDER: Through (Botslein?), I met..

COOK-DEEGAN: Through the touring..

LANDER: Yeah, exactly, through meetings and things like that. And here was this wonderful exciting enthusiastic vivacious person, who I knew in fact had an operative need to know or not know. And she made a big impression, I suspect a big impression on a lot of us. And maybe less so for the folks who are docs and see patients all the time, but for me it made it very, very real. And so there was a concern on, certainly on the part of a lot of us, about ethics. What was not clear was how in the world to translate it into anything. And I must confess I was taken a little aback by the 3-5% to ethics, because it seemed to me to be a little too transparent, to come up with a precise number.

Going back, I don't remember whether in Reston in '88 there was any discussion of it, but I do remember in Reston '88 we were drawing up budgets on how much to go to training, how much to go to computers, how much to go to physical mapping, how much to go to archiving clones, and I don't recall there being a line item for ethics, that's just my recollection, it's all in the public record, check it. But you would have thought that if people saw it as an integral part of the project, it would have been a line item. I suspect it dawned on them later that not only was this a vague concern that we had, but there had to be a way to reflect that in the bureaucracy that was being created. So, I'm not casting aspersion on the motives, it's more that it took awhile to recognize that one can even address ethics programmatically, and I think it'll take awhile to see if we can even address ethics programmatically, we've had very little experience doing it.

It is a novel thing, it is by the very nature of the fact that a specific proportion is called out, I think a little suspect because, one would like to and one does with every other part of the genome project, say, we allocate it based on the merit of the applications, how much good it will do, and it seems a little artificial to declare it set aside in advance. On the other hand that may be necessary, because you're reaching out to a different community, and you've got to indicate how much you're talking about, and things like that. So it's a fine call, and I don't really know how I come down on that, or what really went on. But it took awhile for folks to realize that it should be there programmatically, although you can find a lot of threads in everyone's private discussions, that we're raising a lot of ethical questions.

I was of course very sensitive to it, because of conversations with (John Beckwith?). I had taken (Beckwith's?) course at the medical school when I was learning biology, I sat in, I never actually took any courses, but I sat in on (John Beckwith's?) course, his reading course in microbiology, in which he also brings up social issues a great deal. And, in that course he had a full section on sociological problems, and after the course John and I had talked more about it, and I had started coming to his, what was then called

the sociobiological study group, which was sort of running out of steam on sociobiology, it was a sort of very left-wing sort of thing, running out of steam on sociobiology. I started bringing up the issues of genetic screening, which I thought were very important. And, I eventually interested (Beckwith?) in genetic screening, and the group eventually changed into the genetic screening study group. Largely because of a couple of meetings that I had organized where I was bringing up (RFLP's?), and I taught John about (RFLP's?), which was a delight. To teach a geneticist, to watch (John Beckwith?), who is of course one of the world's greatest microbial geneticists, struggle with diploid genetics. Keeping track of two damn chromosomes drove him crazy, and for the longest time, he couldn't figure out, you know, segregation patterns and things, I mean he couldn't, it didn't come naturally to him. Which is funny for me, because he's such a great..

But we held a number of meetings where we talked about (RFLP's), and the group eventually just changed, because sociologically they didn't have any content to argue about anymore. And the genetics meeting was lively. And (Botslein?) was violently opposed to my talking to (Beckwith?), because he said "it would come to no good. (Beckwith?) is a smart man, but he runs with a crowd that's scurrilous, and will misuse everything, and you'll be taken in", and I again belonged to this rabidly moderate position, that reasonable people sitting around could agree, and I eventually started persuading John that (RFLP's) were a good thing, because (RFLP's) were in fact a weapon against sloppy genetics claims, the twin studies and things like that, without mechanism. By demanding that if people were going to call things genetic in humans, they actually cloned the damn gene or at least mapped the gene, one could in fact enforce a much higher standard. And that appealed to John an awful lot, that scientifically, one could up the ante on what constituted human genetics, in a rigorous way. It appealed to him as a scientist, as well as from the point of view of (palsy?), which in my feeling as well, that there's no question is human genetics. There's a lot of low threshold of proof in human genetics, and the proof of genetics ought to be a gene.

And it blew (Botslein's) mind that I could actually get (Beckwith?) to agree on this, and that they actually had fairly similar positions, that we needed to do a very good job of this, because we knew good genetics was the antidote to sloppy eugenic thinking and sloppy biological deterministic thinking.

And so that was the crucible in which my own views about ethics were formed, going back and forth between (Botslein?), who strongly believed that there were potential genetic bases to alcoholism and to child abuse and to things like that, and to dyslexia. And (Beckwith?) who was concerned about sloppy thinking, and they both were concerned about sloppy thinking. They came with very different perspectives about the role that environment might play, and the level of interaction. David has his own hierarchy, (Botslein?) had his own hierarchy of how much was genetic, how much was environmental, and (Beckwith?) had his, but it forced me to think very clearly about those interactions. And so my own views come very much from that.

Sort of recognizing again, just the ridiculous oversimplification people make about mechanism, and how you can reach such ludicrous conclusions, by just leaping to correlations, like I've talked about. Now what's going to happen with all that is much harder to say. I've thought an awful lot about the policy issues, I'm not so sure I can predict so well what's going to happen. I worry a lot, because it takes a huge amount of talking to explain this to people, to try to give them a sensible perspective on why genetics is a wonderful thing to do, but provides sort of meager answers to the real worries that everybody has.

And I find myself constantly, as I found myself at Princeton just this past weekend at the trustee's meeting, having a lunch with some of my trustees, who occupy august positions in society, in our Congress and in corporations and in journalism, and having the discussion over lunch start revolving around, "well isn't it appalling that you can't really talk about genetic differences and ability among the races, that it's become an unspeakable thing, isn't it important to know those things?" And I leapt into the fray, and tried to explain that this was nonsense, suppose there were differences, they presumably could be, they were completely dominated by environmental effects, and knowing that it was genetic didn't mean it was unchangeable, blah blah, all my usual arguments about this, and slowly winning some agreement on that point, especially from the younger trustees. A small group of 8 of us were talking.

But just recognizing that very smart people who I respect an awful lot, were backsliding again into the, "we want to know genetic differences among people, because it will tell us what their real limitations are", and this equation of genetics and limitation. I'm not sure I'm that optimistic on that. I'm very optimistic on protecting genetic privacy, and we'll get our laws on protecting information, and things like that, and I'm not an optimist on what I think is the real $64,000 question about genetics, which is how much people decide is determinate. I just see this landslide of pros in the press of nature

over nurture, these things, and I feel personally overwhelmed, trying to battle that. I feel that there aren't very many of us who are going to attempt to battle that at all.

But there aren't very many of us who I think, care about the distinctions. There aren't very many of us who are prepared, and somewhat experienced in how you fight that in the public arena. And I'm sort of tired in a way, I mean the fights over DNA fingerprinting took a lot out of me. I realized if you were going to try to win a public issue, what it took. It took just a huge commitment to it for a long time, and that was when it was in a tiny arena with a handful of players. I mean, two companies, and the FBI, and a couple little things. The thought of really trying to go to battle, to really reshape people's thinking on genetics, is daunting. And I can't say I'm that optimistic that we're going to win that. And I do think those are big stakes.

COOK-DEEGAN: What would winning that mean?

LANDER: What would winning that mean.. winning would mean abolishing this nature-nurture dichotomy as a dichotomy. Realizing that for very few things, does it even make sense to speak of nature versus nurture, and apportioning determination into those two categories such that they add up to one. Recognizing what we mean by interaction and (hepastatis?) and response to environment, and that things may be good in some context and not in others, just having some degree of complexity and richness to it.

I watched the slow progress on IQ, trying to root out IQ from public consciousness, as if there was a single linear measure of intelligence, to an American public that would be absolutely appalled by the notion of "AQ", namely athletic quotient. If I tried to promulgate the myth of athletic quotient on the American public, that there was a single AQ number on which I evaluate Bo Jackson and Larry Bird and all athletes, I would immediately be leapt upon by people saying, "no, no, there's no way you can compare center fielding, hitting a basket from this far out", whatever, there are obviously a whole distinct range of different characteristics, people can be good on some and not on others, nobody would let me promulgate AQ, and yet you have a world where people will handle IQ very quickly.

But I watch people like (Gardner?) and others, through their books, in a kind of stereotyped way, substitute IQ for 12 dimensions, or 6 dimensions, pick your number of dimensions. But it's obvious that to win that debate, one needs to enumerate some alternative number of dimensions, it's not enough to say it's a complex interaction. I don't believe (Gardner?) really believes in the magic 6 or 12 or whatever number it is, my suspicion is that this is the way that one reshapes the debate, is by getting people to agree to 6 or 12, and then recognize, well there are many, and people, once it's multi-dimensional, start thinking differently, and then you can win the debate. That's slow, it's made very little progress so far, a little bit.

I suspect that same battle is going to have to be fought, and it's really a battle, and it's really going to have to be fought about strategically, what metaphors you substitute. And so I give that IQ example because I see a real substitution of metaphor, for single dimension to 12 dimension. And parents instead want to get their kids measured on their musical IQ, and their spatial IQ, and their interpersonal IQ, and we'll get tests for that, but in the long run it's a push in the right direction, because it's a way to displace.. Once you move the statue, it's much easier to begin rearranging the Pantheon. But when the statue's weighing down heavily there, it's much harder to.. We've got such heavy, heavy monuments in the genetic Pantheon that we're going to have to move around, and we don't have leverage on them. And we're going to need to invent alternative conceptions, whole pre-packaged alternative conceptions, if we're going to move these things around, and that is just plain work. I don't see a lot of people doing it yet. And for my own part, I've been weighing in much more heavily on trying to actually do the science for the next couple of years, and don't know whether I'll have the time, the energy, or the ability frankly to do it, but I feel very strongly about it, because..

I don't know, I feel strongly about social issues, political issues, whatever, and I think science is so secure that I don't mind challenging science in certain ways, because.. I've always come from a school that one shows one's loyalty to something by thinking that it's worth criticizing, by thinking that it's worth rethinking and finding the weak points, that the enterprise is valuable enough that it's worth criticizing, one doesn't bother criticizing things that you don't think are worthwhile. This has always been a strong theme with me, that the people who really loath a field ought to be its first critics, and its first line of friendly attackers and nudgers and controllers. There's I think a majority view that you circle the wagons, and you protect science. I may be an optimist, but I don't want to do that. I think we do far better by going on the offensive, as I try to do with these ethics talks, of pointing out all the problems. And saying, that notwithstanding the problems, we should do this, but we'd better damn well address the problems. I don't know if I'm optimistic on that.

COOK-DEEGAN: How rigid do you think the genome project is..

LANDER: We have to go, we can always meet again, and you can ask me more questions if it's ever useful for you..

COOK-DEEGAN: You've talked about a lot of good reasons to do it, and how it makes sense and all that, but, what's your sense of urgency about it?

LANDER: Well, two things. Right now it's very urgent to do something, because the project's stuck it's neck out so far, that it damn well better have results to show for it. So in its very narrow sense, I think that it's urgent that the human genome project.. (background interruption).. I think just politically it's important that something go on with the genome project, so in that very narrow sense, the genome project at this moment in time, is an urgent matter, because if it doesn't deliver itself of something, it will collapse of its own weight. How urgent though is it in a broader sense, how important is it to do the human genome project right now: I think the narrow goal of physical genetic maps is really urgent, because we're at the critical point for being able to attract bright young people into mammalian genetics, and having this be the decade of mammalian genetics...

*** END OF INTERVIEW, 2/3 THROUGH TAPE SIDE B.