GENOME INTERVIEW TRANSCRIPTION: Renato Dulbecco, 12/16/90

SUBJECT: Renato Dulbecco, December 16, 1990 at his office in the Salk Institute.

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 minutes from the beginning of 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: It is December the 16th, 1990. The following will be an interview with Renato Dulbecco at the Salk Institute in his office. It's about 2 o'clock PM on the 16th of December 1990.

DULBECCO: I would say that the first time that I publicly mentioned this idea was at a meeting in Los Angeles, not even really a meeting, it was the opening of the (San Coloc?) laboratory, which I think was some time in May 1985, if I recall correctly. And I gave this talk, I remember, to a kind of stunned audience, and then, I got very little comments. I remember I went, asked (Joe Sampo?) just after, saying "why don't they say anything? Am I totally dumb?" He said, "oh no", and somebody else who was there said "oh no, the reason is because we are starting to think about it, it's a new idea". So that was the first thing, and then there were the (Sance? Science?) and this other meeting there, which I think I could find a reprint of that, these are not really important things..

COOK-DEEGAN: But for historians..

DULBECCO: Historians, exactly.

COOK-DEEGAN: What was the background of that original paper? When I talked to you in 1987 you had mentioned that, I went over my notes from the '87 meeting and your editorial and stuff, you'd said this came out from preparing the talk I presume for Cold Spring Harbor.

DULBECCO: Yeah, I remember sort of taking out a pencil and thinking in a new way, an unconventional way. See, what would you do if you forget what you've been doing, what works well, and so on. I had this idea, and I talked to a number of people here, and they seemed to think it was a reasonable thing, and generally I got encouragement from everybody to do it. That's the way it went.

COOK-DEEGAN: How did it turn into the paper for Science?

DULBECCO: Well, because I thought.. see, I've talked a little bit about that, and got mixed reactions. So, I thought, in fact originally the paper for Science was not meant as what came out in the end, as a perspective. I wrote the paper more than anything else as a kind of review. It was much longer than what came out. I sent it to Science, and the reviewer said, "in a way it is not really a review, it is not really a scientific article in terms of..", so I sent it, and then (Dan Conshon?) called and said "well, it doesn't fit any of the regular classifications, but we're now starting a new series of articles called perspective, or we've just started. Do you mind if we publish it as a perspective?". And I thought it was a very good idea, because actually it was a perspective more than anything else. So I shortened it, focusing on what I want to say, and sent it back to him, that's it, that's the way it came out.

COOK-DEEGAN: That article, I think you probably already know this, but just to go over it; that article was what instigated the Cold Spring Harbor.. in June of '86. And of course it was Paul Berg who made the connection, he was the one who wrote Watson and said we should hold this meeting. One of the things, he was intrigued by the idea. But he said, he was talking with me, that he was a little puzzled by the connection to cancer research.

DULBECCO: I know, that's what comes with the work I was doing there. Unless somebody's been involved with that work, one cannot really appreciate the motivation for that. The motivation is this, that.. I've been studying breast cancer experimentally, and we developed a series of markers for following specific problems, beginning in mammary cells, which characterize different cell types, and see what happens as cancer evolves from the initial stage into the more malignant stage. And in fact the first thing that you notice, and you notice it all through, is considerable, tremendous sometimes, heterogenic.. namely that you have a structure, if looking at this cell, at the beginning it looks almost like a normal structure except for some of the (mutations?) in certain areas.

But then if you go look at markers you realize that none of them is really truly a normal cell. Because the distribution of these markers is different from what you expect to be in the normal. In the paper which I published on that, I made some thirteen different evaluations which I could identify, the normal distribution markers, and I imagine there are more than that.

So ultimately the goal of cancer research would be to cure cancer, that's the goal. In order to cure cancer you need specificity. How can you find specificity, there must be specificity, how can you find specificity if cancer cells from the very beginning are so highly heterogeneous? Because each cell is different from any other. They probably have something in common, which is equal. But how do I find what is equal and common, with this variety of changing gene expression?

So, how do you do this, to identify all the genes, how the genes change in the cancer cells, and which genes, and I don't know which genes, because I don't know which is the important gene. And then you go back to the old microbiology, in which I was originally trained, where you want to understand some function in a cell, where you don't know what genetic control was. You antagonize the cells, and collect the mutants, and look for a mutant that will affect a particular function, and once you've found the mutant, you work with mutant found in combination with other markers, from here you went, and then you've got the gene. Then once you've got the gene, you try to understand what the function was. Because this gave you the possibility of looking for a protein, using other methods.

So, how can you do this, you cannot take cancer and a normal cell and use mutations and a whole array of genes and then try to find which ones are those expressed in cancer cells. So, the only way is to know what the genes are, and then from the genes you go to the phenotype of the cancer cell, that's the logical point.

But as I pointed out in the article, this is the process you would use in any system which is highly heterogeneous. For instance, if you wanted to know about the key cells and the key genes in the function of the brain, where you have thousands of different cell types all mixed together. Well, the same approach would be valid. When you know all the genes, you look for the cells where the gene is at, said in a simple way of course, it's not a simple thing. But I wasn't concerned with the practicality of the thing, rather with the logical approach.

COOK-DEEGAN: If someone had had the idea at that point, in a reliable method, which we still don't have, but people are thinking about, had presented you in 1985 with the idea of, "well let's not do the whole genome, let's do CDNA's, or let's get some way, an intermediate stage"..

DULBECCO: Well, this takes time for these things to evolve. I presented the extreme case, never the practical case, everyone understands that. You have to get started the ball rolling, and then you talk about it. The reason that I didn't think the article.. the same generality could be obtained through CDNA, is the CDNA's are expressed in a variety of cells, and you don't know in which cells. And there are cells that you don't know how to get them and extract the CDNA. You think of the early stages of development of the embryo, where one cell is probably different from any other cell. So how can you find this out? Again, you have to start with the genes and then you can find out. So, that's my skepticism. No, I'm sure CDNA is a tremendously powerful method, you can get maybe half of the genes this way. But I don't think you can get 100%. And maybe the most important ones we won't get, because they are expressed in small amounts, and so on.

COOK-DEEGAN: That in fact relates to something else that I wanted to ask you about, and that was in fact from your book, "The Design of Life", in fact I'm planning on quoting this. You kind of define life in here, "life is the actuation of the instructions encoded in the genes". I wanted to ask you to elaborate on that for just a second and then I'll go on to more of these historical questions.

DULBECCO: Well, let me see.. I know what the argument would be, the argument would be that in addition to the information that exists in the gene, you have the input you get from your environment. But, this is discussed later, in fact, in the book. But on the

other hand, even that, you see if you do not have the genes which prepare the substrate on which the environment can act, the environment can't do anything. Let's take an example: children born here learn English, children in China learn Chinese. Obviously, which language they learn depends on the environment. But they both must have a structure, a logical structure in the brain, the network, which allows them to learn a language, and that certainly is made by the genes. Because you can see that animals obviously don't do so, so there are the differences.

COOK-DEEGAN: One thing I, the other major thing, we've talked a little bit about the Science paper, the other major thing I wanted to get an understanding of from you is how the Italian program got launched, because that happened very quickly.

DULBECCO: Actually, that was born at that particular meeting in Washington. I will try to find the date. The reason is, I gave a talk in the morning, and I remember that I got into an argument, first it was (Bob Garlo? Gallo?), because (Bob Gallo?) was saying it would be terribly costly, so why do you want to spend all this money. And I said, if the physicists can find 6 billion dollars to build the superconducting supercollider, then why can't we find one or two billion dollars to understand all of mankind? Then there was, what's his name, the Italian physicist who's involved with the superconductor, and he got mad, he complained publicly that we should not argue among themselves, we should all fight together against the various sources of funds, and work together. I didn't mean to attack him at all, just taking that as an example, very appropriate, it seems to me.

So, then there was the lunch where (Weingarden?) talked, he picked up those ideas and talked about that, actually, quite a lot. Then there was the head of the Italian national research council, (Prof C. Bernardi?), professor (Rossi Bernardi?). He came and talked to me, and said "it's interesting, maybe we can do something in Italy, the money situation is much better than it was in the past, we have funding, we are flexible, why don't we talk about that?" And so we started talking, and we decided how it could be done, and it was clear that in Italy, there wasn't any one institution who could do it, because none had all the necessary talents and facilities and so on, but that we they could come to a consortium of a number of universities and research institutes that it could be achieved. And in fact we went through the names and so on of the facilities and we realized that it was true, so that's how it started.

It was there that we got the people together, we spent quite a bit of time deciding what it was that we should do. Because everyone has different ideas, and it's a completely new field, and I was there purely to try to facilitate, certainly I wasn't there to tell them what to do, because it's not what I'm used to doing. So, facilitating this, and finally, we all agreed to concentrate on.. actually there were, first of all, there were two focusses, one was a segment of (low mark?) toward the end of the X chromosome, and the other was chromosome 22, because there was a group which had to be in the line, in the cell line which only chromosome 22, hybrid line, human chromosome 22. But then there turned out to be there were many more people interested in chromosome X and chromosome 22, from biology. So we decided to take that.

And there is a line, a ("spown?") line, in (X-3000?), which covers just the area, and we decided we don't do that, that would be a waste of time.

COOK-DEEGAN: And how would that get translated into funding?

DULBECCO: Well, the funding is done, each institution has its own funding, because the system in Italy is this, that the (CNR?) doesn't fund the real projects, it funds units, operating units, which are groups, and they can be anywhere. So, under the umbrella of the genome project also they started the funding of, I don't know, about 15 units, that was the beginning, and finally they were funding about 30, actually. And everything.. because they had very good people working in (Yocs?) and Naples and Rome, they have (cross-bonding visual cloning?) technology, most people have it, they are very good cytogeneticists, people can isolate chromosomes, by sorting, they have people who are interested in trying to sequence some determinant area, maybe taking some hint at the different CDNA, or from (CPG island?) or from (zinc fingers?), you know, following these hints.

And in fact they are.. so you see it's, now a number of islands would be detected, a number of genes here and there based on this characteristic, and then they would try to put them together. You have these (Yak? YAC?) clones, a complete library of (Yak?) clones, this was done essentially at (St. Louse? by Shesinger?), because (Ducho? Duche?) was the one who worked there. And so, it would be then kind of natural to try to put them together, organize them.
I think also, one of the interesting things is the fragile site, which is connected with mental retardation. And, I think, it seems to me that the last time I talked to them, that they may have (cosmids?) which are very, very close, or within naturally, I don't know

what the recent developments have been, they were trying just to test this road, to put these (cosmids?) into a normal line, see whether they can make it fragile.

So, I think the project actually went well. It's not the type of project Jim Watson would like, because it's not massive mapping or massive sequencing or anything like that. It's a kind of compromise, where you try to do the things that people want to do. But coordinated, so that finally things get into some kind of.. finally emerge. So it would be the reverse of what some other authorities do, they map first, and then they find interesting things. Here, they are looking for interesting things, and then they connect them. After all, both processes are good.

COOK-DEEGAN: So the role of the government there was really just to fund things the normal way, and the genome project was really an informal kind of arrangement?

DULBECCO: Well, in this (CNR?) they have a project they call a different way, they have what they call a strategic process, project, which means that sometimes they don't know where to get it (funded?), it is approved on a temporary basis for a year or two, to see whether it is worth investing that. And then there are the, what do you call the others, which are the real serious projects, in which they invest for a long time, you see. So they start as a strategic project, and then they finalize the project.
COOK-DEEGAN: That was your first two year..

DULBECCO: First two years were strategic project, now it's become a finalized project, now it's assured of funding for a number of years, five years I think. Funding is now really very great, the amount of money spent every year is only one half million dollars, but this doesn't include personnel salaries, it only includes equipment and materials. So, it's much more than it seems, because of the way of the economies..

COOK-DEEGAN: And that money is used also to pull this group together periodically?

DULBECCO: Yeah, I don't know whether, we probably have a separate logistical fund I think.

COOK-DEEGAN: One thing I wanted to ask you about also is, you kind of as you mentioned before, you kind of started the ball rolling. I wanted to get your sense of how, over the course from the original ideas, 1985 until 1990, with the official Watson-determined starting date, what's your sense of how the definition of a genome project changed?

DULBECCO: Certainly the definition of the project has undergone tremendous fluctuations. And, I remember (Russ Dolittle?). He was at the meeting of the National Academy in Washington. And he talked, and said that when he read my article, he thought I had gone out of my mind. But then, thinking about it in time, he realized it was a good idea, see, how people change, you know.

It seems to me the first thing was being considerably positioned, it was very foregone, and then slowly, I'm sure nobody, still people are not entirely convinced or are convinced only part, and all the discussions that have taken place seem to have been very productive in terms of showing how this project could be done in many different ways, it doesn't have to be done just in one way.
There can be people devote themselves to make labs, there can be people who start the (CDNA's?) for instance, or specific features along the chromosomes like, as I said, the (CPG or the zinc fingers?) and so on. These are all different possibilities, and finally they all converge. In fact, I understand Jim Watson, that he is undertaking to get the map done, and it has to be done, there is no question, it could be extremely important, especially for human genetics and so forth, diagnosis of hereditary disease and so on. But on the other hand, I hope that still there are other directions which parallel this one, and they are equally supported, because I think the final result will only come from a concurrence of different approaches.

COOK-DEEGAN: What do you think the technical transmutation was over that period?

DULBECCO: Well, actually not as much as one would have hoped. I think the major thing that happened is the (YACS?) is a very important way of cloning, on the other hand (YACS?) also has many weaknesses, like multiple clones, which are quite frequent. But nevertheless, once one knows there is a danger, then one can cope with that. But I think there is reason for (YACS?), because they allow large.. to put together things which are quite distant. And the things like (jumping libraries?, i.e. genetic libraries?) has been very, probably exist already I think.

What was disappointing is that sequencing has not become more effective. I would hope by now we could easily do 50,000 bases a day, but that's certainly not yet the case. So, there is where I think there is lots of additional work to be done.

COOK-DEEGAN: What's your sense of, if you were to define the genome project in 1990, would it still be sequencing the whole genome, or would you change that, whole definition?

DULBECCO: Well, no, I think that, sequencing in the beginning, to me sequencing was everything because I wanted the genes, and you can not get the genes except through the sequencing. But on the other hand, one again must be sensible, which means, access the genes. One the other hand you can use (CDNA's?) to define whatever gene you can, produce (CDNA?) without going.. and then you've located this gene into the map, input into the genome. Then what do you do once you've done that, there are still lots of areas.

And of course, people say "lots of this now is junk". Well, I don't know, I don't subscribe to the idea of "junk". At least it's a record of evolution, and if what is in the genome is not utilized for genes, it's a repository of sequences which are being useful for evolution. And you can see that in the extensive use of gene conversion, mainly by watching a phenomenon where there are genes, pseudo-genes, genes which are not sequenced, which are not used for anything else, but they are drawn in and used for making active genes.

The more you look, the RNA editing, which is very exciting, one of the most interesting things, I don't know if you know, the RNA editing, it's just phenomenal, (tarantula, parasonics??). So again, you would not think at the beginning, of the sequence that you would probably not have thought of as a gene, but they are, essentially genes disguised. And you are to do something to make them a gene.

So, it's a very difficult thing. I doubt that, I could not see at the present time, anyone getting involved in the master sequencing, at the present time. Simply because, still the technology is not adequate. So what I see, is to learn about the interesting sequences here and there, interspersed with the genome too, by one means or another. Find an indirect way to identify genes, maybe through (CPG islet or zinc fingers or binding sites for RNA polymerase?), I mean the whole technology which is used now..

And finally we will be faced with what remains. What remains there would be some genes, undoubtedly, because a lot of genes would not be discovered, and there would be all the other sequences which are involved in (gentrification?), combination, translocation, selection, evolutionary selection, evolution and so on. And I think that will depend on how much interest there is in these other things, that will determine how much will be done. In the end I think everything will be sequenced, but not as a massive project, more as a stage-wise, stepwise evolution..

COOK-DEEGAN: What.. if you were to kind of summarize this five-year piece of history, what would you say were the most significant events, what are their scientific, you've talked a little bit about the scientific, (YACS?) and stuff like that, but kind of including the whole realm, including political events and all that, what do you see as being the most important things..

DULBECCO: Well.. I don't know, there are.. probably the most significant event, was the decision at NIH to take it on, because unless they had done that, it would have remained a kind of project of DOE, and it would not therefore have had the stature that it has now, endorsed and supported by NIH. And the fact seems to be there is interest in Congress, now political support in society is very important. The fact that it has become international, because many countries are involved in one way or another, again not in any terribly organized way, and this is good, I don't think too much organization is needed in this type of things. I'd think this is really the most significant event.

COOK-DEEGAN: When I interviewed you in '87, I asked you a question about "big science" that I wanted to repeat again. What's your sense of, I mean you've followed this debate for five years, what's your sense of what's going to happen to biology over the next two decades or so?

DULBECCO: Well, in a way, biology is not small science anymore. Because, look how much of science gets done, or biology gets done, in biotechnology industries. And very important things get done by technology, and it's supported by large capital funds. If you think of all the money invested in biology, between the biotechnology industries and NIH, nationally, you get billions and billions of dollars..

*** INTERVIEW STOPS 2/3 THROUGH TAPE SIDE A.

*** TURN TAPE OVER, REWIND TO BEGINNING OF SIDE B. INTERVIEW RESUMES AT BEGINNING OF TAPE SIDE B.

*** INTERVIEW RESUMES:

DULBECCO: So, now, it depends on the.. no, what I was saying is that science and biology are reaching the point where it is required, both big and small science. There are still, I'm sure, lots of very important discoveries will be made by people in small laboratories, pursuing their own interests. But on the other hand, then when you get the beginning, to fruition, to the final conclusion or whatever it would be then, then it has become big science. Because you know, the fact that it has spent, the two laboratories, which I don't know, many scientists were involved for 10 years in the cloning of cystic fibrosis gene, and spent something like 100 million dollars to do that, well to me, that's not small science, that's big science already. To me the difference doesn't exist anymore. Or at least, they're not exclusive, there's not an exclusion, it is not true that biology has been until now, until today, small science. It's really been big science for a number of years.

*** END OF INTERVIEW.
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