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**Dame Anne McLaren DBE FRCOG FRS in interview with Dr Max Blythe  
Oxford, 3 July 1998, Interview I Part Two**

MB Anne, in 1952, you go to University College London. We'd said that you were going to move to Medawar's department. Let's take that in now. It would be nice to know about the research you conducted, how that came about, what you selected to study.

AM Okay, well we applied to the Agricultural Research Council for a project grant, and if I remember rightly the grant application was entitled 'Extra Chromosomal Inheritance in Mice.' And the reason for that topic was that a fellow student of mine back in zoology days called Tony Milne(?), who always had an eye for odd things in the literature had come across this maternal effect in the literature, where two inbred strains of mice which differed in lumbar vertebrae – that's vertebrae between the ribs and the sacrum – one had five, the other had six lumbar vertebrae... In fact it's a question of whether the sixth is sacralised or not. And in the crosses between these two strains, the progeny significantly resembled the mother, always. And he mentioned this, and this seemed to me an interesting interaction between genetics and development, since I'd been frustrated over my Guyer(?) and Smith(?) and the lens antibody story.

MB You moved therefore to fascinating developmental and environmental issues.

AM The question was, which particular bit of environment? Because it could be that it was a postnatal effect, through lactation, though that isn't very likely because the vertebral pattern is laid down pretty early. Or it could be a uterine effect; something exerted through the uterus of the mother, during gestation. Or it could be something in the cytoplasm of the egg already laid down during oogenesis, during the development of the egg, and present in the cytoplasm. And we knew that the technique of embryo transfer – transferring early embryos from one female mouse to another – had been successfully done in the States some years before. And that was the obvious technique to use to distinguish between the cytoplasmic effect and the uterine effect. The milk effect was easy to dispose of quickly because of cross fostering, so forget about that. But we did the crosses and we confirmed that indeed between these two strains, C57 Black and C3H, there was this difference in vertebral type and two-thirds of the progeny in each of the reciprocal crosses resembled the maternal strain. So then we took the F1 hybrid embryos and swapped them over between the females of the strains, and looked at the vertebral type of the young. But, that sounds easy and straightforward, but it took a long time because first of all we had to get the embryo transfer technique going. In order to do that we obviously didn't use inbred strains because they don't breed well – you have small litters, they're not very fertile. We used good, random bred strains, and we induced ovulation with hormones so as to get more eggs. And in the course of doing that we did work on the actual technique, how the number of eggs shed related to the amount of hormone given. That was interesting to the Agricultural Research Council of course who were paying us.

MB Yes, so this was a study done on the trophin rate(?).

AM Yes, that's right. And what would happen if you let those superovulated mice go on and get pregnant, superpregnancies, we looked at that. We looked at the relation between foetal weight and placental weight and litter size. That was a lot of work.

MB It was like opening an Aladdin's cave of research opportunities.

AM That's right, that's right, and...

MB Can we take in some of those, Anne? Probably...

AM Yes, sure.

MB Let's just go back to the actual transplantation, because you say these, this was a skill really that took time to get.

AM It took time to get, and it took all these other things to be established first.

MB So they were all going around the same time?

AM Yes, that's right, that's right. And it wasn't until right at the end of the 1950s that we finally solved the problem, and published the paper on the basis for the lumbar vertebrae maternal effect...<sup>1</sup>

MB So what we're actually...

AM ...but throughout the 1950s we were publishing papers on superpregnancy, and the technique of embryo transfer and that sort of thing.

MB Yes. So you're, we're talking about five years, six years of actually working?

AM We actually worked together in London for seven years, but it would've been like five years before we got an answer...

MB Getting the techniques all sorted...

AM ...answer to our original question.

MB .and then you could go on with the main, the main question.

AM That's right, yes, yes. And we were fortunate because very often one only gets a three-year grant, well in those days one only got a three-year grant from the Agricultural Research Council. It would now be called a post-doc. But in fact, we got a total of seven years and at the end of that time of course we had to look for proper jobs!

MB This was, this was because the research was actually producing such a range of publications that they had, they felt they had to put you on.

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<sup>1</sup> A McLaren, D Michie, 'Factors affecting vertebral variation in mice. IV. Experimental analysis of the uterine basis of a maternal effect', *Journal of Embryology and Experimental Morphology*, 1958, 6, 645-59.

AM That's right, yes, yes. At the end of three years we moved from the University College to the Royal Veterinary College, because we had so many mice we'd outgrown the mouse facilities at University College.

MB This was Haldane's fly room? Was this a...

AM It was a room in Haldane's fly house, yes.

MB Right, yes, and you'd taken over!

AM We had too many mice.

MB How did you negotiate that transfer to Camden, was that to the Royal Vet School? Was that easily done, did they invite you? I mean, I just wondered why you...

AM I guess we looked around for anywhere in London that would have mouse space, and the Royal Veterinary College had surplus mouse space.

MB And you had four good years there.

AM And I think we arranged it through Professor Amoroso<sup>2</sup> who was the professor of physiology there, but we weren't in his department. Fortunately, Donald realised that it would be very much to our benefit not to be in any particular department. And it turned out that that was very, very wise because the departments were all at loggerheads with one another, and as a little separate unit...

MB You could stay quite clear of that.

AM We could stay clear of that, and we could use the facilities of all the departments. We used the controlled temperature rooms from the animal husbandry department, the x-ray equipment from another department, and so forth.

MB So you kept out of the cross fire...

AM Yes, as far as we could.

MB ...but managed to take on all the advantages...

AM As far as we could.

MB ...and have a good relationship with the places. They obviously were good years, yes. Just looking at the domestic scene, because that was, that was an important time for you in your marriage. Whilst we're still at University College, London, we should say that you had a first child, you had a daughter?

AM Yes, yes, a daughter, then...

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<sup>2</sup> Professor Emmanuel Ciprian Amoroso.

MB Born one year before leaving...

AM That's right.

MB ...UCL. Because I've got a feeling that you said they were marvellous because we had to take baby in, and people, people helped us to...

AM Yes. Our colleagues, our colleagues were extremely supportive, most generous and, yes, kind, kind to our children.

MB Because I was interested in how one coped with having a family at the same time as being so committed to laboratory work.

AM Well, yes.

MB And you said it was, it was relatively easy because people were supportive.

AM Yes, yes. We didn't take the children in every day, obviously. We had an *au pair* girl in the flat in London who looked after them most of the time. But when we did take them in, and, you know, when the first one was tiny obviously we took her in, and...

MB But you were to have a son soon afterwards when you got to, when you got to Camden.

AM Yes, yes. No, people were very, very supportive.

MB It's nice to have that part of the story taken in.

AM No, they really were.

MB And you got quite interested in motherhood particularly, not... Because I think you interviewed some mums around who'd also kind of had babies around the time of yours, about their pregnancy experience?

AM With not so much the pregnancy experience, but it was the question of embryo transfer. Because since we were doing embryo transfers in animals at that time it was obvious that eventually this technique would become available for treatment for infertility in humans. I didn't know how long it would take, in fact Louise Brown<sup>3</sup> wasn't born until 1978 so that was twenty-five years later, twenty years later. But the technique was there, it was going to be extended to farm animals, and it was interesting to think of how the social and ethical implications would figure when it was applied clinically. And since one's friends were having their families at the same time, I remember asking one or two women would they feel the baby was more their own if it was an egg from somebody else and they gestated the baby, or alternatively whether it was their egg that they gave to what we would now call a surrogate mother and it was gestated by another woman? And, it was a tiny sample, it can't have been more than four or five, but most people said they'd feel it was more their own baby if they gestated it and gave birth to it. And I think I'd have felt that as well.

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<sup>3</sup> Louise Brown was the first 'test-tube' baby, born in 1978.

MB And that mirrors the kind of findings elsewhere in, over more recent years. So there's a little bit of social research there going on in the, in the background apart from the...

AM I always interested in...

MB How fascinating.

AM ...well, you know, we were working for the Agricultural Research Council, I was always interested in possible applications of one's work. I think that was why I was working on mice, and not on *Drosophila* or worms or anything else.

MB In this early, kind of moving with this early ball, if I can use this sports term, I mean you were quite early in this field, seeing the way that...

AM We were the first people in Britain to do any embryo transfer. And that meant, in fact, that it was very difficult to get the technique established because we had nobody to go to and say 'Show us what a mouse egg looks like. Show us what an eight-cell embryo looks like. How do we get them out of the reproductive tract...?'

MB You had to make all your own mistakes?

AM That's right, that's right. But we struggled on. And while we were at the Royal Veterinary College John Biggers was working there too, and he had a nice culture system going for chick bone. He was working on chick embryo bones, growth in culture. And so as we had these early mouse embryos, he cultured some of these embryos from eight-cell stage up to blastocyst, and then I put them back into the uterus of a foster mother and they were born as normal, healthy mice. And we mated them and they were fertile. And that was actually the first time it had been shown that mammalian embryos could be cultured *in vitro* – outside the body – and they would develop normally thereafter. So that was an interesting experiment, and he was...

MB That must have been a spectacular time, and that must have caused a lot of publicity around...

AM Yes, we had quite a lot of publicity about that.

MB There's one thing we've not looked at, I just think we might cover as we go. You were looking at a wave that hadn't beached, I mean, but the prospects of it all were quite clear to you, I think, that this would be a massive thing for medicine and have world-wide implications for fertility, for childbirth.

AM I hoped that it would be possible for the technique... I knew that Bob Edwards, who was, you know, a student at the same time that I was, he was also interested in early embryo development and embryo transfer, he was doing the same sort of thing.

MB Where was he based at that stage?

AM Edinburgh.

MB Edinburgh, yes.

AM And then he came down to Cambridge and started working on the human reproductive system. And, yes, I had a great admiration for him, so my guess was that, you know, he'd pull it off and that one would in the end see Louise Brown being born. But of course I didn't know how long it would take.

MB A classical story, isn't it though? The momentum building up, all towards this incredible situation we have at present.

AM And all through the late '60s and 1970s – I'm going on a little bit now – there was a lot of discussion on social and ethical implications of the new reproductive technologies. It didn't come as a total surprise...

MB And you must have served on committees about that...

AM Indeed.

MB ... being central to that.

AM Yes, yes.

MB We might put a major committee or two on the record, because there were critical committees. I'm thinking Warnock<sup>4</sup>, is that wrong?

AM Oh, well that was later, that was well after Louise Brown. MB That was later, yes. But thinking before...

AM Yes. I remember there was a British Association Committee<sup>5</sup>, that must have been early 1970s.

MB Yes, seventies, yes.

AM I think it was Walter Bodmer who chaired it. Shirley Williams was a member. We met in the ... what's that liberal club called in Pall Mall, round the corner from the Athenaeum, famous London club?

MB Yes it's famous, where they, where a film that I remember started out from, Round the World in whatever days...<sup>6</sup>

AM Well Shirley and I had to be smuggled up through the tradesman's entrance and the back lift, because of course women weren't allowed...

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<sup>4</sup> The Warnock Committee (committee of inquiry into human fertilisation) was set up to consider the legal and ethical consequences of embryo research, and proposed that experimentation on the embryo would be acceptable up to fourteen days after fertilisation.

<sup>5</sup> This refers to the committee of scientists and others (lawyers, politicians and theologians) organised by the British Association for the Advancement of Science, to discuss issues such as genetic engineering, *in vitro* fertilisation, transplantation and their effects on society.

<sup>6</sup> Round the World in 80 Days (1956).

MB The Reform Club is it?

AM Reform Club! That's the name of it. Yes, that's right. But that was later.

MB Just while we are talking about Shirley Williams and politicians, perhaps I could make a, make a *cul-de-sac* kind of tour, and just say that you were not immune from political interests. You'd got a strong political sense.

AM No, I was interested in politics and always very left wing, because when I went to Oxford it was that 1945 election and I followed that very closely. And I was delighted when Labour got into office.

MB Did you . . . you took part in campaigning?

AM I was more of an observer at that stage, and then the big campaigns after that were against atom bomb tests throughout the 1950s, and I was going around lecturing on the genetic effects of radiation, long-term effects of radiation...

MB I think whilst you were in Oxford. . .

AM 'Ban the bomb', all of that.

MB . . .yes, you'd set up a peace committee, helped to set up a peace committee?

AM Oxford and District Peace Committee, yes.

MB We ought to have that, just looking at this political animal that's in there, Anne, because it was strong, you did feel strongly about it. . .

AM Oh, I still do.

MB Yes, but I'm talking about then, I'm just trying to get that time absolutely crystallised out.

AM Yes, yes. No, there was a lot of political activity.

MB It was, it was very strong.

AM Yes.

MB How did that go down with the family, all the socialism? Because I don't get...

AM I didn't see much of the family at that time. The Oxford and District Peace Committee was quite active.

MB Dorothy Hodgkin was involved, I think?

AM Yes, yes, she was a member of it.

MB This was the first time you met Dorothy.

AM Yes, that's right.

MB Incredible to meet this, this soul, who was also dedicated politically to this end, I mean...

AM Yes, in fact that was the, those were the only years when I really saw anything of her, because our paths diverged after that.

MB Golden moments. But this was the political side; I just wanted to tease some of that out. We'll get you back now to the research. But the responsibilities of this committee work, that must have been quite, quite a happy part of being political and being involved – the wider field, the ethics, the implications down the line.

AM Yes, yes. It all interacted. But going back to the lumbar vertebrae, if I may, we struggled on and collected our data. We devised a technique where we didn't have to kill the mice to count the number of lumbar vertebrae; we could x-ray them. We used to stick them down on their backs with sellotape, on the x-ray film, and x-ray them in big batches. And we collected quite a lot of data, and it had to be analysed very carefully statistically – and Donald was extremely good at that of course, because all his Bletchley Park experience was statistics-oriented – because each litter had to be analysed separately. And there were complications because sometimes you got an asymmetrical mouse, which was where the sixth lumbar vertebrae was sacralised on one side and not on the other. But it was frustrating because the data really wasn't making a great deal of sense, and it wasn't telling us either yes, it's uterine, or yes, it's cytoplasmic, and that's always a frustrating time. And then one day we were sitting in a pub chatting, and realised that we hadn't allowed for the sex effect, because there's a difference between males and females in the degree of sacralisation as well as the degree of asymmetry. And when we looked at the data again and allowed for that, it made much better sense and it turned out that it was highly significantly a uterine effect. So it was an effect exerted through the uterus of the mother and not the cytoplasm of the egg.

MB And did you go on at that stage to try to look at what that effect might be?

AM Well by that time it was the end of the 1950s, the end of our grant period. We checked that it wasn't simply growth rate or anything like that, it wasn't related with size. I checked that it wasn't the body temperature of the two strains. There was no difference that was relevant there. And really I think even if we hadn't moved away there would have been no way in which, at that time, one could have solved it...

MB Technologically...

AM .technologically.

MB ...the story wasn't there.

AM Because it wasn't really until the late 1980s that all the question about the Hox genes, Homeobox genes(?), which lay down the pattern of segmentation of the, of the vertebral column emerged. Nowadays, one knows just which Hox gene it is, I think it's



group 11 Hox genes that determine the sacralisation or otherwise of that sixth lumbar vertebra. And my guess is that today, if somebody went back and looked at that, they might find that perhaps there was a subtle difference in timing of development between the two strains. Or it's been shown that that particular Hox gene, the expression is responsive to retinoic acid, so maybe there's a difference in retinoic acid or some related metabolite coming from the mother, which is different between the two strains. Something of that sort.

MB But as you say the sync, the timing, availability...

AM Could never have done that in the 1960s.

MB ...it's colossal. You couldn't have possibly got near it. It's still not known.

AM That's right. So I'm glad I didn't go banging my head against that brick wall.

MB It was back to your old style, though. Like I'm not going to read all the Dickens; I'm going to do something else. You put it aside.

AM Yes, I'm afraid I'm not a sticker in that sense.

MB The chemistry, I put aside.

AM If I come up against a big problem, I prefer to go sideways.

MB It's actually served you well, Anne.

AM It has, yes, yes. I've been very fortunate.

MB I just want to come back to two issues that we got into that would be nice to know about from that period. We talked about the superovulation and the superpregnancies. Can we, can we just have outcomes on that, because that took part, it was going to go on, it was going to span into your next, into your next kind of existence in another research centre? But some results had come out in that, in that period of the fifties?

AM Right. Well, we were comparing the number of eggs shed by young females in response to hormones, older females, and the extent to which those eggs would successfully implant in the uterus and whether you could get pregnancies resulting. And then yes, when I moved to Edinburgh I continued that work and I looked at the degree to which eggs were shed from right ovary versus left ovary – the asymmetry business – and the relationship with placental weight. So there was a lot of, a lot of later work on that, and of course my job in Edinburgh was again on the staff of the Agricultural Research Council...

MB I'm just going to keep you...

AM ...and they were interested in ovulation.

MB ...yes, from that for the moment, but in the results I think you found that, exactly as one might expect, the casualty rate really mirrored very much the

overloading of the, of the uterine environment.

AM Yes, yes. In fact, the greater the number of embryos implanted, the smaller the number of babies born alive. One got a U-shaped curve; up to a point it increased but then after that it decreased again. So from the point of view of agricultural productivity, one didn't want to push up ovulation rate too high.

MB We can get to 1959, when you go north...

AM When I move to Edinburgh, yes.

MB ...to Scotland, to Edinburgh, Let's just tidy up the edges of the London existence before we travel. You're a mum, three children by now.

AM Well, the last was born in Edinburgh, yes, yes.

MB In Edinburgh. But this is, this is part of the plot by now. The marriage is coming to an end?

AM Yes. And scientifically we were going our different ways.

MB Right, so there is a major bifurcation of a, of a team that was. Donald went off to work in the University in Edinburgh, in a surgical...

AM That's right, the department of surgical science, for Professor Woodruff – Michael Woodruff – on tissue transplantation.

MB I should say that I think the thing that surprised and excited me in looking at that family relationship you had is that it still continued.

AM Yes, indeed.

MB It still was immensely fruitful and supportive and meaningful to both of you over the years.

AM Yes, yes. No, we went on being good friends, yes.

MB Yes. A classically important relationship that goes on and goes on and goes on. Let's get you to the Institute of Animal Genetics. Waddington's<sup>7</sup> brainchild, is that right?

AM Professor, Professor Waddington, yes, he was my boss.

MB He's an amazing character.

AM Indeed, indeed.

MB I think underestimated. Am I right?

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<sup>7</sup> Professor Conrad Hal Waddington.

AM I agree, I think he isn't appreciated scientifically nearly as much as he should have been.

MB Yes. But you'll make that right, because you have a...

AM Well, today I've been interested that quite a lot of his lines of work are now becoming fashionable again, and people are referring to his early work in the literature, yes.

MB You mentioned Waddington earlier when we talked this morning and said that he was one of the names in the literature who was an exciting writer at the time.

AM Right, on evolution, yes, yes. Well of course that was, that was well before I knew him.

MB Yes. So you were already in touch with his work and thinking to some extent. You went there. Was that an exciting institute to join? I mean what was the stage in '59?

AM Oh enormously, enormously exciting. No, it was the most wonderful scientific atmosphere I've come across anywhere. Partly because of the intellectual excitement. What Waddington did was to get grants from all over the place – I mean probably more than one hundred grants came into that institute – and he put them all in a bit pot and stirred them up, and used them for whatever he thought was most in need, most in need. And one of the things he did was to subsidise the canteen there, and at that time I think it was the only canteen on the campus and people used to come from all over – zoology, molecular biology – and there were...

MB So it was a seminal meeting ground?

AM ....these wonderful lunchtime conversations. Yes.

MB A star place...

AM Tremendously intellectually stimulating, I mean quite apart from the people in the institute itself, who did genetics...

MB And was Waddington a presence, was he around? I mean...

AM He was abroad a lot, so he wasn't...

MB Right, I just got a feeling he was, he was always into something.

AM Yes, yes. No he...

MB So he wasn't a natural part of that stimulating conversational environment.

AM Not so much. When he was there, he was very stimulating, but he wasn't there much.

MB But he was the top man. A powerful administrator.

AM And he organised the institute in such a way that everything was laid on. There was a graphics department, a draughtsman who used to draw diagrams and beautiful drawings of mouse embryos. There was an excellent photography department, statistics, excellent statistics expertise, very good library of course, histology was done for one.

MB This was ahead of its time.

AM There was even a film unit. There was even a film unit, so if one wanted time-lapse cinematography of one's embryos developing, one went along to Eric Lucie(?) and got the film done.

MB It happened.

AM Yes. Very good animal facilities; mouse, rabbit... It really was an amazing, amazing institute. Early computers. The lot. And, of course when I left to set up my own unit I realised for the first time just how fortunate I'd been, and that all these facilities didn't grow on trees. If one wanted them one had to set them up oneself.

MB I'm just getting to this ... Conrad Waddington was it?

AM He was always called Wad, but I think his initials – CH – actually stood for Conrad Hal.

MB He took all these grants, like a supremo. I mean I think he'd been head of bomber command or done something in the war and been quite powerful in the RAF. He took all this money...

AM It was what's called operations research, and one never knew quite what it was but it was obviously very important.

MB Yes. He took all this money, and dished it out as he felt fit?

AM That was the impression that I got.

MB And other people got that impression because he got into bad light subsequently.

AM I'm afraid he did, yes, I'm afraid...

MB Was this with the research councils?

AM ...the accountants...

MB Oh, right.

AM Yes, yes, I think they finally...

MB Because it didn't end well, I've got a feeling it didn't end well.

AM No, he got into some trouble I think. I don't know the details, yes.

MB But that's sad, because he deserved a better epitaph.

AM Yes! But as I say his reputation is now very high, very high.

MB Let us take in the research that you went with, Anne. You're still committed to the maternal influence field.

AM The, well yes...

MB And the superovulation?

AM The reproductive biology, the superovulation, the maternal influence. I did some work on immunocontraception; immunising mice against sperm, immunising female mice against sperm, which induces infertility. And that again is a technique that much much later was taken up for possible clinical use. I mean it's still under investigation as a possible new approach to contraception.

MB Do you think that there's mileage, real mileage? You feel that that's got a large future.

AM Yes, whether it will be immunisation against sperm antigen, rather than one of the other antigens that are being tried... hCG – that's human chorionic gonadotropin – may be the most, the most optimistic one, or zona pellucida. There are a number of different approaches but I think that the immunological approach is a promising one, yes.

MB So this fertility area became the field you increasingly were known for. I mean...

AM Yes, and with Waddington's help I and Alan Beatty, who was working in the institute, got a big grant from the Ford Foundation for reproductive work possibly leading to new forms of contraception, and...

MB It didn't go into the pot, you managed to keep...

AM Yes, yes! And of course that enabled me to take on a post-doc or two and a graduate student or two. And I did a lot of work on implantation, because the implantation of the embryo in the uterus is a very critical point of reproduction – certainly in the human it's the time at which a lot of pregnancies fail. And therefore it's a promising target for contraception as well as an important aspect of infertility. And I did a lot of work on that in mice. I was unable to identify the signal that the mouse embryo gives to the uterus which induces the first implantation reaction which is crucial to the success of implantation in the mouse, and actually that still hasn't been identified. [It is] partly because I was up against a brick wall there, and partly because I realised that the mouse model of implantation was not a good one for the human – it's quite a different type of implantation, pattern of implantation – that I moved on and gave that up, and went more back to the...

MB It's a classical challenge, isn't it? What is the, what is the message, the signal, that heralds this incredible response on the part of the uterus to accommodate a

blastion(?)<sup>8</sup>?

AM That's right. I knew what the systemic message was that would sensitise the whole uterus; that was oestrogen, which was derived from the ovaries as a result of the mating signal. But what the actual local signal for each blastocyst in the uterus was, is still not known.

MB The classical question.

AM And yet it's very, very definite, starts at a particular time. I could identify three, four, five, six stages immediately following on...

MB Really, well we've got a, you think we've got a...

AM ... but what the signal was...

MB ... classical receptor-ligand kind of sequence?

AM I think we have, but of course in those days one didn't know about receptors, one didn't know about ligands. There was no molecular biology.

MB Yes, hasn't it come a long way, we've got a...

AM It certainly has.

MB ...I thought the names of receptors could be counted on one finger.

AM Yes, yes. No, it was a very different scene. I tried to get into DNA, because in the early 1960s I went to a congress of zoology in Washington D.C., and...

MB In 1961, I think.

AM '61, that's right, and heard Roy Britten talking about the Britten and Davidson<sup>9</sup> DNA hybridisation work that they were doing. And I thought that was absolutely fascinating, because it seemed to me that if one could hybridise DNA from different sources it would be like an antibody-antigen reaction. And one could do the same sort of subtractive hybridisation that one can do with antibody-antigen and maybe pick up, you know, differences in the DNA between species that were too distant to be able to cross them sexually. And I worked for quite a while with Peter Walker in Edinburgh, I was able to enthuse him when I got back to Edinburgh and he was very, very helpful and spent a lot of time with me trying to make this work. And we did get some results, but...

MB He was in the university, working on the molecular biology side.

AM He was in the zoology department, that's right. But unfortunately the technology in those days was only capable of identifying hybridisation based on highly repeated sequences. And of course those aren't the sort of...

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<sup>8</sup> Dr Blythe might mean blastocyst here.

<sup>9</sup> Eric Davidson.

MB Yes, those are not the...

AM ...differences between species that I was interested in. So although it was interesting and useful experience it didn't lead to very much.

MB But philosophically, you got deeply tied into the possibilities of that.

AM Yes indeed, that's right.

MB I mean, that was an exciting period, and it could have gone miles if there'd been opportunity. It eventually came good because Ed Southern...

AM That's right, Ed Southern was one of Peter Walkers' post-docs at that time, and it was shortly after that that he invented Southern blotting, which nobody now hardly even remembers. The Southern of Southern blotting is Ed Southern's surname, yes.

MB So those were fascinating early sixties. The DNA work just got going, two or three years I think you were regularly going over to the university, it was quite a busy time.

AM That's right. Yes, yes, all through the mid-sixties, yes.

MB Yes. What actually followed in the later sixties? What came to take its place?

AM Well, I was doing embryo culture back in the genetics department, the same sort of culture that John Diggers had started off doing at the veterinary college.

MB So you went back to that.

AM He'd moved to America, and was carrying on with that work in America. And I was very interested in the new technique of making chimeras, where you aggregate embryos from two different strains together to make a compound embryo, twice the normal size, but it regulates its size and is born the normal size. And of course if you have...

MB You say, I think you said it regulates the gastrulation somehow, is that right?

AM Yes, that's right. What seems to happen is that one whole cell division is inhibited...

MB Switched off, yes.

AM ...switched off, so it, from being twice the normal size it goes back to normal size again.

MB Yes, it comes back into line. Tremendous adaptive mechanism.

AM It's clever that it knows how big it ought to be, isn't it?

MB Yes. But that must have been absolutely... I mean, that must have taken over a bit.

AM Yes, well it meant getting the culture technique set up first, because unless you

have a good culture technique you can't possibly make chimeras. And once the culture technique was working and the embryos were growing in culture, then we were able to make aggregation chimeras, and I had this strain of mice which had eight or nine different Mendelian recessive mutations in it. And so chimeras between those embryos and normal wild-type embryos were extremely interesting from all sorts of points of view.

MB Take me into that story a little bit, Anne, give me a little bit more on that.

AM Well, let me see. Obviously the first thing one looked at was the pigmentation, the coat colour, because that's the most striking thing you see in mice and the easiest to look at.

MB Can you get... you get zones, you can get zone effects really pronounced?

AM Yes, they're patchy, they're patchy, that's right. And...

MB That goes with hair as well, I think you said you were counting hair and granules of pigment.

AM Yes, one can look at individual hairs, and one could see the chimeras. And even within the individual hair, a single hair could have some of the characteristics of the mutant strain and some of the, of the wild-type strain. And some of the genes act through the pigment granules themselves, but some act through the environment of the hair follicle, so again you get an interaction between the gene expression and the environment in which it's operating. The agouti gene, for example, is expressed through the hair follicle, but the albino gene is expressed through the actual pigment granules, the pigment cells.

MB You were really into a field that was very much where you'd looked to be. I mean, this was cells surrounded by environments that were quite curiously variable... A cell normally knows what's around it and there's fairly constant ... great consistency.

AM That's right.

MB All of a sudden you were stacking around cells in a new environment.

AM That's right, that's right.

MB That's very much your developmental area.

AM In a normal animal every cell is surrounded by other cells of the same genetic constitution, but here one could look at cells that were surrounded by other cells of a different genetic constitution. And that gave some very fascinating, fascinating results. I looked at the coat colour, at the individual hairs, with Grüneberg<sup>10</sup> in London. We looked at teeth and we looked at skeletal characteristics. And then I looked at the reproductive tract, and that was the thing that led me on to subsequent work, because of course half the aggregation chimeras you make are going to be, on average, between a female embryo and a male embryo. And most of those develop as males, which is interesting in itself, a few develop as intersexes, and a few develop as females. And following up that story, and also looking at how the germ cells, deciding whether they're going to turn

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<sup>10</sup> Hans Grüneberg.



into sperm or eggs, were effected by that environmental interaction, that proved a fascinating line of work throughout really the seventies and eighties.

MB Right. That went right on. But classically important to fertility research.

AM Yes, yes, and very interesting to me.

MB Grüneberg, and that work on teeth, that was quite, quite remarkable.

AM Grüneberg was an amazing, an amazing man. He was a meticulous worker who knew every corner of every bone in the mouse body, and every cusp on every molar and tooth. And I would never have had the patience or the knowledge to have worked that out, but with his help we got some quite interesting results.

MB Fascinating strains you got of mice with curious, curious teeth!

AM Yes, they were the tabby mice!

MB Tabby mice.

AM Yes, they had funny teeth.

MB Yes. Thanks for putting that on the record for me. Anne, we're getting you through the seventies, we've already indicated the things which would go on into the eighties. This was the great pattern of the seventies that we've got into; the chimera story was the great part of the, of the second half of the sixties, going into the seventies.

AM That's right, yes, yes.

MB How did that result... I think you went, about 1974, to a new, to a new appointment?

AM Well, it was all going very well in Edinburgh, and because it was going well Alan Beatty and I thought we could ask the Ford Foundation, rather impertinently, for a large sum of money to build a centre of reproductive biology in Edinburgh. And so we wrote up a big grant application, and they gave us a quarter of a million dollars. And at the same time the Medical Research Council were wanting to set up a unit of reproductive biology. And those two schemes came together. Edinburgh ... through a bid that was put together by David Baird and Roger Short – they won the bid for the MRC Unit of Reproductive Biology – so the four of us got together and decided that the centre should be built in Edinburgh and should house the unit. And that sort of plotting...

MB That came about...

AM ...was the early seventies, but of course in the way things are it took a long time to be actually planned and built. And meantime I had been attracted to London, partly because my children were getting to university age and the centre of gravity of the family was moving south, and I'd been in Edinburgh for fifteen years, which is a long time to be in one place. So the Medical Research Council set up a new unit, and I became director of it. It was called the [MRC] Mammalian Development Unit. Those were the early days of

computer databases, I wasn't allowed more than two names in the title of the unit, otherwise it would have been called something rather different I think. So it was called Mammalian Development, and we had all sorts of funny envelopes addressed to 'mammary development' and I don't know what else. But anyway...

MB Where was that set up, Anne? Where was it?

AM It was set up at University College [London], in the same mouse space that Grüneberg had recently vacated, because his unit had come to an end, and...

MB Right. So you were eventually coming back to UCL.

AM That's right, and I'd of course visited Grüneberg in connection with our joint work on the chimeras, and so I knew his mouse space was good mouse space. And I went and looked at it and measured it, and so we moved in there. Unfortunately, and this was a shame really, unfortunately the Lister Institute packed up at just about the time that we were moving in, and the Medical Research Council rescued the very important Blood Group Unit of Race and Sanger<sup>11</sup>. And there was nowhere else to house it except in our space, so we gave up a third of our space to the Blood Group Unit.

MB So you sacrificed right away?

AM That's right, so the unit was never actually on the scale that I would've liked, and that made problems with accommodation all the way through.

MB Yes. Because you'd got it all set in your mind by then.

AM That's right, yes, yes.

MB What was the time you came down? Was that '74 you came south...

AM '74, yes, that's right.

MB ..back to London.

AM Yes, yes, back to London.

MB Anne, at that particular point, getting you back to London, I'm going to leave it for today...

AM Right.

MB ...and we'll take up the story of the later years, and all their fascination, next time we meet.

AM Okay, okay. Fine, well thank you very much.

MB Thank you very much..

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<sup>11</sup> Robert Russell Race and Ruth Sanger.