

Jean-Philippe Deslys Interview

Office of NIH History
Oral History Program

Interviewee: Dr. Jean Phillippe Deslys

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Jean-Philippe Deslys Interview

Interviewer: Tell me about your educational background.

Interviewee: I wanted to do medicine so I took the fastest way to make my medical studies. At the end of my studies I had compulsory military service. So I had to go to the army for my classes and I took this opportunity to go into a lab.

Interviewer: And what year was that?

Interviewee: It was in 1985. So that was my first contact with TSEs and prion disease.

Interviewer: Who did you work with?

Interviewee: Dominique Dormont who was at this moment a Captain and after that he upgraded regularly. And so I was incorporated in his team. He gave me the choice between three subjects. One was HIV, but he told me that I would have to follow the protocols. There was no liberty, so it was not interesting for me. The other one was on laser, and here too there was no liberty because these were very expensive devices. And the last one was on what they called unconventional viruses or agents and on this particular subject there was nobody and I had full liberty to do what I wanted, so I took it. And it was interesting because it was a change. He told me that nobody knew exactly what it was, that it was hydrophobic, difficult to purify. So it was a real challenge. I had just submitted my thesis in medicine on growth media for bacteria, which had problems of lipophilic immersions and things and were quite unconventional, too. So I thought it was a good idea. I began on this subject and very soon after that there was in France the problem of growth hormone, because the first case was published. It was in U.S., the first one, in 1985.

And then the government wanted a reference laboratory to test the different protocols of purification of growth hormone to validate them and take measures. No lab in France was able to do that so only this lab could do the experiment. I was with Dominique Dormont and I validated the different protocols of purification of growth hormone, meaning the one of Pasteur Institute, and the ones of the other companies.

Precautionary measures were suggested by Dominique Dormont including urea treatment as a final step of hormone production. For the moment, to my knowledge, all the batches of growth hormone produced after mid-1985 which included these steps of decontamination have not been incriminated in contamination of children while for growth hormone we

have a big problem in France because we have the main cohort in the world, with almost one thousand children exposed to the risk between the beginning of 1984 and mid-1985. It is a critical period and among them almost 80 have already developed the disease and each year we have new cases. So I saw the first case in France in '89. It was the youngest case in the world. So it was a very bad sign for the future because the shorter the period of incubation, the higher is the dose of infection, so it implied that other children had probably been contaminated with the same batches of hormone.

Interviewer: So this is still a continuing problem in France?

Interviewee: Yes.

Interviewer: New cases are still occurring every year.

Interviewee: Yes, but which are linked to the same contaminating event, meaning contaminating period. All are linked to the same hormone produced by the same manufacture. In fact it was the Pasteur Institute. It's somewhat the same story which has been reproduced in U.K., U.S. and in France. Each time it was growth hormone purified by non-industrial laboratories.

Interviewer: Why do you think that is? Different sorts of laboratory practices?

Interviewee: Yes, clearly, that's our conclusion; it's not at all the same mentality, the same habits. In industry they are very strict about following good laboratory practices. And so it diminishes the degree of liberty, but increases the safety, and that's the goal of industry. So we think it's why the same phenomenon occurs in the different countries.

Interviewer: Because you're right it seems like it was a similar situation in all three countries. It was something that they didn't regulate in the same way they did other pharmaceutical products.

Interviewee: Exactly. It was an orphan drug. It was done only to save lives but there was no market, so that's why industry was not pushing so strong and there was another problem which was linked the limitation of the hypophysis, so limitation of dollars. So somewhere it was completely atypical. People began to do that not for money of course, and after that it was accepted by regulatory authorities as an exception.

Interviewer: It was something that was helping people and so it was something that became accepted practice.

Interviewee: It was a weight of history after that.

Interviewer: Do you think that there is any way that problem could have been foreseen or do you think that it seemed so unlikely that it would have been difficult to imagine?

Interviewee: No I think problems could have been foreseen, but people who were in of this did not believe that it was possible. This is something that is constant in the different crises: before the first crisis, people don't believe that it can be possible.

Interviewer: So there were warnings?

Interviewee: Yes. I remember that in the report of the inspection concerning public health which was a very hard report of the practices of Pasteur Institute and other things they clearly found suggestions four years earlier saying be careful you could have Creutzfeldt Jakob disease or this kind of things in brains, etcetera. But as these were rare disease and the problem had not occurred before, these suggestions were not taken into account because they thought it was only a dream.

Interviewer: So do you think it's possible that in that critical period when it seems like so many people were exposed, that '84 / '85 period do you think it could have been just one donor that had Creutzfeldt Jakob disease?

Interviewee: I can't say too much about this because I'm involved as an expert in a judicial trial. It's difficult because from the mentality today, it is very easy to judge what would have been needed. But at the time, it was completely out of their mind. So they were completely focused on the fact that they wanted growth hormone, that it was a miraculous therapeutic and everybody was asking for hormone and did not want to hear about side effects. You have the same problems still today, even during the Olympic games. Everybody knows that it's a very bad thing for athletes to take steroids and different things and they're going to pay in terms of fertility and many things, independently of the fact that it is forbidden and in spite of this they continue.

Interviewer: And you don't see the downside until there's a crisis.

Interviewee: I think that you come to a very important point - the difference between the evolution of the risk assessment and the risk perception. The risk perception can completely modify these things. I remember a conference that I was doing in front of specialists of transfusion. So they were all educated, they were doctors, and explained to them the problems of prions in the muscle, etcetera. So the conclusion is that if there was something in the muscle it was very limited. And the conclusion of one of the doctors was, "I will stop eating meat today." I said, "Why? I explained that the risk is limited, and what are you doing?" She was smoking. And with her

education she knew perfectly well that cigarettes are very dangerous. In spite of all her education, she told me that she agreed that logically it was true, cigarettes were more of a risk than prions, but she did not feel that way. If this can happen with such educated people, then with the public, which has no scientific background, no medical background, any fear can develop.

Interviewer: How do you overcome this sort of problem?

Interviewee: It's a problem of communication and, unfortunately, scientists are not prepared to communicate. You know perfectly well that journalists don't speak of trains that arrive at the right time. By definition they always point the finger at bad news and never speak a lot about good news. It's what I fear for the situation in U.S. People for the moment are doing exactly what we have done in Europe, what we have done in France and in all the other countries, even in Japan, first to negate the problem.

Secondly, there is nothing to see. And then the public is listening to the authorities saying there is no problem because it's so much simpler in communication to say there is no problem than to explain things. This over simplification is a terrible weapon with a terrible boomerang effect, because when the problem occurs then you have the other excess which appears, and then everyone is panicking and saying people were liars, they have hidden the truth, we were not informed properly and then you have a big crisis and that's exactly what happened in all the countries until now.

Interviewer: What would be a better way of doing it? If there was another country that about to have its first cases what would you advise them to do in terms of communicating and managing?

Interviewee: Now the situation has evolved because now you have a counterargument with the fact that there is not a dramatic increase in the number of cases of vCJD [*variant Creutzfeldt-Jakob disease*]. The recent experience of almost ten years now since the first real case of vCJD -- the official case was in 1996 but the first one really began in 1994. Now it would be easier for authorities to avoid an over-boiling of things. It's not easy because they can say look in this country where they had the problem ten years before us.

Interviewer: Where as they couldn't do that in Britain --

Interviewee: No.

Interviewer: Because they didn't know what was going to happen.

Interviewee: Even in other countries because at the beginning during the first years there was the curves that had a dramatic increase so we had no idea if it would be less than 100 or more than half a million cases in humans. It was crazy. And that's a big concern. Politicians are waiting for scientists to say it's black and white. Science is never black and white. It's always gray more or less. The more you give information to be accurate, the more difficult it is to communicate. People want things simple. So when you begin to explain things to people, it doesn't matter how much you explain, at the end the question is always the same one: Well you seem to be honest, so in practice, do you eat meat or not? Dramatic but it's always the same scenario. And if you think about it when you go to see your doctor he explains to you very complicated things about your disease, the evolution, etcetera, and at the end, if you don't trust your doctor, you change immediately, but if you trust him at the end you say, "Okay, you are in charge of my health so tell me what I have to do," and there is this oversimplification. And this is a human phenomenon that I have observed. I think that the population and the politicians want the same thing from the scientists. The difference is that scientist are not prepared for all for that. Doctors are prepared because unfortunately they have to deal from the beginning of their studies with disease they can't treat. There is another dimension that we have in medicine and that is that at least at the beginning we are not expected to try to make money on their disease. There is no economical impact. While in industry, people are immediately expected to try only to make money. And unfortunately, as you immediately speak of billions of dollars. In front of that even the most honest man tends to forget his mind. So it implies that people do not believe what this industry is saying.

Interviewer: They're suspicious.

Interviewee: They are suspicious. And scientists are not clear. They are not prepared to communicate and they feel very bad. It's very special to discuss with a patient and to take charge of the suffering and all the psychological impact. Even in medicine, though, people are not prepared properly. Unfortunately doctors are becoming more and more like technicians of medicine and not anymore doctors taking charge of the suffering of the patient. What people are wanting is the opposite. They want to be able to trust people and to know that they're going to do their best.

Interviewer: How is it different trying to communicate with a politician or someone who is going to look at things from a policy or a legal angle versus trying to communicate with the public or a journalist?

Interviewee: It depends on the context. On prion disease it's a very special thing because all of them have eaten the same thing. So they are concerned the same way. If I want to be a little nasty I will say that the politician does

not think as a journalist who does not think as a consumer. A politician thinks in terms of the next election. So unfortunately you often have the feeling that if the decision is good only for something which we will cure in ten years he doesn't care, because it will be out of his scope of his politician life.

Interviewer: So if it's something that is a long-term risk, and often times these are long term when you're talking about TSEs [transmissible spongiform encephalopathies] because they take many years of incubation before they appear, so that can be a problem then when you're trying to communicate the importance of a situation to a politician.

Interviewee: Yes, but things have evolved since justice came into this field. Before AIDS in blood, politicians were completely untouchable, including highest functionaries in ministries etcetera who are not politicians, who can be doctors, councilors of the minister, etcetera. Since the scandal over contaminated blood they have been charged. There were trials. Their careers have been ruined. So now there is the other excess meaning that they tend to use the precautionary principle as an umbrella. I have the impression that the precautionary principle is not used to protect populations but to protect politicians and decision makers from accusations and charges. But that is the feeling that I have regularly.

Interviewer: In France there were both high ranking officials and scientists who were brought to trial as a result of HIV contamination of blood? And so you feel that that had an impact?

Interviewee: A terrible impact.

Interviewer: So what about the relationship between scientists and officials? Do officials look more to scientist for information since then or less? Are they more interested in knowing about science?

Interviewee: They are more interested in having reports justifying their decisions.

Interviewer: Okay given that that's their interest, what's it like when you are at a governmental advisory committee meeting?

Interviewee: This committee, which was headed by Dominique Dormont, the Interior Ministry Committee, was designed, in this context of complete uncertainty, to give neutral advice on which politicians could take regulatory measures. What I've observed as a member of this committee, as an independent expert, was that there is a game that the politicians play. When they don't want a response they don't ask a question, and when they need something they ask a question and tend to use the reply to say that's what the experts have asked.

Interviewer: Wait, say that again.

Interviewee: When they want a response, they ask a question. For example - is it necessary to destroy brain? But the role of expert is to make a risk assessment not to do the management. The management is the field of the politician. He has been elected for that. He has a responsibility of that. We have no legitimacy in front of the population. But the game that we have discovered is that the politicians try not to take the responsibility but to put it on the experts. And regularly the experts say, "No, no this is management. We do assessment, and then you take your decision."

Interviewer: So they would try to ask questions in such a way to make it look as though you were making a decision about which management option was better.

Interviewee: I could take a theoretical example, you make a risk assessment and you say, "Well if you take this measure would involve one death per year." After that, do you take the decision to avoid this risk or do you say that the economical impact and all the other factors are such that it's not a good measure. For example if to avoid this death you need so much money that you are not going to protect two million people and then because of lack of protection you're going to lose 100 people. That's a balance of risk. And moreover we have no idea of the other implications in the other fields.

Interviewer: Right because you're only doing TSEs.

Interviewee: Exactly. So that's why it's really the responsibility of the decision makers to make the balance between the differences and then to take the decisions.

Interviewer: How do you communicate probabilities to a politician?

Interviewee: The problem is that with the example that I was giving it's possible only with diseases that you know and after several years you see this measure has this impact, these measures have this impact and so that's what they are doing with HIV. With our diseases, the problem is we have no idea of the future impact. So we could only say if it was for us a good direction or not, but you could not go very far in the implications. Now you have enough years of experience.

Interviewer: How do you communicate that kind of uncertainty to a politician or any official anyone who is in a position where they have to make a decision whether or not enact a certain measure? How do you communicate to them the uncertainty?

Interviewee: It was communicated by the system. This commission had questions from different ministries. So we were doing reports corresponding to these questions and after, they analyze the reports and make their own reports for the ministries, the decision makers that make the decisions.

Interviewer: Let's say there are different potential outcomes. Let's go back to the example about prions in muscle, and there are just beginning reports coming out about the level, very, very small levels in human muscle in sporadic cases, know it's been shown to be in sheep scrapie, things like that. When there are different possibilities for the level of risk and you can imagine different scenarios, how do you communicate that?

Interviewee: You make a worst-case scenario and you begin to calculate on this basis. So, for example, when you detect nothing in muscle, which was the case previously we don't say that there is nothing. We say that it is under the level of sensitivity of the different methods which implies that, in this case, it is 10,000 times lower than into the brain. So like that you can do calculations. We had this kind of thing for example for milk and that's why when you do calculations on milk from cattle it seems to be safe, but on sheep you have a problem because this milk contains a lot of cells and these kinds of calculations do not allow you to say that milk is safe. So that's a problem.

Interviewer: But in general you tend to deal with these sorts of situations where there are multiple possibilities by calculating a worst-case scenario.

Interviewee: Yes.

Interviewer: What about the argument that by always using the worst-case scenario you are prejudicing the interpretation?

Interviewee: When you calculate the worst-case scenario you are allowed to make more optimistic projections. But what people are asking is always: "is it safe so?" To reply to this question with a guarantee is impossible. So the only possibility is to address the worst case scenario.

Interviewer: Right I see. So that's usually what gets communicated from the committee to the officials is the worst case and then they can decide based on that what they think should be done. Okay so then to go back, if you don't mind if we go all the way back to what we were talking about before when you were working for Dormont. What was it like to work with Dormont? You said initially when you started working there this was something that nobody else had worked on the lab, right? So you were the first person really delving into this area?

Interviewee: All of the people that worked in the lab there was a tradition on this subject in the lab. So of course there were students before me, but when I came there was nobody.

Interviewer: There was nobody so it was just you and how did you decide what to work on? I mean you mentioned the growth hormone crisis came up right after.

Interviewee: The growth hormone was one thing because it was a requirement of the authorities and for the other things I was free. So I decided by myself and what I decided to do was to develop new techniques because I thought it was via development of new techniques, more sensitive, more accurate that we would find new results and understand new things.

Interviewer: And when you say new techniques, specifically new techniques for what?

Interviewee: I developed, for example, sensitive and rapid western blot. While it was very time consuming, it was equivalent to what is done now with rapid western blot that you see.

Interviewer: What were the changes that you made to the protocol to make it more rapid, more sensitive, easier to do?

Interviewee: I've played on the buffers, on the migration, on all of the steps in fact. But that's personally my way of working. So analyze a protocol and I try to imagine where I could improve it to solve different problems.

Interviewer: So you developed a western blot; what other things did you work on at the time?

Interviewee: My year of military service was up. So after that I began back to work. I worked in two laboratories - one in the hospital and the other Dormont's. I was still there because I was fascinated by the subject. So I developed other techniques such as gas chromatography and development of media.

Interviewer: Gas chromatography for detection of the prion protein?

Interviewee: No it was on bacterium because at the Hospital I was working on bacterium.

Interviewer: But you said you continued coming in and working with Dormont?

Interviewee: Yes. Until 1989. In 1989 I had the possibility to have full time - it was officially two half times. In fact it was two full times, so I finished at one or two o'clock every night.

Interviewer: Oh my gosh! Sounds awful.

Interviewee: And I was not paid in Dormont's laboratory.

Interviewer: Really!? You were doing it all purely volunteer.

Interviewee: Yes, I was paid only at the Hospital. In 1989 I had the possibility of a full time position in both laboratories. So I chose prion disease because it was more mysterious and fascinating for me. My colleagues at the hospital told me that I was crazy because nobody was finding anything on this and it was safer to go on known things and to have a scientific approach. But I have always been interested in challenges.

Interviewer: And this was a challenge.

Interviewee: A real challenge at that moment. Nobody believed in it.

Interviewer: In those early days, what did you think about the infectious agent? Prusiner's prion hypothesis had only come out a few years earlier, what did you think at that time about it?

Interviewee: I thought that it was not the PrP.

Interviewer: You thought that it was not the PrP?

Interviewee: Yes. My lab was not favorable to the protein only hypothesis and unpublished data they had indeed didn't go in this direction. So I made a bibliography. I was fascinated by the strains and indeed it did not fit with the prion hypothesis.

Interviewer: At the time what was your thinking about why strains didn't fit with the prion hypothesis?

Interviewee: Because you had only one protein and twenty strains. And the explanations of Prusiner were not convincing. He was denying the strains in order to maintain his hypothesis, which was not for me the scientific way of resolving a problem.

Interviewer: As time has gone by have you become more convinced that PrP is the infectious agent?

Interviewee: No I still think that there are other possibilities. Prusiner himself had to modify his theory and to admit protein X or something else. So at the end I think he derived an enormous advantage from working on the protein because we see the protein. Colleagues told me that they not understood how I could work in this black box without knowing what I was working on. Indeed all of our experiments have been conducted having in mind that

strains were completely fascinating and that we are to try to understand how they work. And that's why we were in a good position in 1996 because with Corinne we had inoculated monkeys, we had inoculated mice, to try to understand what was happening with the strains, and notably with BSE because it appeared to be different and we wanted to understand the phenomenon. In fact, depending what you have in mind, you don't construct the experiments in the same way. So when you believe in the prion hypothesis you construct everything focusing on the PrP and that's why I think Prusiner for many years – I think that it's only in 2000 that he finally accepted the BSE was responsible for vCJD. During four years he pretended in front of millions that the BSE agent was not responsible for vCJD. For me when a hypothesis induces such false conclusion we have a problem with the hypothesis. The comparison I took at this moment is that perhaps Newton's laws are false, but to live on earth they are perfect.

Interviewer: Right exactly you don't have to know everything in detail of what's going on to get a general feeling.

Interviewee: I always insist with my students that I accept perfectly, as Bruce accepts, that people think it's a protein infectious agent but I don't want them to make all their conclusions based on this. There is PrP. There is an infectious agent which perhaps is PrP, but perhaps is something else, and from that you can explain things. If you focus only on PrP as doing everything then you come regularly to false conclusions and that's a problem.

Interviewer: What did you think at the Neuro-prion meeting when Prusiner presented his data about polymerizing the synthetic PrP and then creating infection?

Interviewee: These are very interesting data. I think that he has convinced more people than before, but I'm not so sure that it is a reality.

Interviewer: So what to you would you need to see to be convinced of the prion hypothesis?

Interviewee: I think that we would need to be able to construct strains *in vitro* and to pass them to normal animals.

Interviewer: So non-transgenic animals?

Interviewee: Yes, because with transgenics you really don't know what you are doing. If you take the virino hypothesis, which for me is a very interesting one even if perhaps it is completely false. But it has the advantage of explaining strains and maintaining the interest of PrP. I would say the modern virino hypothesis because you know that Dickson was fighting

against Prusiner so each of them would not want to hear about the other one.

Interviewer: So you think a virino hypothesis in which the PrP protein –

Interviewee: Is a core.

Interviewer: It is is a core. Is a part of the agent. Is an important integral part of the agent but that there's something else with it.

Interviewee: What I think, derived from the virino hypothesis, is that the agent can replicate independently of PrP. So when PrP is there, it acts as an effector of virulence, and so it explains why these agents are so difficult to destroy. But by itself it can replicate and that could explain what we observed when we transmitted BSE without PrPres. So not only were the publications that were written on strains very puzzling, but when we constructed our own experiments to try to solve this with BSE we observed this phenomenon, transmission without PrPres, and because it was the first time that it was observed, for us it was fascinating. It demonstrated that the prion hypothesis as explained by Prusiner is not a good one.

Interviewer: So that to you is the most convincing experiment from your lab that the prion protein might not be the integral component of the agent?

Interviewee: Exactly. The agent was able to transmit, to replicate, and to kill the neurons without holes in the brain without any accumulation of PrPres. So this complete disassociation between what was claimed with the PrPres being the infectious agent responsible for neurotoxicity and what we observed. Clearly for us it was an enormous thorn in the heel of Stanley Prusiner. I don't think that what we observed is linked to non-PK resistant PrP which would be linked to something else, I don't know.

Interviewer: Okay so you're still open to the possibility -

Interviewee: I keep an open mind. But clearly there was another possibility which was that a transmissible infectious agent, which could be very common, but which could become virulent only when it acquires the capacity of transforming the PrP of the host because then it's not destroyed fits better. And when I compare that to the already existing hypotheses, it fits with the virino hypothesis. In a modified way, but it is the closest one. So for me there are two good hypotheses. First, the virino hypothesis, that there is a nucleic acid or something which can support the strain tropism. Second, that there is specific information or something derived from PrP. But PrPres by itself is not an infectious agent and when you listen to Stanley Prusiner he always says, "Well, PrPres has a byproduct. It's PrP*

molten globule which is interesting.” He’s evolving. So I think that somewhere the two theories are going to merge at one moment, but I want to keep an open mind because I still don’t know if the infectivity is a nucleic acid, a protein, or something else.

Interviewer: At what point did Corinne start working with you?

Interviewee: She came in one year later, in 1990.

Interviewer: From almost the very beginning she was working with you?

Interviewee: She came as a student. She had just finished veterinary school so she was very young, she was twenty-three or something like that. And so we started together for the experiments and that’s an excellent period of my life because there was a fantastic complicity between us. We thought in the same way and it was very refreshing for me, because before I worked a lot alone so it’s a little tiring, or with students but who had less possibilities than Corinne. So there was not this complexity, there was not this intellectual challenge. There is also the fact that she had courses which were not only scientific. The other students had only had science. And so with Corinne I had this possibility to speak with somebody who understood the limits of the things because in veterinary science, as in medical science, we are losing a lot of patients or a lot of animals because we don’t know how to treat them. So first we need to develop a certain humility. Scientists imagine that science can solve everything. Veterinarians or doctors know that medicine or veterinary science cannot treat everybody, clearly not, and we are in front of many things that we don’t know how to solve and the mind is not educated in the same way.

Interviewer: So in terms of caring for primates or higher-level animals especially, was it useful to have someone with skills working with animals?

Interviewee: Immediately she loved to work with animals, me too, and the problem is that there was no budget. But fortunately our animal care facility operator, he’s a fantastic guy and he helped us a lot. So he found for us monkeys that were not used anymore by other teams.

Interviewer: So then you didn’t have the upfront expense of purchasing.

Interviewee: Exactly. So we managed to begin our experiments. We did them secretly because unfortunately Dominique Dormont was not following us. He thought that there was no interest in doing what we were doing.

Interviewer: Really!?! You’re kidding? So you’re talking about the inoculation of the primates with BSE?

Interviewee: Yes.

Interviewer: So you had presented the idea to Dormont and what did he say? He said he wasn't interested? Why?

Interviewee: But in fact in all the ideas that we presented Dominique Dormont was a very nice guy but I think that he was not made to manage science because he had not a feeling of when things were good or not. He always waited to have information from other laboratories. He was not confident in from what was produced in his own laboratory. It comes, I think from the fact that he was not an experimenter. All of his cursors had been done in books and he had not published anything by himself in fact. So he had done trials. He worked in Gajdusek's laboratory. He went in Charmaine's on HIV also. So he did it as a student, but somehow he never became adult at this level and so he was very reluctant. That's my point of view.

Interviewer: Well that must have been hard though for you.

Interviewee: Yes. It has been very complicated because we were not sustained at all. We were alone.

Interviewer: What was your motivation?

Interviewee: We believed in what we were doing.

Interviewer: Of course. But with these early studies, were there any that he supported?

Interviewee: Oh yes there were several. We tried to infect cells, that was the requirement from Dormont. And all those were not lucky. In fact the problem is that all the experiments that he asked for failed. And the experiments we decided to do behind his back turned out to be successful.

Interviewer: So what else did you work on?

Interviewee: BSE in mice and also all the controls with scrapie, with other things. We had different models and I worked a lot with Corinne on western blot improvement. So I was very proud, because we developed a very sensitive western blot.

Interviewer: The western blot that you developed, the technique that you developed, is that something now that is used by other laboratories?

Interviewee: Now it has been given to Bio-Rad. It has been improved more, given to Bio-Rad, because in fact what I had discovered at that moment has been discovered by others, but several years later... And so the confirmation test of Bio-Rad is not as sensitive as the Elisa.

Interviewer: Okay so because the Elisa is the one that you developed with Grassi.

Interviewee: Exactly.

Interviewer: But then the western blot that Bio-Rad sells is based on the western blot protocol that you worked on over the years and improved and improved and improved and now that's the confirmatory test for the Elisa. When did you get to know Jacques Grassi?

Interviewee: We met him in 1996 during the summer I think because of the crisis. So he came to visit us because he wanted to develop antibodies.

Interviewer: So he had the idea of wanting to develop some specific antibodies for detection.

Interviewee: Yes because his specialty is the development of antibodies and he had done immunometric assays for other antigens. So it's really the specialty of his lab.

Interviewer: So what part did he do and then what part did you do?

Interviewee: In fact here, too, we had a small problem with Dominique Dormont because he did not want us to develop that. So what I wanted to do was to develop antibodies against bovines of course, but Dominique Dormont said no because other groups were on that. So he accepted only on man. So I decided to do it on hamsters for two reasons. One is because I thought that because PrP was similar in many species, so I hoped that I would find similar haplotypes. Second because I knew that hamsters had higher quantities of PrPres. At least 10 times higher. So at the level of purification and immunization of animals, after that I made the bet that this model would give the best results. I had another weapon which was that I had identified all the antibodies which was not used in the German lab. They had been developed by Cressman, I've forgotten her name, in the lab of Hunsman [sp phonetically]. We had collaboration with him and I understood that the team was disappearing because each five years they change position. So I saw there an opportunity as I knew that Jacques was perfectly able to culture the cells and to extract the antibodies because this is very classical for professional labs and the lab of Jacques, he's equivalent to a professional lab for production and purification of antibodies. They are very good at it. And so I managed to negotiate with the Germans the fact that as they were going to lose their specialist for antibodies, better than keep the cells in liquid nitrogen to make material transfer agreement and to obtain the cells and to purify the antibodies with Jacques and to provide them after that with purified antibodies. And to have also the opportunity there was a commercial interest to use the

antibodies. And as I had tested their antibodies I knew they were very good and it turned out that despite negative comments of my boss and all those in the CEA it was true and so they accepted. And like that we were able for the first time to have antibodies that we could produce at a high rate and so these were the first antibodies which were –

Interviewer: So there were already monoclonals at that point

Interviewee: Yes.

Interviewer: So there were already monoclonals from Germany that were just frozen, waiting to be used in a sense, and the people who had created them had been forced to move on. So you knew that they were good antibodies, but when Grassi came to you, you knew that he had the skills –

Interviewee: The technology to – because I asked Dormont to develop this technology but he refused.

Interviewer: The technology to produce monoclonals?

Interviewee: Exactly. So Jacques Grassi was really an excellent opportunity for that. And so he produced the antibodies and, in fact, he was the first one in France to be able, after that, to distribute these antibodies to all the research groups.

Interviewer: Were they all made against hamster?

Interviewee: No these were made against recombinant human PrP.

Interviewer: Okay, then Jacques Grassi made his own antibodies against?

Interviewee: So these were the first ones because they were already done. And the second were what we called after that SAF because they were made from purified hamster brains. So PrPres that was purified here. We immunized the mice and when mice were correctly immunized and boosted, then Jacques came and recovered the spleens and used them for fusions and made the antibodies and so with that he made the first set of antibodies.

Interviewer: That were made against hamster SAF.

Interviewee: Exactly.

Interviewer: And then those could then be distributed in France, they were shared amongst other researchers.

Interviewee: Exactly.

Interviewer: Like who? Like what kind of groups – which groups did you share?

Interviewee: All those who wanted them.

Interviewer: So you were completely open. You would give them to anyone who wanted them –

Interviewee: For noncommercial use.

Interviewer: Okay. Did they have to pay you a fee?

Interviewee: No.

Interviewer: There was a material transfer agreement though, right?

Interviewee: No I think it was free because we managed after that to be financed by the Geis Prion to do this kind of thing.

Interviewer: To make them available?

Interviewee: Yes. Money was distributed to the different research areas by the government.

Interviewer: So the government, the French government, provided to be able to produce –

Interviewee: No it provided money for research, and in this budget one part was taken to make antibodies available. I was coordinator of the antibodies.

Interviewer: But they were then being produced in Jacques Grassi's lab?

Interviewee: Exactly. They were produced there and then after that was interest of the network given to different labs including mine of course and tested by western blot, by immunohistochemistry on bovine, mice, hamsters, to know exactly what these antibodies could do. So that was the general idea.

Interviewer: And then what happened?

Interviewee: And that gave me the idea of the network because I saw that even labs that were competitors, putting them in a good system could create very efficient collaboration.

Interviewer: Were you surprised initially when you saw that people were able to collaborate?

Interviewee: Yes, at the beginning, because the money was given in a compulsory system. We had to collaborate and I did not like it, because I don't like obligations, but it turned out that scientists were adults, contrary to what is regularly said or seen, and a consensus emerged very quickly, in a good way, on what we could share. And that's what we are pursuing in the network NeuroPrion. We are competitors but there are things for certain tasks it's more intelligent to share things and to work together and it is at this level that the network is very efficient.

Interviewer: So in general is that sort of the basic framework that you have for how the network should work?

Interviewee: Yes. Exactly.

Interviewer: So basically people have a motivation or reason to be in the network on even just a very basic level because they're going to get something out of it, they're going to get access to certain resources. Whatever the group can decide that will be made available for sharing and that sort of thing. So you've got this sort of on the one hand the motivation, and then once you get people involved then they might give something too.

Interviewee: Yes and that was the first thing. And the second observation that I made is that it was a fantastic tool to overcome the blockages, because when you have a group like that and that one of the guys says, "Yes, but this reagent I want to keep it for myself." I say, "Okay you keep it, but there is another one who can give it." And so like that you can go to the group and the first one understanding that he cannot block the system then thinks differently and adapts and then a real collaboration appears. And this was really an excellent experience. So we saw people who were reluctant in the beginning and after who want to enter into the system.

Interviewer: So at this point in time you had these antibodies that you were able to share, and then what did other people share? What did it bring other people into sharing – or how did it bring other things into the –

Interviewee: All the antibodies were shared after that.

Interviewer: So all the antibodies produced in other labs were then also shared freely?

Interviewee: Not all, but others. But as we provided for free our own antibodies it was difficult for them to provide nothing. If they provide nothing then all the experiments would be done only on our antibodies which would be then the only ones referenced. So it became their interest to do the same thing. And there I discovered the interest of this kind of collaboration, and that's the idea which is behind the network NeuroPrion.

Interviewer: What about outside of France? Initially – I mean back at this point in time in the mid-90s I guess, were you also sharing antibodies with groups in other parts of Europe and in the United States or did it start out with just France?

Interviewee: No, it was just France at this point.

Interviewer: Okay and other – certainly there are some groups like the New York group with Kascsak that have been very good about making their antibodies available, but then there have also been groups that don't make their antibodies available and how do you feel that affects the system?

Interviewee: It's not a problem if you have other possibilities because the absolute reagent does not exist. There are always other possibilities.

Interviewer: Especially when you're talking about antibodies. You can imagine multiple antibodies to a similar epitope.

Interviewee: The advantage of this system is that it avoids to oblige people to do things that they don't want to do and it helps them to change their mind understanding that they will have more interest in collaborating than in staying alone, and by collaboration all the group is strengthened. So that's really the interest of the system. So you can like that move people without forcing them to anything. You give them opportunities. They take them or they don't take them. That's their entire liberty.

Interviewer: So that's when you said you started forming ideas about collaboration being a good way to go, but how long was it between then and were there any other permutations before the network of excellence?

Interviewee: Now during this time you had all the story of the test.

Interviewer: Okay, so let's do the test.

Interviewee: It was in 1996. I wanted to develop a test previously but here, too, I had opposition from my boss, so I was not able to patent anything because he thought that it was not interesting, that it was not our job. So he wanted pure science not applied science. After the beginning of the crisis I was contacted by the Ministry of Agriculture and I discussed with them.

Interviewer: So this was prior to the BSE crisis that you were already working on this with Grassi.

Interviewee: 1996 is the test, before 1996 I developed methods of purification of PrP which is the one which is still used in the EFSA and that I developed in 1993 and 1994.

Interviewer: And what are the important innovations?

Interviewee: It was buffers, once more, and we had no ultra centrifugation. So the elimination of the ultra centrifugation was important because it's a cumbersome part so we came with no more ultracentrifugation, but we still needed three hours of centrifugation. But with that we could propose it for research laboratories, which worked perfectly well and we had very good results with a good western blot behind. We had purification, detection by western blot.

Interviewer: And that was using regular centrifugation rather than ultra centrifugation.

Interviewee: Exactly. So that's why I wanted to patent for research laboratories or for hospitals who are to make diagnosis of Creutzfeldt-Jakob because it worked remarkably well. So it was refused and in 1996 when the crisis occurred I went back to see my boss to say, "We have to develop a test," and he refused once more. So I had no possibility of doing it officially. But I was contacted by the Ministry of Agriculture and they asked me my opinion on the way of avoiding a crisis. I told them that for me the only way was to develop a very sensitive test that could be used on a large scale systematically at a slaughterhouse to guarantee that no contaminated or, at least, no dangerous cattle would go out of the slaughterhouse, to protect the consumer. They told me that it was great idea, but was it technically possible? And I said, "I think so." They said, "Who could do that?" I said, "I think that I could do that, but I'm not allowed to do it." They said, "But couldn't you do it discretely?" And I said, "Well fortunately its summer so I can spend my holiday on this to see if I can do that or not." I spent my holiday on it and I discovered buffers that allowed me to have the same results that I had previously in 3 hours with only 5 minute centrifuge. So then it began to be at a level that was compatible with an automatic test, with high though-put. So I went back to the ministries and they said, "Okay perfect." I asked them for help, I asked them for technicians because during the rest of the year I cannot work on this. Unfortunately it was blocked once more by my boss so I had to wait until the following summer to be able to work on it again.

Interviewer: Then the next summer, what happened?

Interviewee: I made all the controls, because during the first summer I discovered the positive thing, but I had not finished the controls. When you want to put a patent you need to avoid it to be overcome. A patent is to protect

something, but if you leave doors open on the left, on the right, on the back it doesn't help. So it needs at least as much work to control that.

Interviewer: As many part of it needs to be specified as possible.

Interviewee: Exactly.

Interviewer: So you didn't want to just go with the positive and the centrifugation and the buffers. You want the controls and everything.

Interviewee: Exactly. So that's why it took another summer to make all these controls.

Interviewer: So when you said, "To make the controls," what did you need to do to optimize the controls?

Interviewee: To verify that, for example, there was a specific component in one buffer. To verify that by changing a little the composition you changed the same result. That's important because in a patent they want a window - say you protect from this to this concentration with this component or this mixture but not the others.

Interviewer: So you had to develop or optimize methods for measuring different components?

Interviewee: I've tried many things on buffers to go around the phenomenon to know what are the limits.

Interviewer: So you tried all different variations and you developed a system that worked, but then you tried varying it so that you could figure out what made it work best, what inhibited it from working.

Interviewee: Exactly. So it began to be very complicated to me all these experiments.

Interviewer: I can't imagine what your notebooks look like.

Interviewee: But it worked.

Interviewer: How were you doing detection at this time?

Interviewee: I was doing it by western blot.

Interviewer: Western blot. So you were using western blot as your method for validating whether it was working.

Interviewee: And we began to use I think it was at the end of '97 the first date. I don't remember exactly when, but it was late, because during this time Jacques

developed the Elisa system meaning he tested the different antibodies, the German antibodies, and he found a couple of antibodies which gave the best results. And then the patent was put on the purification method.

Interviewer: When you say they gave the best results, on BSE prion?

Interviewee: Yes. On bovine.

Interviewer: On bovine. So you specifically were looking for the best detection possible for bovine PrP basically, optimizing it for that.

Interviewee: Yes because the goal was to have a bovine assay. So he figured out what were the two best.

Interviewee: Yes. And then we were ready to reply to the call of Europe. It was at the beginning of 1998.

Interviewer: And at that point how was he doing the Elisa? Was it a plate format?

Interviewee: Plate format. Ninety-six well plate format, coated with one antibody. So that was a sandwich assay, and detected with a second one which was linked to an enzyme which was at that moment acetylcholinesterase which turned out to be peroxidase when BioRad took them because it's a more classical industry approach.

Interviewer: So initially it was developed as a sandwich, as the sandwich assay?

Interviewee: Yes because Jacques had the expertise with this kind of test and he knew that it was with that you had the lowest background and the highest sensitivity. So we completely agreed.

Interviewer: And both of the antibodies are specific to bovine PrP?

Interviewee: Yes. In fact, in PrPres we have to have a denaturation step. So what I developed – oh yes, I had also this problem in that it was perfect for western blot but did not work properly for Elisa because the buffer for a western blot is not compatible for Elisa. So we had also to develop another buffer, but we had done all the experiments, which was compatible after that with the experiments of Jacques. What I've described, in its final form, finally was approved by Europe in 1999.

Interviewer: Wait, wait. So PK treatment and denaturation. Can you tell me a little bit about how you decided how much PK to use or how little or?

Interviewee: All of this was worked out to give the best ratio of signal versus background.

Interviewer: Defined within the Elisa?

Interviewee: Defined in western blot first.

Interviewer: Defined first in western blot. So you had already defined in western blot how much denaturation.

Interviewee: And second in Elisa we made again the experiments to verify that in Elisa what we had found previously with the western blot fit.

Interviewer: But with denaturation, wouldn't it be different in Elisa than from western blot? Because with western blot you want it to be completely denatured right? And whereas with Elisa wouldn't sometimes the antibodies –

Interviewee: No, no we want it to be denatured, too.

Interviewer: Okay so the antibody is bound best to denatured PrP?

Interviewee: Exactly.

Interviewer: They bound best to denatured bovine PrP, okay.

Interviewee: And the concern is that for western blot you have SDS which is a powerful detergent, but which is very nasty for antibodies. So on the coated antibody he could not support the SDS, so that's why we actually had to find another buffer.

Interviewer: So you had to find another buffer –

Interviewee: Without SDS that would denature it enough without preventing the antibodies from binding. And that was quite complicated because we want to denature PrPres, which is very resistant, and not to denature the antibody, which is not resistant. So that was complicated.

Interviewer: And so you tried lots and lots of different things?

Interviewee: Yes.

Interviewer: And did the answer end up being a single thing?

Interviewee: Yes.

Interviewer: And what is it? Is it a trade secret?

Interviewee: Yes. It's a special composition but here, too, we defined categories of chemicals, which had to be associated and we defined the preferred thing.

Interviewer: So you found that basically it was a lot of trial and error working up to this?

Interviewee: Exactly.

Interviewer: And then with PK treatment.

Interviewee: PK treatment is before. It's before the centrifugation.

Interviewer: And how did you work out how much time or how much quantity?

Interviewee: We defined all this...

Interviewer: For the western blot?

Interviewee: Yes.

Interviewer: So in terms of PK treatment the same amount and the same time of treatment approximately is what optimized the western blot.

Interviewee: It's a little more complicated than that. In fact you have several possibilities and, for example, if you have a low amount of PK that you let it for a long time it's the equivalent of a short time with a high amount. After that you have to decide what you want exactly. So we imagine a certain number of things and for the test, our ideal was a very short test. So that's why we focus at the end of a 10 minute treatment with PK which is very different from what is reported of a one hour treatment. So we modified the PK, we modified many things, until it fit perfectly under 10 minutes. Shorter time is difficult to be accurate because two minutes can arise very quickly and longer takes longer. So that's why we decided that 10 minutes was the best compromise. And once we decided this, after that we came back to the different chemicals and to adapt them to this time.

Interviewer: Got it. So then you could decide how much PK you wanted and how much other stuff in order to make it work in 10 minutes.

Interviewee: And for example this kind of an approach brought us to define PK concentration very differently from what is done, and that's why our test is much more sensitive than the others because we have less PK. We have been able to develop a buffer in which we can have low amounts of PK which then preserve better PrPres and when you listen to Stanley Prusiner explaining that his test is extraordinary, the CDI, because he doesn't need PK treatment, and that the other test, such as Prionics, have a lot of PK

and that's why his test is better. But if he looks at our test we have low amounts of PK and when we look at his test when we did the evaluation for Europe he added PK.

Interviewer: Really?

Interviewee: Yes, because without PK he had problems of false positives. So, in fact, all this is cooking. You have to find the good compromise and immunohistochemistry it's always the same thing, a good compromise between high signal and low background. If you increase your signal but at the same time your background, you have not won anything. So that's why he was obliged to put a little of PK.

Interviewer: Otherwise he was getting too high a background.

Interviewee: Background and false positives and that's also why Prionics has problems because in their conditions of buffer; they put a lot of PK to have the good band shift, but in these conditions they are losing sensitivity and they are losing also all the strains which are so-called PK sensitive.

Interviewer: Because the BioRad test from my memory of the conference is the only one that's reproducibly been able to detect these atypical forms of scrapie.

Interviewee: Exactly. That's why also we were the first ones to detect them. We were called by the EFSA two years ago and they said, "We have a problem. We have false positives with BioRad and we can't confirm them with anything." So we asked them to have the samples to see what was happening and immediately I thought, "Oh yes, but if they're doing the classical western blots they are using 5 times or 10 times higher amounts of PK."

Interviewer: So when EFSA said that they couldn't confirm it with anything they didn't mean IHC they meant western blot.

Interviewee: And IHC. But in IHC, in classical protocols, you also use high amounts of PK. That's also why after we had this discussion with Thierry I explained to him and I made a report explaining why it was not false positives but abnormal strains. At the beginning he thought I was crazy, but he made a lot of experiments and immunohistochemistry with all the protocols he also found them positive and Martin Groschup also found them positive with another western blot which was different, and in which there is more aggregation. So the result is that with other techniques they were able to confirm them.

Interviewer: So initially you were able to get samples from EFSA for some of these animals that had tested positive on BioRad but not on the other test?

Interviewee: We are speaking of sheep here.

Interviewer: So did they give you actual samples of homogenized brain? Or did they give actually like did they give you brains like half brains or something?

Interviewee: No, no very small things. Very little amounts. But I don't remember if they were yet homogenized or if they were still not homogenized.

Interviewer: So you couldn't run an IHC with what they gave you?

Interviewee: No.

Interviewer: So they gave you samples and you were able to double-check that, indeed, that basically your test would detect those as positives, but it wasn't until Thierry.

Interviewee: No, no, no. Because we confirmed it in western blot.

Interviewer: Oh you confirmed it in western blot. In your western blot?

Interviewee: In my western blot using various concentrations of PK we demonstrated very clearly that these strains were PK sensitive. That they were abnormal PrP, that at low concentrations of PK PrPres was present, and that when we increased PK concentrations then it disappeared.

Interviewer: Okay, got it, that makes sense to me. So you doubled-checked it basically using a western blot.

Interviewee: And it's on this basis that I wrote this report saying that these were atypical strains. They did not believe me at the beginning and they were unable to confirm it by other methods. They have published it now.

Interviewer: At that time did BioRad have a check western blot available?

Interviewee: No.

Interviewer: So was it because of that incident or was it because of the detection of atypicals that they commercialized the check western?

Interviewee: What I understood is that commercial practice of BioRad at the beginning is that they did not want western blots because they wanted to sell Elisa and that for them western blot was a competitor and was used by Prionics. After that they integrated that it would be useful to have confirmatory test as sensitive as the Elisa. So then they accepted the western blot.

Interviewer: I see, but it was partly due to the atypical cases that they decided to?

Interviewee: No. No it was before. Yes, the problem with the false positives, it was before.

Interviewer: So really it was the problem of false positives that caused them to want to have this confirmatory western blot? But then they came to you to develop that, too – that they used your protocols?

Interviewee: They came to me. I proposed to them to do it because we have regularly meetings to discuss their problems. For a long time I've told them that they had to develop this. I've also been telling them for quite a long time that they will have to develop immunohistochemistry and they are still reluctant to do it. So for the moment I do it alone.

Interviewer: Okay so you think that actually, in an ideal world, there would even be an IHC confirmatory test?

Interviewee: Yes, of course, because all these tests are rapid tests. Even IHC is a slow rapid test. Compared to inoculation to animals, it's a very rapid method. So my approach is to say, you begin first by Elisa which is the simplest one to check a lot of samples. Of those that appear not to be negative, which appear to be positive then you make a western blot and if after the western blot you still have a problem, you do IHC. So each time you eliminate 99 percent. Then on the Elisa you eliminate 90 – 99 percent because almost all animals are negatives. You have very few positive animals. On those who are positive for Elisa or who are doubtful you are first to repeat the Elisa, that is the first. You have to check the repeatability, but that's classical. After that on those that you need to confirm then you have the western blot. And on some cases, I would say 5 percent of cases, you have problems on western blots. So then you have to do something else and for me the immunohistochemistry is great.

Interviewer: And so right now what's wrong – I mean other countries – I mean countries do IHC, for instance in the U.S. they do IHC as a confirmatory –

Interviewee: You have a historic problem in countries meaning that testings are given first to people who were in charge of surveillance and so who were doing immunohistochemistry. So they want first to do everything by immunohistochemistry. And I remember a discussion with Mark Head [sp?] two years or three years ago where he understood what I said, but he was convinced that immunohistochemistry was the solution. So now he has changed his mind under the pressure of the samples because when people begin to see so many samples arriving they have to have a method which is able to treat them in a reasonable time.

Interviewer: But is your idea to improve the IHC by making it faster?

Interviewee: Yes. Making it faster, more automated, and also reproducible. For the moment, depending on the lab, the IHC gives completely different results.

Interviewer: That's not good. So that's one of the problems?

Interviewee: Yes. For example, the atypical samples they are negative in IHC in the reference laboratory of Waybridge and positive in laboratories of Thierry Baron and Martin Groschup. So that's a concern.

Interviewer: I see, so just because of the different conditions the tissue is exposed to you get very results.

Interviewee: Exactly the problem of IHC is it is a very complicated method. First, at the level of fixative, of the inclusion, then at the level of the antibodies. You have artifact from the Proteinase K treatment, from the autoclaving, from the formic acid treatment. You have artifacts everywhere. Even if you have the same protocol, you are not sure to have the same results with the currently available protocols. So what we've tried to do is to develop something which would be equivalent to what we have developed for Elisa, for western blot, meaning a kit where, depending on the technician, you will not have a variation.

Interviewer: So you'd work out the best conditions and then the least variable.

Interviewee: Exactly because immunohistochemistry has information that you don't have in western blot, even in the Elisa, which is the localization. Because Elisa it's white or black, with the quantification of course, but above the cut off or below the cut off. So you don't know where you are. Western blot you have the banding aspect. So you have another piece of information. In immunohistochemistry, you have the localization. So you see that you have more and more information with the different techniques.

Interviewer: What you outlined is the ideal way of doing these sort of test is interesting, too, because what you would then do is you would get all of these bits of information. You'd get the banding pattern, you'd get the localization, so that in the end you'd be able and as we're finding out is more and more important with atypical forms of scrapie and atypical forms of BSE how to differentiate them becomes an issue.

Interviewee: What we are doing also is defining methods of concentration to inoculate animals in order to have faster results because even with immunohistochemistry we know that some strains will need to be inoculated because they are unusual, so we will need a result. And if we

need to wait one year, it's not really adapted to what our public health authorities are requiring. So we tried to combine what we know about purification with different animal models, transgenic lines of course, of mice. What we could propose also is a standardized model that could be used for many things.

Interviewer: A standardized transgenic model, like an over-expressing model?

Interviewee: Yes, but inoculated in a way that you would have reduced incubation periods because to wait one year is not acceptable. So my idea is try to have things giving results within two months independently of the sample or things like that.

Interviewer: And this is something you're still working on? You're currently developing?

Interviewee: Yes.

Interviewer: There's high utility for all of these things and it brings back you know when you were talking earlier about Dormont and how he was not supportive of you doing these things because it wasn't basic science it was applied science.

Interviewee: Exactly he wanted basic science.

Interviewer: And can you talk a little more about that divide, why do you think that exists?

Interviewee: You have people who are fascinated by basic science. They don't care if there is no application to what they are doing, it's only the intellectual approach which is fascinating for them. On the opposite, applied science does not exist if there is no basic science. So my positioning and the positioning of my group is this one -- I think that many intelligent people are doing basic science, but that we are clearly lacking people applying it to society's needs and if we don't solve society's needs there will be no budget coming back for research. So what I've defined as a priority for my group is to be at the interface between basic science and the needs of society and to find the best associations, the best compromises, to solve society's needs to re-fund basic science because it is indispensable and I profoundly respect people who are doing basic science, but I find that there are so many intelligent people who are doing it; I don't need to do the same thing.

Interviewer: Do you think that when applied science succeeds in taking basic science and finding applications for it in the world that money comes back to basic science?

Interviewer: No it doesn't work. That's why I'm doing NeuroPrion. Because if you are waiting for industry to re-fund basic science, you can wait a very a long time. They will never give one penny or one dollar.

Interviewer: Right that's the problem, right?

Interviewee: Yes. So the only solution is that scientists occupy the field by themselves because scientist are able to understand that it's a vital thing that basic science is funded, but industry only sees their own interest. So NeuroPrion is affiliating all public research teams. So we have a common interest in science, and in this I know that researchers who are in basic science, many of them are not good in doing applied science. It's not their way of thinking. And on the other hand, if we want to make applied science, we need basic science to continue. So we have a common interest. And more generally if society does not have strong research, society will die. We see what is easy to do can be done in China, in all the countries with people paid with very limited salaries, so if our society is not able to invent new things our society will die. It's written. So the only thing is to invent new things and the inventions need to be fed with something, and that is research.

Interviewer: You don't get technology without the basic science, but that connection is not always made by people in government or by industry.

Interviewee: No it's not naturally made.

Interviewer: And your idea is that because scientists understand this connection, the integral nature of that connection, that they'll make sure that the money that is produced by applied research will go back into basic research. Okay so then if we can go back to your first collaborative experiences with sharing the antibodies that you and Grassi had worked on and then, from there, if you could talk about your developing ideas about collaboration and when the NeuroPrion idea came into being.

Interviewee: The prion crisis is linked to a public health problem. It's an economical problem. And if you compare what has been wasted by Europe, meaning 19 billion Euros, with what has been invested in research, which is less than 1000 times that amount, you understand that there is a big problem. The lack of anticipation, the lack of investment, leaves you without protection and you lose a lot of money and research is still poor. What we are seeing, and it's very easy to anticipate, is that as the number of cattle affected by BSE is decreasing the number of vCJD is not increasing dramatically, then politics are going to shut down the budget for prion research and it's already happening.

Interviewer: And is that a problem in France as well as other countries?

Interviewee: Everywhere. And then we know perfectly that if we leave things going like that, research is going to slow down, a new crisis is going to appear because all the investment which has been done has not produced enough and so we have not developed the big weapons, the guarantees, etcetera, and we are going to waste again billions.

Interviewer: The next time that there is a BSE crisis?

Interviewee: For the next crisis. So my goal is to determine how we can maintain the mobilization and the funding of the research team to offer to society the guarantees they need.

Interviewer: So in a since you're trying to make an argument though about a potential?

Interviewee: Exactly.

Interviewer: Because you're saying, "Look this has happened with BSE. It could happen again."

Interviewee: What are you doing when you are buy insurance? You are paying someone five percent of what it would cost if it was occurring. Put five percent of 90 billion Euros. You would see that – so somewhere what NeuroPrion is going to propose is the assurance that the maximum will be done to avoid a new crisis, from diagnosis, to decontamination, to treatment, to risk assessment with scenarios, or with communications, all what can be done. For the moment we have only three million per year, which once divided between all the teams is nothing, but it is enough to mobilize people to oblige them to collaborate and to put them in a good direction. So now my fight is to find extra funding to fund the necessary things and to obtain the results. So I tried to create a foundation. I've contacted people in the Meat and Bone Meal affairs, in transfusion, so many in France for the moment. I'm going to visit also TSE funders in U.K. I've contacted politicians in France, and as soon as I will have been able to do something strong enough in France I will try to do the same thing and to help my colleagues do the same thing in the different European countries to figure out how we can afford practical solutions and then to discuss, to say, "Okay, look at the economics," because for the moment people prefer not to see the problem and are still waiting for the next crisis and we know that if you find positive cattle in the U.S. you will have a crisis. You have lost already billions, but it would be much more terrible. I speak of the meat industry because you still have the problem of meat and bone meal. Since it has become forbidden, we have lost 400 million Euros in France, almost half a billion Euros per year for nothing, and it's still being wasted. And it will be wasted in Canada and the U.S. if

you are to eliminate meat and bone meal there also. So I say okay, if we find a solution which could guarantee the safety of these animals, what do you propose as money coming back to science? That's one target. Another one is transfusion. So what can we guarantee in terms of a sensitive test or in terms of decontamination systems to protect the blood supply? After that you have the other decontamination systems. You have seen that we have just published in Lancet a new decontamination system which is very original, so that's occurred in collaboration with U.K. and U.S. groups and I've been fascinated by this. It's vapor of hydrogen peroxide. I was fascinated when they explained to me that they were using it to decontaminate anthrax spores even in buildings with computers or in planes. So it means that something which is strong enough to decontaminate one of the more difficult agents to decontaminate, but without side effect on very sensitive electronic devices, and that was very interesting. So that's why I insisted on testing it. At the beginning they did not want me to test that. They sought other things. But we discussed with them our experience. We said, "What you want to test is peracetic acid. We could test it. But the experiments are long, time consuming, expensive, so it's better to try to find other solutions." And that's the way we discussed with industry. We are not here only to validate. We are here to try to find solutions. So from their discussion to say from their experience what they think and from our experience what we think, and putting this on the table and comparing our respective experiences, then we can find innovative solutions.

Interviewer: The sort of mechanism that you're proposing is almost opposite to what is normally done. I mean if you think about basic science funding, usually there's a certain need and you try to fill that need or you write a proposal and you get funding on that little piece of basic science which then could maybe be used for applied science eventually. What you are proposing is so interesting because it's a very different way of thinking about how funding should work. I mean it's completely anomalous to what we're used to thinking about. You're proposing that if we're successful at producing these applied technologies using the basic science and technology that we already have and that we can improve, you will then give us more money to develop basic science that one day might be useful for another applied technology.

Interviewee: Exactly. It's exactly that. It's a virtuous circle that we are trying to produce.

Interviewer: And how have discussions on this been going or how would set that up in a contractual form?

Interviewee: It's under progress. Unfortunately during summer it's not possible in France, but next week it will be possible again. So since the inauguration

of the buildings in May and all the delay that we had after that, it has not been correctly developed. We had to manage many things, and now we have new battles with our authorities. But they have no solutions. We see that for research we are at the limit of the system. Researchers were in the street protesting the lack of budget, etcetera. We have to find new solutions. What we propose is a consequence of the economical analysis of what is happening. For example, if you look at the crisis. If here I do nothing, I wait; they are going to waste a lot of money, billions. To try to see what were the ideas and then so I submitted a letter of intent explaining what I thought necessary, and I explained that in prion field because of the economical impact we needed to use science to protect society and what I proposed was an integrated project. So I proposed to finance science and not to finance integration, but they replied after that all this was analyzed by experts etcetera and many proposals were done and what came out all this was something which looked almost identical to my proposal but saying that they wanted a network of excellence. So then I had to understand what was a network of excellence [laugh]. What they wanted us to do to understand the philosophy of Europe and to see how to adapt it to the goal we had.

Interviewer: So you said it was very similar in some ways to the proposal you had given them.

Interviewee: At a scientific level. But for the instrument what I proposed was an integrated project. So I thought something that has 10 partners or something like that with enough money to solve the problem. The main goal was to finance science. And what I understood is that they refused to finance science saying that Europe only had money only to finance 5 percent of what was needed, and that already many things had been funded in prion research. So they wanted first was to try to fight against fragmentation and once we could demonstrate that we could associate and be complimentary then they would fund more. So I was disappointed because it was not at all my idea, because it was much more complicated for me, but I understood that it was the only way. So we took the challenge to create a real network of excellence. I went to meetings in Brussels to discuss with many people to understand what was behind this, what were the possibilities.

Interviewer: Because the whole concept of a network of excellence was a new idea.

Interviewee: It was a new idea. It was an idea very criticized and that's why they are hoping a lot of us because I think we are the more original one and the more active one, the most visible. We are the only one who organized such a big meeting at the beginning. The others have in mind to create it at the end of the network, four years later. But we're obliged because the

crisis is now in Canada, in U.S. it's tomorrow. So if we can help we have to be ready.

Interviewer: Have you thought about taking it to the U.S.?

Interviewee: Oh yes, I'm interested, but for the moment I do not have the contacts.

Interviewer: Okay, so that's something you would need to develop. Which is why you're thinking to start with France where you have contacts.

Interviewee: Exactly because from what I know from the mentality of U.S., they want to see results first before putting in money. So I have to make the first demonstration of the viability of the system, because each time I create something new people begin to deny it saying it will not work. So they let me do it because first I'm difficult to stop and second perhaps it can work because each time I succeed. But they're always reluctant. People are naturally reluctant to novelty. So they always wait to see if it works or not.

Interviewer: They don't want to be the first ones. They don't want to be the guinea pigs, so to speak.

Interviewee: Exactly, exactly. They want somebody to take the risk and when the risk is taken and that it works then they are ready to come and to be part of it!

Interviewer: Right, exactly. They want to get on the bandwagon but they don't want to start it.

Interviewee: Exactly.

Interviewer: And how did you come up with the idea for the structure of the network, you know with the executive committee and the various subcommittees?

Interviewee: Oh very simple. It's an analysis of the mentality of the researchers. Researchers refuse to be managed. So the only way is to give the power to them, to form a kind of parliament. If I was deciding everything myself, knowing that the majority of them are older than me, I would be accused of many things, so it would not work. So the only possibility for me is to give them the power, but once you say that you say okay but it's good thing to give them the power but the system has to work and with 30 or 32 people the executive committee, so the only way to have it working is to prepare the work for them. So they take the decision, but you prepare the work for them. And then to prepare it alone I'm going to suffer so I need advisors for others because if I don't do properly the work it will be refused in the executive committee. So I have to test it to see how it's accepted. So it's the idea of the coordinating group with the many leaders

representing the different things, and so you see a pyramid of structure but which is opposite to monarchies. Monarchy is where the king decides and the others execute. Here the guy alone begins to think, takes the advice of those to prepare for the coordinating group, that prepares more, and the decision is at the bottom of the pyramid not at the top. It's an inverted pyramid.

Interviewer: It seems like it's so hard to get across this idea of what it is that you want to accomplish with the network of excellence. How do you deal with people who just want money for research and don't understand the broader concept of what's going on?

Interviewee: If they don't use the possibility of the network they will grow weaker and weaker. So all the intelligent ones will understand it.

Interviewer: Eventually, right? You're giving them time, right? Because it takes some time.

Interviewee: Yes it will take time. We need to let people have time to understand what is in their interest. If the system is well done, it's more interesting for them to work in a group than to stay isolated and all the intelligent ones are going to understand it. If some of them don't understand it, they will stay alone. The research for which they will be funded will be done because the system is done to verify that they do what they are funded before. So it would be equivalent to what was occurring before. And for all the others it would be progress. You can't impose a new system to people. They have to adopt it.

Interviewer: How long is the funding period?

Interviewee: Five years.

Interviewer: Five years, and then after that is there going to be a determination made at the E.U. level?

Interviewee: Yes but in fact for me it's nothing because we're not going to wait 5 years. We have not waited to have the contract signed to have the first conference and it was the biggest one organized like this. I'm not going to wait to the end to create the foundation. I'm trying to create it now. Which means that next year it would begin to work. So people will have time to adapt to the system. I will have time to improve it in order to make them as happy as possible. The system is done for all of us. So I will modify it and improve it until everybody is satisfied.

Interviewer: And then are you hoping that within 5 years' time that the NeuroPrion network can continue on it's own.

Interviewee: Yes. I think more than that. I think that the system that we are creating here, if we are right, is going to develop and we are going to have enough funding to fund other research, not only prion research. And so we'll have to decide if we are going to go towards Alzheimer's or decontamination of other pathogens and diagnostics of other pathogens. Meaning problems of society once more because we are going to have more and more crises linked to emerging pathogens.

Interviewer: So then the idea would be to have this be something that would spread to other disciplines as well?

Interviewee: Yeah, we will open the system and let others do the same thing in their field.

Interviewer: So you're going to keep working in the area of diagnostics in your laboratory.

Interviewee: People tell me that I will not be able to do it because I have more and more administrative things to do. But I try to delegate more and more the administrative things. That's why you are seeing that we have now Jens Shell that we have Steve Savado. Before you were coming I was looking for patents and I'm going back to the lab to create new things, because that's what I love.

Interviewer: So you want to continue doing that in addition to this administrative stuff by making sure that the administrative work can in a sense be done.

Interviewee: I don't like routine. So when I am creating, I'm interested in any domain. But once it's created, I'm not interested anymore.

Interviewer: We were talking about this collaboration that you were involved with the antibodies and then you mentioned that there was a call for proposals from the E.U. and that you responded to this call, you wrote a letter of intent.

Interviewee: Yes, so we were selected and it took a long time before we had the samples, almost one year.

Interviewer: Yes.

Interviewee: And so the evaluation was done in 1999 and so four test were evaluated and it was our test which was the most sensitive one. It was 30 to 300 times more sensitive than the others.

Interviewer: So that validation that was finished in 2000? But the idea for having some sort of a network like the NeuroPrion network was something that you had been thinking about even before?

Interviewee: No, no it came somewhat naturally. It has been an evolution.

Interviewer: When they made the call?

Interviewee: I had not this in mind. No, but it was the only door left open. So it was higher than what I thought I would be able to do, but as it was the only solution.

End of transcript