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

RD: Okay.

XN: You first aired your idea to sequencing the human genome in Washington, DC, on Columbus Day 1985. How did this grand idea of yours come about?

RD: The idea came because I was working with viruses that cause cancer in animals, oncogenic viruses, and these viruses had a variety of genes and, finally, it became clear that they cause cancer in the animal, because some of these particular genes were active in the cancer cells. Being active means they do produce the messenger RNA and the protein. The fact that genes of the virus were active in these cancer cells was a very interesting thing.

XN: Absolutely. So you sort of had already studied the viral genome and you thought that the next logical step would be to the human genome, is that correct?

RD: Well, I mean, the connection came this way, that we knew that cancer in men is not always caused by viruses. Actually, most of the time, it's not, so there must be changes in the cell of the body itself that somehow can cause them to become oncogenic. And in fact, the connection to this came by the fact that there is a virus that causes cancer in lymphocytes, and this virus carries a gene of the cell in which some sequences have been altered. This is the oncogene, which is actually a normal, cellular gene that has become altered. So you see, this means that there must be an enormous variety of connections between cellular gene[s] and oncogene[s]. That was what pushed me to sequence the human genome, because if you think of all the genes in the cell that have the potential of becoming oncogenic, then how are we going to identify them? Of course, there are two

ways. One way would be to study each particular gene and then work in various cell types and see where it is active or not. And this would be certainly a good way, but a very difficult, very slow way.

XN: Right.

RD: Another way is to sequence the whole genome. Sequence means to make a photograph of all the genes of the cell. And that of course, would be probably more difficult and more demanding, but the result would be much more interesting and useful. So that's where I decided that we should go to sequencing the whole genome. And in the beginning I always thought of the human genome because I was thinking of cancer in humans and my interest was to try to understand human cancer in order to possibly control it. So that was my idea. My idea was to sequence the human genome in order to be able then to explore all these sequences and determine where there are sequences that seem related to a specific gene, and then examine these and determine whether they are present in cancer cells and the type of protein they make. In the beginning there were lots of colleagues interested in the problem.

XN: Right.

RD: And…in general, they were very competent in biology. And so I discussed this project with them, and they approved, said it was a good idea, that I should go ahead, and so they encouraged me to go ahead. But then I hoped that by doing this I would stimulate some of them to start really working in that direction, but nothing happened. So, after a while, I didn't want to wait any longer, and I decided to write a paper in a journal that is read by many people. And so I prepared the paper.

XN: It was *Science*, right?

RD: *Science*. And you know the publication that I made in *Science* has a title: "A Turning Point in Cancer Research: Sequencing the Human Genome." This was in 1986. And it's very interesting, the immediate notoriety that this article had occurred because it came out the day there was a big meeting at Cold Spring Harbor for people working in cancer. They did not know of the article, so they couldn't discuss it at the meeting. But at the end of the meeting somebody knew about my paper, and he started talking of it with other people, and there was tremendous interest. That was the reason that my paper had a very strong impact, because of the connection to this meeting. So that's the answer to the question, why and how I thought of human cancer.

XN: Yes. Do you think that linking your sequencing proposal to cancer research, a pressing and practical area with a potential for direct human benefits and clinical applications, improved its likelihood of acceptance within the scientific community?

RD: Well, of course. That was the ultimate goal. It was not even discussed at the time because it was much too early, and in fact, has happened, because now we know many, many genes that are connected to cancer. And so, by sequencing the genome of a person,

studying an entire person, we can determine whether any particular gene is active or not. And so, this activity, if a particular oncogene is active, then there's a better chance that a person with that oncogene develops that particular cancer. And so, there's a way to really screen for people who are exposed to a certain cancer. And then, if there is a candidate gene like that it's also possible to counteract it in such a way that the chance of cancer decreases. So you see there is really a medically practical application.

XN: When you first came up with the idea, had you heard anything of similar proposals by Robert Sinsheimer and Charles DeLisi?

RD: No. I never heard about that. Robert Sinsheimer, he was my colleague at CalTech. We were together and I really never realized that he was interested in things like these.

XN: And so your article was, you said, generally accepted by the public. Did this happen immediately or was it sort of, slowly over time, more gradually accepted?

RD: That's an interesting question. In the beginning there was tremendous discussion and the discussion, of course, was plus and minus. In the beginning, when the paper was published a majority of people were against it because they objected especially to the fact that there was no good technology to sequence a genome as big as the human genome. And so, they thought that maybe the idea was good, but it was impractical. I remember going to a meeting at the National Academy of Science, and I had a talk there, and after my talk, a man, a geneticist, really a very well known geneticist, got up and said, "What's the point of going forward with this?" It would be like taking a tree and wanting to know exactly each leaf. And then, of course, I objected: "Well, the leaves of the tree are all equal, while the genes of an individual genome are all essentially different. And this difference causes the different effect of the genes." So I mean there are other people who didn't support this objection.

XN: So would you say that scientists were for your idea in principle, but against the big science? They would rather do it step by step?

RD: Oh yes. But you know, in the end, when they finished up what they've been doing, all these people changed their minds and in the end, they were all in favor, and in fact, they all joined the effort.

XN: What was your reaction to the reformulation of your idea into a broader initiative that focused initially more on linkage mapping and physical mapping instead of actual sequencing?

RD: Well, I mean, sequencing is an approach to mapping, because you can scan the whole genome and look for particular sequences which are connected to certain genes. So it is a way to discover the genes.

XN: Okay. So, when you proposed this idea, it sort of marked the start of the Italian Genome Program. What were your responsibilities with this program, and how did it play out?

RD: The problem with the Italian Genome Project is that as you know, in Italy, things are always done in approximation and there was no adequate financial support to do the work, so everything was done in very, very small pieces. There was enthusiasm, and they're really, really good people that got involved. I went to Italy to direct this, to get started in a very reasonable way. In effect we concentrated on a small fragment of a human chromosome and the various people took responsibility for certain parts, and they did sequencing and searched for genes of special interest, and so…this went on for several years, at a very low level, because I said the finances were very limited. Finally, after the fourth year, I think the government didn't want to support it anymore [laughter], so, that was the end of the Italian Genome Project.

XN: When you were working on that project was it difficult to balance your time between the Italian Project and your research at Salk?

RD: No, because when I went to Italy, I spent maybe ten days there. These ten days were dedicated to examining various aspects of the Genome Project. And then I came back here to La Jolla and then I was dedicated to the work of the Salk Institute. I would stay here two or three months before going back to Italy. So, my participation in Italy was very discontinuous.

XN: Interesting. So when the Human Genome Project finally got underway, what was your involvement?

RD: I didn't get involved in the Genome Project because there was so much technology and we didn't have it—the technology. So, I had to abandon it.

XN: So you weren't directly involved with the Human Genome Project, but were you able to use its fruits in your own research?

RD: Well, I knew the results obtained in other laboratories and so I considered it—I thought of that. And my ideas which developed were no different from other ideas. So, I didn't really enter in the discussion, but I followed it closely all the years.

XN: Right, and I'm sure you've seen the October 13 issue of *Science* this year.

RD: Huh? Excuse me.

XN: I'm sure you've seen the October 13th issue of *Science* this year, the one that highlights 189 genes associated with colon and breast cancer collected from an examination of over 1,300 candidate genes?

RD: When? Which issue?

XN: It was this year, actually, on October 13th.

RD: October 13th?

XN: Yes.

RD: Of this year.

XN: Yes.

RD: Okay I have to go and look because probably I have not yet seen this issue of *Science*. What was it you said?

XN: There's an article in that issue of *Science* that highlights 189 genes associated with colon and breast cancer.

RD: Oh yeah, right.

XN: So you didn't get a chance to look through that yet?

RD: Yeah I mean, no I haven't seen it really, so I will have to go and see that.

XN: How does it feel knowing that your vision is constantly becoming more and more of a reality?

RD: Well, that's great [long pause].

XN: I was just wondering, where do you see cancer research going in the future, both in the immediate future and later, once we have a better understanding of the human genetic component?

RD: Well, the understanding of the genetic component is essential for studying cancer because in cancer, see, there are so many aspects. There is the regional cancer, and then there's cancer that undergoes what is called a progression, which means, it varies, it becomes altered in many ways. And that is because certain genes become activated. So one of the important goals in cancer research today is to identify all the genes which are important in a particular type of cancer, because if we think of developing, someday, therapies really effective in the treatment of cancer then we need to know exactly all these various alterations. So, that's become a very, very important thing.

XN: Now in cancer, there are many different cell types, and you…do they, as I understand, within each tumor, different cells display different phenotypes within different areas of the tumor?

RD: Yes.

XN: Could you talk a little bit about that and maybe the genetic influence on that?

RD: Yes, in fact, the studies which have been done on cancer, breast cancer and on other cancers, show that there are continuous variations. And then you should picture all of this variation, not just that all cells are different. There is a group of cells that have the same variation, this means that a gene in one cell has become altered and caused the variation, and then as the cell multiplies all the genes that come from that have the same variation. So, this variation is clonal.

XN: And you also talked about progression, could you sort of explain…progression is the part that we don't understand yet, and the part that genes could sort of reveal, right?

RD: Yes, but of course, that's why…going and studying all the genes in that particular cell is necessary. That would really explain these changes in progression. So, for that reason, the knowledge of the genes and the genome is essential, because then you have a point of reference, and the genome would be the basis, and then you can go from the knowledge of a particular gene in the genome and pick that gene to study the cancer. So, I think that the genome has been crucial to progress in cancer research. It continues to be so more and more.

XN: How has animal cancer research impacted human cancer research?

RD: Well, you know, their genomes are different from the human genome, so the cancers are certainly different. But cancer even in animals can be used for special questions. For instance, if you are interested in a certain type of gene which is active in human cancer, then you can go and see whether it is active in animal cancer. In that case, you would have a large number of cells to use, to study that particular gene and its effects.

XN: Okay. Though your proposal to sequence the human genome did not win you another Nobel Prize, what was its personal significance to your overall career?

RD: I don't know, because in the beginning, there was lots of interest, but then so many people got involved and started. And then in the end my contribution was completely lost, because all these people were working very actively and many results were obtained. So, in a way I'm sorry that really there has been not much recognition of my work. Although I think that it was really a key to development of research in this field.

XN: And you would say that it was key because it was the first major public airing of the idea within the scientific community?

RD: Yes…and it was published so that everybody could read it and discuss, so that it started a new trend because everybody talked about this possibility, so then naturally, people got involved in doing it. There were lots and lots of people who went to sequencing the various genomes, and they made a sectioning of the genomes into segments, characterized by certain sequences and then worked on these sections. And

then all these sequences were put together to see where they had to contact so that they could extend slowly to the whole genome. These principles were used very extensively.

XN: Why do you feel that your contributions have gotten mostly overlooked? Looking back on the genome project today was it just that there were so many people that contributed that it became such a big deal?

RD: Yes. Well, you know, in a way it is a big deal, because it's a big work to sequence any genome.

XN: Absolutely.

RD: And you know, I started the idea with the human genome because I was interested in cancer clinically, but in the end, lots of people went to other genomes and now we have the sequences for almost all genomes that you can think of.

XN: What lesson did you learn from watching the Human Genome Project unfold?

RD: Oh I see. [laughter] That's a good question. Well, I don't know, nothing really special. And actually, I never really asked myself this question. Well, really, the lesson would be this: that you can have a question which is very difficult to answer, but if you get enough people involved and serious people, serious work, in the end you can get the answer. So one should never give up on a really interesting question.

XN: That's a pretty good lesson. Though it would seem an obvious strategy today, sequencing the entire genome was, at the time, a radical idea. Can you elaborate on why such a major effort would be necessary to further cancer research, and small science would be insufficient?

RD: Well, in effect the consequences of the sequencing the genomes went way beyond cancer because all genetic work is done in a variety of species so if you go and look at the literature and papers in genetics you will see that, sooner or later, the genome question enters. And the genome use is very important.

XN: So as you watched the genome project, what were your thoughts, just seeing that your idea—just a small idea—had become such a revolutionary reality?

RD: Well, you know these things happen. [laughter] And you cannot predict when you start which kind of results you're going to get, so the important thing is to be clear to your ideas so that people can understand it and if they want to take advantage of that, they can.

XN: Do you have any advice for aspiring young scientists today?

RD: Well, you know, the lesson of the human genome is there, that you take a field which is very interesting and where you can see there may be development. So that

really, I think, is the beginning. And then, to work very seriously and watch what other people are doing too.

XN: Can you sort of talk about how important collaboration was with your colleagues at the time? [pause] Can you sort of talk about how important collaboration was with your colleagues at the time? [beeping noises, RD's wireless house phone battery died; I called back]

XN: So my next question was just could you sort of talk about the role that collaboration played when you were working in this field at the time?

RD: Oh yeah, collaboration was always very important. And usually, my collaboration was with young people who came to the institute to learn, really. Usually they came from other places where they learned some new technology, and I always took advantage of that, because technology is essential in enterprising biology. And so, you see my papers always included quite a large number of young people as co-authors, and they are very important because first of all, like I said, sometimes they bring in new technologies which are very important. Secondly, they are very enthusiastic and work hard. So this is mostly my collaboration. Occasionally, there has been some collaboration with other, mature scientists for specific reasons, but this can be quite rare.

XN: Right. And also, can you sort of discuss the role of conferences at the time, and what role that played, and sort of spreading this idea throughout the scientific community along with your *Science* article.

RD: No, what do you mean? The conferences?

XN: Yeah could you just talk a little bit about your experiences at the conferences—the scientific conferences?

RD: Yes.

XN: Like the one at Cold Spring Harbor, for example?

RD: Well, I think that some are really very, very good. I think the Cold Spring Harbor meetings are really excellent. So, in one of those meetings I got up, I went to talk about my work. And I took advantage of the questions, the comments, that I received. It's a great occasion because it's a kind of friendly environment full of people, you really know them. And so then they can come and discuss and you learn quite a lot. And so, I'm very favorable to these meetings.

XN: Is there anything that you would like to elaborate upon, or clarify, or explain further, regarding your role in the early stages of the human genome project?

RD: Well, I think that my role was just this paper—"A Turning Point in Cancer Research"—in *Science* because that was known and discussed by many people so there, the point was made there. Then, after that of course I did follow up the developments and occasionally I suggested new approaches. So, I became part of it, without being really a major force.

XN: And, are you still doing continuing cancer research today?

RD: Well, I've been doing that until maybe two years ago, but then two years ago I had some problems with health and also [laughter] I broke a humerus by falling. So, you know, I'm an old man. [laughter]

XN: Yeah, it'll happen to everyone, I'm sure—including me, sometime.

RD: Yes.

XN: All right, well, if you don't have anything else to clarify, I've gone through all my questions, and I thank you so much again for your time.