Oral History: Jacques Dubochet / 2016/11/3

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2016_11_03 JACQUES DUBOCHET_TRANSCRIPT

Key

AFL: = Archivist, Anne-Flore Laloë
MB: Interviewer, Martin Beck
JD: = Participant, Jacques Dubochet
[??? at XX:XX] = inaudible word or section at this time

AFL: So we're here today, it's November 3rd 2016 at EMBL Heidelberg. This interview is part of the oral histories project of the EMBL archive. I am Anne-Flore Laloë, the archivist at EMBL. Please would you introduce yourselves?

JD: I'm Jacques Dubochet, retired professor at University of Lausanne.

MB: And I'm Martin Beck, I'm a Group Leader at EMBL. Jacques, thinking back at your time at EMBL, was there anything that you particularly remembered that stood out as an experience when you have been a group leader here?

JD: Yes of course. [Laughs] It was a great time in my life and there are so many things which stand out. But of course we were living in a little village somewhere, two children, that's important. And yes, here the remarkable thing that has been discussed so much, it was this freedom and this possibility to try what you could do and the atmosphere was Sir John hired me with a very, very ambitious project but completely open thing. How to deal with water in the electron microscope. And then we - typically a research project open and you

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don't know where you do but the atmosphere is that you have extremely good condition mentally first and materially of course. This is a special place. I understood that the Crick Institute in London is starting on the same way. Good luck to them.

MB: There's one EMBL rule which is let's say everyone who has faculty can particularly appreciate the importance of that and that's the nine year rule. Now you have some distance, I don't. So I was wondering what are your thoughts today about the nine year rule?

JD: You may know that I have been one of the very few who got a permanent position, under very strange conditions that we perhaps don't need to recall here. [Laughter] Though we could, it's a very interesting thing. You will delete or not?

MB: You can go ahead.

JD: So probably you know this was a very interesting thing, when Professor Philipson became the Director they didn't understood well each other, with John Kendrew at the beginning. And clearly Philipson told us at the beginning, before coming, that now it's time to have a medical doctor to be more medicine oriented and all these physicists, don't know what to do with them. But and so – and we got this – four of us got this permanent position hours before Kendrew went away. And hours after Philipson took the position we were down in his lab, in his office, and he told us that he was not happy and that he will consult his lawyer to see how our contract could be nullified. This was a bad start, but then it went perfectly well, it changed and the collaboration was excellent and it's amazing that I was the first one to get the Lennart Philipson medal. [Laughs] But at that occasion we did spoke about that. But I think this was for us an amazing thing and of course it was very pleasant to think that well I have this permanent position at the time and this was – so it's more open for life. But then later I found that – I thought that all my life having to be under the pressure of being so creative, we had Kai Simons here and Kai Simons was a great – he was much better than I and he continued to be extremely creative <5:00> probably still, I don't know. I hope so. But I thought no that's too hard for me. I was happy then to go in teaching and then I was 20 years in research in teaching, very much research, very little teaching, but I love teaching also. And then later then I come to this Science and Society Vaud as we already start here. Okay.

MB: We like to talk with you a bit about the early days of cryo-electron microscopy. And first of all I would like to hear when and how you became aware of the potential of cryo? How and when did you become aware of the potential of vitrified specimens?

JD: Ah yes, ah, vitrified, we should not start to speak with vitrification. That came later.

MB: Okay so let's start with cryo-EM

JD: So I was still in Basel in my post-doc. Then I was impressed by freeze drying and I had very – I was impressed by what I could obtain by thin layer – by spreading the material on the grid and freeze drying it on the grid. Beautiful T4 for just freeze dry on the grid, very nice. And then there were also some photographs where we had – what was I saying? Experience with other people where observing the ice in the microscope, Nigel Unwin was I think the first one who did that in a way close to us and he was more showing that there are – that he was studying the damage in ice. And not so much but also thinking in term with ice we could do something and then you know what the thing has been told and written. And once we were exercising with water in the microscope with this very primitive specimen holder. And then once – Alasdair McDowall decided to change the cooling agent to use liquid ethane and so he had this drop of material, amorphous material in the microscope, called me and we first thought that this was a drop of liquid ethane or solid ethane but it should not have been because we knew it should have been gone and so we warmed it slowly at -135 and it turned into cubic ice and we knew that we were very familiar with all this form of ice. So and this was ooh, the moment of – and then the thing has been written, the paper was refused by Nature because 'you can't bend nature'. This was the famous sentence, this was a joke with the word and the reason why it's because there has been 40 years of very solid science by the group of Luyet and all these people who came to the conclusion that vitrification is basically impossible and we should know that until now we don't understand what it really is.

MB: I was actually going to ask you how the scientific community perceived this at the time and you already partially answered this question. Is there anything - ?

JD: Well you know we were not the first, because when we submitted to Nature, Nature had in press the paper by the Austrians who had obtained the same from x-ray demonstration, they demonstrated by x-ray on spraying directly in – now I forget if it was in liquid nitrogen or in liquid ethane, but they used similar methods. And so we were not those who discovered vitrification and but the discovery of vitrification was very important. Because before it was rejected <10:00>, people thought it was theoretically impossible and there are

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– and I had to learn all that at that moment. And so since we could repeat it, here it was very easy to see. The people in Austria, they couldn't see what was going on, and so the people of water came and loved to visit the lab and so I had – we had some beautiful time learning from the water specialists. And so I learned a lot and one morning, very early, we had a phone call from oops this was Pierre-Gilles de Gennes, Nobel Prize on well spreading of water on a surface and things like that and he was teasing me on the telephone, explaining, asking if I knew why we could get this very, very thin layer. In fact one of his lab came before in our lab to see how it works and so he phoned us and he explained to me on the phone the trick of thermal entropy. It's difficult to – if you have a thin film it's difficult to start the hole. You must have a hole at the beginning. Therefore you must somewhere fuse the upper and the lower layer and this is thermodynamically difficult. And so voilà.

MB: Do you remember the first time the process worked. What did the images actually show?

JD: Well the first thing was this droplet of ethane, no of water, just a droplet of water.

MB: It was just water.

JD: Yes, that was the first and the first publication we had, which came one year later in the Journal of Microscopy was just water. But then rapidly we tried to put things, typically they were DNA, but the second breakthrough – so the first breakthrough this was Alasdair Macdowall and he did – he decided by himself now I try it with ethane. Of course we discussed all this kind of thing but he did it and he called me and the other was Marc Adrian who was minding for himself. He never liked to have things told to him and so – and we had discussions, he had the idea to work without supporting film and I was completely opposed, I told him you're crazy, there's no chance, it was thermo-dynamically impossible and so forth. And he did that, it was difficult until he found, but then you had this photograph, at the beginning without perforated carbon film 400 mesh grid. This means 18 micrometre square and on that less than 1000 Ångström thick layer. Now that's a factor 200 thickness to dimension, to length, which was very uncommon. And then you had this famous photograph of plenty of T4s on this thin layer. And he had another thing which was not correct – of course I'm a serious microscopist, I focus correctly and Marc Adrian found out that –

MB: The underfocus.

JD: He must underfocus in an untolerable way. And now – I knew all this theory and I knew that but he has been the one who make it true. Yes.

MB: We went through some ancient documents <15:00> in the EMBL archive, actually you wrote this, it's your Annual Reports from a long time ago.

JD: Ah yes.

MB: And we've been impressed by the fact we essentially found the who is who of cryo-EM as visiting scientists, including Tokuyasu, Ron Milligan, Murray Stewart, Richard Henderson, so we were wondering why did all these people come to visit? Were these collaborations or why have they been attracted?

JD: Well Milligan, Ron Milligan, he's the first one who came, because we were in close contact with Nigel Unwin and Ron Milligan was the technician of Nigel Unwin. And Nigel sent him here to learn the method and so we had a number of people coming and we had this course, this EMBL course –

MB: Had that started at the time or earlier?

JD: It started earlier, yes. Yes, so Murray Stewart was one of those, he came to the course. I think so, if I remember correctly. With Henderson it was different – we had contact by phone, by a different method. I had more contact – I was very shy at that time and [Laughter] and I didn't thought that. So I was impressed by Henderson and also Nigel I knew him personally, he was my hero. And we had a very strangely parallel way. The first time I was visiting him I slept in his room, and what did I find under the bed, a telescope, 15 cm telescope, that Nigel had made by himself and grind as a young – as an adolescent. And I did exactly the same, same kind of microscope, telescope, 15 cm opening, self-grinded. Okay, well very good. He was a physicist of a solid state – no, he was more in the nuclear physics I think. I've forgotten. Perhaps – or perhaps he was also in the same solid state – amazing. And so he was my hero and Henderson is a guy from x-ray, and x-ray was not my business and so I had great admiration for Henderson because and so bon, we are about similar age, but he frequently gave me advice and he is the one who convinced me to write this review on cryo-electron microscopy which was published 1987 or so and which has been an enormous success. And he gave me good advice how to write, which kind of photographs to put in and so forth and this was a very, very – well I learn a lot from that.

MB: Okay. Is there or has there been an early event in your life or career that has strongly influenced you?

JD: In my life?

MB: Mm.

JD: Of course. Yes, yes. Well yes of course there are plenty for everyone, no?

MB: But is there anything that you would say is of particular importance that you would like to mention?

JD: Yes, I think I'm a scientist and this when a child, we were living in valleys in the mountain because my father was building a dam there and this was before 1950 and this was a region very, very primitive. This was – it was not archaeology but it was very strange at this time how that works, this mountain village. And very Catholic and, okay <20:00> and I was five, so I was afraid from the night as every children, and my solution was quite obvious – I need to understand and you know, the earth turning like that and here, and this – and you see, all my life I fight to understand because this helps me. And also I was 22 or so, or 20, I consider myself as a [??? at 20:38], social uncapable.

MB: Oh I might disagree with that.

JD: Yes, but this was my feeling, no, and so and science was my grip to survive and the social I found it difficult, so I had to understand, so I made a long psychoanalysis and I think *c'est la folie*, it's crazy, this is Freudian psychoanalysis, but I think I am very, very thankful that I could do that. And ten years later I thought ooh this was good, twenty years later I thought oh this was very good and so forth.

MB: Do we still have time?

JD: I think nevertheless this should be put in the record that you know when I came here, I came with something catastrophic happened, you probably know, that I have a real big problem. A group of Munich, Siemens Munich had found that beam damage is enormously reduced at very low temperatures. They developed a new microscope with super conducting lens working at four Kelvin. And this – and so I was a specialist of beam damage measurement, this was my PhD, so I had the position here but I was not yet here. So we started collaboration with the people of Munich and this lasted about six months when I was here and then we came to the conclusion that beam damage is considerably reduced at four Kelvin. And then Andrew decided to buy the famous lens. It took two years to have the lens here and when it came we were very well prepared with my colleague Jean Lepault who didn't participate in the first part of the work with Munich. We were very well trained to work with this new machine, the machine was installed very rapidly because Arthur Jones, the boss of the group for microscope arrangement, modification or transformation, had made a good work, everything went well. And we took one week to know perfectly that all our results were wrong. So the – so [laughs] we went to Sir John and he told me aha, bah, what you should do is to make it known. So we very soon published, we had an amendment to our paper and then we launched a big collective effort, so that all the people who could participate to this, come and join the collective effort to see what is true. And so we asked somebody from Berlin, an old guy of the microscopy to take over, to supervise the effort and so on, and it was confirmed that beam damage at very low temperature, it's not useful. And *belle catastrophe*, this was, and this really – okay *bon*. And then well when this happened, I don't know when this was. <25:00> When was this? Ah, no, ah yes arrived in '78, yes, but then this was probably – yes if this is my application to – oh not that's already – at that moment – oh yes, so this was perhaps the moment when there are the first reviews of our work, after five years and I don't know the details but I understood that Sir John told his people of the committee, well if all my head of groups make big stupid thing, big catastrophe, but they produce a real progress, I'm happy. Yes, yes, voila and then the vitrification it was effectively a big progress as you know, and the fact that it, the unsupported film, then we had this cover of Nature with a virus, the Semliki forest virus at 35 Ångström, but 35 Ångström now they are routinely at 3.5. [Laughs] And I don't need to explain, 3.5 is ten times smaller than 35 and this means a thousand times smaller in volume. So the amount of information they get out of the photograph is a thousand times better.

MB: It's also 30 years later.

JD: Yes. That's okay but the progress are impressive yes?

MB: Yes. That nicely leads over to the last topic we'd like to chat a bit about and that's the present and future of science. So what excites you about science today?

JD: Now when you're retired and I have been I think the first or the second director, president of the staff association here and so I've always been involved into science society things and now is retirement, I would say it's full time. And thinking about science, no, of course each time I read a new discovery or something new in Nature I'm – it's a pleasure, I think it's just comparable to sexual pleasure. So for me yes, but so I love this, but I see that [??? at 28:08], but you see what do we do nowadays with gene drive, and drive we have in Lausanne a group of students doing DIY biology.

MB: Do you mean genetic editing?

JD: Yes and this is a group of boys and girls who have bought crispr and get lesson on crispr and they are able to produce a gene drive mosquito who could do well, could change a species. And everybody can do that and we have big, big, big problem with why, what science can do and will do and really it's a must. Our society, the world, must be able to develop, to continue with a science which goes not where it can, but where we want it goes.

MB: I agree. The problem though is if you want society to regulate or to define ethical restrictions they first of all should understand what exactly we're doing.

JD: Yes, but I mean that the first person responsible are not those who don't know, but we are responsible.

MB: I agree. <30:00> Still there needs to be a discussion about it right?

JD: A lot of discussion.

MB: What is your opinion where it should stop? What is your personal opinion where it should stop? Do you think a genome editing of model organisms is still okay? That's effectively something which is done very routinely now.

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JD: Yes, but gene drive for example it's not possible to let go modified mosquito without we have learned before much more. And why not prepare to that? There are new rules, just reading the newspaper, the new rule on how to control the gene drive is coming to the food and drug administration in the United States. Those will decide if you can let the mosquito – are they really the best persons to know about the ecology? No, we have to think much more about that and scientists – and the work of the scientists is not only to fight so that they are free to continue. Very frequently recently with our – last year in December it was in Washington, this meeting to see what shall we do. And my impression is that the major goal was we should be intelligent enough to regulate ourselves in a convincing way so that politicians are not interfering with our work. I think that it's more in that direction. Now I'm getting quite – I must say I'm very worried and I think we are not prepared to control what the science is producing and science is producing great – of course, science is the solution but it could be also the problem. And if we let it free we will have all sorts of problems.

MB: Let's finish with something positive. What advice would you give a young student today who's just starting to do science?

JD: Be sure he likes it. [Laughs] yes.

MB: So thanks a lot Jacques.

AFL: Thank you very much Jacques that was really excellent, thank you very much.

[End of Recording]