The Royal College of Physicians and Oxford Brookes University
Medical Sciences Video Archive MSVA 156

Professor Kenneth Reid FRS in interview with Dr Max Blythe
Oxford, 28th January 1997, Interview I Part Two

MB Ken, in our first interview I got you into the, to the later 1970s, second half of the 1970s, in Rod Porter's unit, immunochemistry unit in Oxford. And, there are a few questions that I'd probably like to begin by asking. First of all, when you came to that unit in the late sixties, 1969, you started off something entirely new there, I think, virtually new – work on the complement system.

KR It had been really brought there by Newton Hyslop who we mentioned before, and it might have stopped with him, the work on the complement system and continued more on antibody-antigen interactions…

MB Right.

KR …and antibody structure. But, I think Rod Porter was looking for something new to work on, and since I took an interest in the complement system I think he encouraged that interest. And I think a lot of the, well I know a lot of the complement work did stem form the initial work on C1q which went on to C1r and C1s, which we mentioned before, which then went on to the other complement components…

MB This just grew, didn't it?

KR …C4 and C2 and C3.

MB Yes. I mean you stamped a new direction on the unit effectively. And that's really what happened?

KR Yes, it was an exciting time.

MB And Rod Porter supported you enormously in that, I mean it wasn't the way you might naturally have gone.

KR … I, yes I, well he said himself he was looking… He did his Nobel Prize winning work on establishing the chain structure of the immunoglobulin G molecule, and doing sequence work on the immunoglobulin G molecule. And, that really established the structure of anti, of antibodies in general, and that was…

MB That was the Nobel Prize that came about four years into your life there?

KR He was awarded that Nobel Prize in '72…

MB '73? Oh, '72, yes.

KR …'72, for work he did in the, in the sixties, in the fifties and sixties.

MB Were there any other things that were coming along, though, apart… The complement system took over – that was the alternative, it turned out…

KR The, he also, Rod Porter was interested in moving some of the unit into cellular immunology, and he made a very good appointment to the unit – Alan Williams joined the unit in, I think it was '71 or '72, and was making his name in cellular immunology. And he was looking at cell-surface molecules, what were their roles in immunity, whether the whole – it's more any lymphoid cells…

MB Right.

KR …Alan had an interest in B-cells and T-cells.

MB Right, surface protein.

KR Yes. And he, Rod recognised his abilities and put him forward for directorship of the cellular immunology unit, which was sited in pathology.

MB Right.

KR Gowans[1] left that unit in, to become head of the MRC.

MB Yes, and he moved in?

KR And Alan was in fact the youngest MRC director ever appointed, as far as I'm aware.

MB And that closed that line of research down?

KR Well, Alan took the cellular immunology work into that unit, and our unit really…

MB Exclusively complement?

KR …worked exclusively on complement in certainly the eighties, mid-eighties. Although we did do some cellular work it was more looking at cell-surface receptors, not working very much with cells *per se*.

MB But, I mean even by the late seventies, later seventies that we came in on – I mean it was largely complement.

KR Yes.

MB And you were the guy who took it there. I'm just coming round full cycle on that. But that must have been quite heavy, did you feel that eventually you would take that unit over?

[1] Sir James Gowans.

KR I hadn't really thought in those terms, and by the early eighties I was looking round, because Rod Porter was due to retire in '85, and it wasn't quite clear what would become of the unit and what was going to transpire beyond '85.

MB So there was a kind of cloud of doubt at that time?

KR Yes, I think most of the postdoctoral scientists were considering their futures and… But then it became clear that there would be continuation in a new building called the Rex Richards building.

MB Yes, how did that come about? What was going, I mean…

KR It's … I think it's fair to say it was primarily Rod Porter's initiative and his contact within the university with people such as Rex Richards who had the vision to see that it would be useful to put a team of immunochemists and physical scientists, and NMR – people who worked on NMR spectroscopy of proteins and crystallography of proteins within the one building. And initially it was set up to house the NMR magnets to look at proteins, and also the MRC Immunochemistry Unit. And then later funds were obtained to put another couple of storeys on the building.

MB David Phillip's unit…

KR Which David Phillip's unit, which… The, the Burke Laboratory of Molecular Biophysics, which was housed in zoology at that time then moved over.

MB Yes, so that was quite a lot of planning. Did that come quite quickly; it had been in the pipeline in the seventies?

KR It moved, it moved on remarkably quickly. I remember that we were doing planning in '83, and we, '82/'83, and we moved into the building in '84 or '85.

MB And you designed it, I mean in house, your floor of that building, very, very precisely…

KR The senior scientists…

MB …to fit the complement needs.

KR …were, were able to design the labs to their…

MB Protein…

KR …requirements, yes.

MB Presumably you had a large cold storage area?

KR We had things … things like a large cold room were essential, and a large room for the protein sequencers, and other facilities for the DNA were necessary, and radioactivity work.

MB So, that took shape very, very quickly. But Porter was due to go in '85.

KR '85, as Whitley professor of biochemistry, he was due to retire.

MB You realised that, you realised though that with the new building that unit was going to have a well-established life.

KR Well, the MRC showed some foresight in the way that they felt that the – they considered the unit would continue beyond that because I was appointed deputy director in '84.

MB Was that a shock?

KR Well, I was slightly surprised – it was a, it was unusual to appoint a deputy director when it wasn't clear what the, you know, the focus of the unit might be if Porter maybe decided to move away or…

MB Had Rod Porter talked to you about that possibility, that you'd be deputy?

KR Yes, well at that time we obviously had to discuss things, and it was clear that he wanted to continue in Oxford and to do his own research.

MB After '85?

KR After '85.

MB In the unit that you would then be administering.

KR He wanted to go back and do benchwork, and he was actually doing crystallography work in '85 on, at the bench himself.

MB Let's just hold at that particular point – '84. You get the call, you are going to be deputy. But, by then, I think in the early eighties you started to see a fairly clear and rather impressive team structure being imposed upon that unit. You'd worked in groups before. Can you tell me about the teams that formed, because that was an interesting period? Was that early eighties, am I right?

KR Bob Sim, of course…

MB Would work with you.

KR …was a student with me, and he worked with Rod Porter and myself on the C1q, r, and s. And then he spent two years in France, and then Rod Porter was keen to get him back, so he rejoined us in the late seventies. And he went on from there to set up his own lab, working on complement proteins and receptors. So that was one main group, which was obviously very closely allied to my own group. And Duncan Campbell, who set up another major group in the unit, joined us in '81 from Aberdeen. He did his first degree in Glasgow and then he moved to Aberdeen to do a PhD, he…

MB Did you poach him, did you go looking for him, or he just came?

KR No, he came, he enquired about doing postdoctoral work, and his background was all protein chemistry, but he very quickly moved into recombinant DNA technology. And he moved on much at the same pace as, Mike Carroll is another person I mentioned earlier, and took on work on C4 and factor B – one of the proteins of the alternative path for the...

MB And collected all those?

KR And he, and these proteins are encoded in what's called the major histocompatibility complex. And these, the so-called, so-called Class III proteins in that complex, and Duncan just set about doing a very solid analysis of all the genes within that complex and identified a host of new genes. And in fact…

MB That's a massive…

KR …this time it's a huge job and it shows a great deal of skill and organisation. And it's one of the best-mapped and fully sequenced portions of the human genome. And, I think this will be recognised by Duncan probably setting up his own unit in the future, and interface(?) with people working on the human genome project.

MB Ken, just let me put one point in at this, at this moment. You talk about Duncan – Duncan's had a considerable reputation for a time, for a long time. People don't tend to move away from that unit, do they? Well always, even in, from Porter's time, in your administration time, I wanted to just establish… There's been a reluctance of people to move on, even though they could have moved probably to Chairs in units.

KR It's true that people have often had offers which seem very attractive, from outside…

MB But they wanted to stay?

KR …but the opportunities in the unit are rather great, because you're given… Well, we've tended to try and give people a very free hand with their own groups, and also the facilities within biochemistry are, I think, second to none in the, the UK. And I suppose the attraction is that you have ready access to postdoctoral people and students who come to Oxford because Oxford … attracts a lot of bright younger scientists.

MB Would the climate in the laboratory also have something to do with it as well? And it was a climate that Rod Porter created, and that you took on as a legacy, and you've tried to make work as well.

KR Well, I think it works very well having discrete groups but groups which are interfacing with each other. And leaders of the groups should be given a free hand. And there should be a framework of people who are there to provide continuity – the

senior scientists and the senior technical people – and that other people should move in and out within a two to three year period. It's a very healthy situation, I think.

MB Just coming back now to Duncan, Duncan's work – the whole move of that into really complex genetics, and a lot of characterisation of genes. I mean, did that fit the unit? Does it belong in another unit outside, or did that fit what you were doing?

KR Well, initially it fitted very well because the genes and the proteins that Duncan was looking at were complement proteins or related to some aspect of the complement system. But then it got more general as he looked at proteins that may or may not have some role in controlling or affecting disease associations that mapped into the major histocompatibility complex. So his remit has grown rather wider and, and I think he's almost outgrown the unit in some respects. And the other person we haven't mentioned so far is Alex Law…

MB Law, yes.

KR …joined the unit in '82/'83. He came as a very accomplished scientist for, well, inter … with an international reputation in the complement system before he reached Oxford, for establishing the covalent binding properties of the C3 molecule, which was an unusual…

MB He came from Boston?

KR Yes, he had, the major work had been done in Boston, but… And Paul Lavine is one of the people he'd worked with, and Law and Lavine is a sort of seminal paper in the, in the complement system in terms of C3 function. And Alex joined the unit and has been with it ever since. And his work – he's continued to work on complement proteins but also advanced into working on cell surface molecules called the integrins, which are very much involved in cell adhesion and other phenomenon which are of immunological interest and relevant to the main thrust of the unit.

MB Yes. So these teams firm up, and become the real basis of the, of the unit in the eighties. We'll take it now to that point where you're deputy director, Porter is to retire – did that shake up, did he have to, because a tragedy…

KR We had a special symposium organised for him in Oxford in '85, and that was very successful. We had people who had worked with him and published him come from all around the world, and contribute to this symposium. And only weeks after that event he was driving to France on a holiday, and he was in a car accident and, and was killed. That was, of course, a great shock.

MB It cast a shadow over the whole, the whole unit.

KR …and he would have retired in the September, but he didn't reach that stage. But the MRC were very helpful and there was a lot of support from, well international support. We were rather overwhelmed with the number of people who wrote to the MRC supporting the view that the unit should continue.

MB And there was a chance at that point that it would go down?

KR Yes, if the director in charge of a unit moves off or dies, it has, the MRC does very often close down the unit completely. But in this case there seemed to be good support for it, for continuity.

MB And Jim Gowans was at the MRCM?

KR And, and Gowans, who of course…

MB Yes, had close links.

KR …was very familiar with the unit's research, because he had been the director of the Cellular Immunology Unit in pathology at Oxford, and was supportive as well, and…

MB But you were kept on?

KR We were told that our next site visit, which was four years away, was going to be an important time. And I was appointed director soon, in – well the end of '85/beginning of '86.

MB Bit of a shock to the system?

KR Yes it was, I mean totally unexpected because we expected…

MB That you were going to go on working with Rod for years.

KR …the senior person there to help and guide us through the first years when he was no longer fully director.

MB So you went on the bridge. Did, did people stay on board? Everybody tended to stay in place?

KR We lost, one person had decided to leave because he was unsure of… Well, he thought there were going to be better opportunities in Canada – Jean Gagnon, who had been instrumental in setting up the protein sequencing facilities in the unit, and…

MB He went back?

KR He went back to Canada. In fact he didn't stay there very long…

MB Returned to France(?).

KR …he returned to Europe, he thought, held himself as a European rather than a Canadian and he returned to France. He was French-Canadian.

MB Ken, moving the story on – you get, after that sad period, that uncertainty period, you start to realise you've got time to do something with the unit, that you are going to have a period in charge, whatever the longer destiny. There were a number

of things that had to concern you at that time. Complement, I think, was beginning to run a little bit thin – you defined so much, and the world research on complement had covered so much…

KR Yes, it was clearly going to occupy thirty/forty per cent of our time for the next few years, but we were looking at other areas. And it, of course, as I mentioned Duncan Campbell had expanded greatly in the MHC [major histocompatibility complex] Class III work, and that was one area which he made an, has made an international reputation for himself. And this was very well received at our next five-year site visit.

MB Right.

KR And Alex Law continued with his covalent binding work on…

MB C3?

KR …C3 and C4, but that was only part of his research interests.

MB That's an incredible alley that – binding. It's so dynamic, I mean…

KR And he's, he really has dominated that area of complement research over a period of almost twenty years. So it, it's understandable that he should continue with it. But he has now developed an international reputation in the integrin field.

MB But you…

KR I…

MB You made a slight move.

KR I moved on from, I still continued work on complement proteins and expression of complement proteins using recombinant DNA techniques. But we moved on to look at proteins. Initially we were interested in proteins that looked like this molecule C1q with these six globular 'heads', and collagen-like, these stalks, and collagen-like end-piece. And the, it turns out there are, other molecules like that in the blood stream and also in the lung fluids. And one of the first ones we looked at was called mannose binding protein, and by its name you would expect it to bind to carbohydrates. And of course C1q binds to proteins – it's a protein interaction, this mannose binding protein which looks like C1q binds to carbohydrates, and it had these…

MB You said we were going to come back to carbohydrates.

KR …had these collagen stalks. It's the same as C1q, and in fact it does, it is involved in activation of the complement system in a very similar way to C1q. And, but the fact you don't need this adapter molecule – you don't need the mannose binding protein in, to interact with immunoglobulin or antibodies – means that it can directly bind to the carbohydrate on the micro-organism and activate the complement system, the classical pathway of complement system. Thus we're, we have a route…

MB Yet another subtlety of the body complex(?)

KR Yes, we have a route to directly get into the complement system. It made people rethink … well, what, which is phylogenetically older, the classical or the alternative pathway. Although I think we said earlier, we discussed earlier we thought people were thinking of the older one, of course now here is a route which doesn't need antibodies which you can use the so-called classical pathway.

MB That shook up thoughts.

KR Yes it's a, it was a novel concept. And we started looking at other proteins of that type, and it, we were interested in complement activation. But it became clear there were two proteins in the lung called lung surfactant protein A, and lung surfactant protein D – the A and the D just ascribe to the order in which they were recognised. The, these proteins have no properties in complement activation, although they look very like C1q. But, it's becoming clear that these molecules, these proteins are involved in innate immunity, because they can bind to the carbohydrates… Rays of carbohydrates on micro-organisms are quite different from rays of carbohydrates you might see on your own proteins or your own cell surface. So this is a way of distinguishing between non-self and self. And the lung surfactant protein A, lung surfactant protein D, are recognising the carbohydrates on the bacterium or virus as being foreign, and dealing with the bacterium and virus by agglutinating it or, and then presenting the material to pagacytic cells. And this is one of the main thrusts of our present research.

MB I mean, I came to surfactant initially from a medical point of view, looking at the kind of physics of the alveoli, I mean the idea that it had some effect on the physical structure, and the resilience. But now, it looks as though they're much more fundamentally endowed.

KR The work on the proteins and the lung surfactant is, only happened in the last few years. And it, it's clear that the so-called SP-B and C, the other lung surfactant proteins, are very hydrophobic molecules, and they're intimately associated with the lipids – the surfactants are mostly composed of lipids of course. And it's, these lipids and surfactant proteins B and C control the surface tension in the lung to stop your lungs collapsing during breathing. But we feel that these other proteins which are structurally very similar to C1q and the mannose binding protein are, the SP-A and SP-D are molecules of innate immunity. And, because the lung is one of the first … areas of, which come into contact with a whole host of pathogens, the surface area of your lung is equivalent to the size of a football pitch, I think it is. And, so this large area has got to be protected in a way to stop foreign organisms crossing certain barriers.

MB So what is the status of this work right now? I mean, are you, are you doing animal experiments? What do you do – are you just characterising the actual structure of the surfactant?

KR We, we're characterising these proteins, now we're looking at the binding to certain micro-organisms. For example, there's an organism called *aspergillus*

fumigatus – it's a fungus which causes infection of the lung and allergy in a large number of patients. And it does appear that SP-A and SP-D bind to the carbohydrates on certain proteins of this fungus, and that promotes agglutination of the fungus and killing of the spores of the fungus. And it seems to damp down the allergic effects that the fungus elicits.

MB It's pleasing, I mean it's a major move, that(?)…

KR So, we're making recombinant forms of the SP-A and the SP-D – these lung surfactant proteins – and are hopeful that these might be of some therapeutic use. And that's one of the major areas.

MB Has anybody actually worked on animals and actually moved immune elements from the system and allowed these to be investigated independently?

KR In other laboratories?

MB Yes.

KR The … for example you can knock out genes now in an animal – you can knock out single genes, single genes and look at the effect this has on the overall metabolism or susceptibility to infection of the animal. And people have knocked out the gene for the lung surfactant protein A.

MB Oh, right.

KR So this is one of the major proteins in the lung surfactant. And it does, it's clear that these animals' respiration is quite normal, so they breathe quite happily. And it had been thought that SP-A might be very important in the structural aspect of the surfactant, that it, that it… It's beginning to look like the SP-A probably does have other roles to play other than respiration, which is our thesis – that we think that SP-A and SP-D are required for defence. And, these animals with the SP-A gene knocked out will now be looked at – they'll be given infections, to see if they're more susceptible to certain infections. And that's the, that's the direction of our research. We, we're now collaborating with people in Hammersmith Hospital to knock out the gene for the SP-D … protein, and then we would look at the role of SP-D in the SP-D-deficient animals to see if that, if that confirms our view that it, it's…

MB Fundamentally defensive?

KR …it's important in defence.

MB So you might rightly(?) have arrived at something more fundamentally exciting than antibodies or complement?

KR I think it could, it could be very, very useful if you can manipulate this first line in defence. And it, you're going to the lengths of thinking of giving, getting this developed into some sort of nasal spray, which might defend against certain viral or bacterial infections.

MB So the possibilities are considerable.

KR Mm-hmm.

MB And that is…

KR And if it is involved in allergy of course this might be useful in damping down allergic reactions, although the, obviously there are cellular elements which may be just as important or more important in this area.

MB But this is where it's all at right now?

KR Yes.

MB Fascinating. Ken, just in our last few moments, we might just have a look… You've run the unit now for … ten years, a little bit more. It's taken these teams along – it's gone from being thirty/thirty-five to a staff of about forty-five. It's never had problems of finding grants and funding as far as I know. Is the future looking good?

KR The future is looking quite promising. The … we'll probably have major turnover in the senior staff for the first time for a while, but I don't think we'll have any difficulty in filling the positions. And the outside funding – we, I suppose twelve years ago we might have only had about ten/fifteen per cent outside funding, and say fifteen years ago we were told not to go to outside the MRC for funding. But it's the way the times are going. Now we're actively encouraged to get our funding from as many bodies as possible, and so we're reaching the proportion of more than fifty per cent of the funding coming form non-MRC sources. And we've been quite successful in … certain charities, arthritis, and certain councils like the Arthritis and Rheumatism Research Council, and certain European funding bodies have awarded us grants…

MB One of the…

KR So the future is quite rosy.

MB Yes. And you now have the Chair in immunochemistry in Oxford…

KR Ah, yes.

MB …since 1991.

KR It was a bit later than that – in '93 I think it was, yes…

MB Oh, right.

KR …that I was awarded the Chair in immunochemistry by Oxford University.

MB A bit unexpected?

KR Yes, it was a very pleasant … surprise.

MB So your story's come through a number of phases. Oxford looks as though where it's going to be at for the remainder of the time running that unit. The family that we talked about very briefly earlier on – you said some children came along and you were quite busy, or Margery was, on that front – this family's pretty well grown up, gone off to university… How about, how about liking this kind of post-family at home period? Does that give you more work for the bench or are there other interests that are evolving?

KR I seem to have less time for the bench, I'm afraid, because the paperwork… Because although science has got more complex and more interesting, there's certain aspects of administration, with assessing people and safety requirements, which are, when added to writing papers, and this… I mentioned the outside grants funding – we, of course you have to write for these grants for outside funding… And I'm afraid that's taking more and more of the senior scientists' time…

MB But you lived through the team…

KR …and all the senior scientists in the unit are finding you have to spend more and more time talking and writing rather than benchwork, I'm afraid.

MB As I was saying, you've lived in a library for helping the team.

KR I think it's up to the person, it depends how the person wants to organise their responsibilities – whether they can delegate, or how much teaching they want to do, this sort of thing.

MB But you're staying in close contact with the surfactant work?

KR Ah yes, there's going, certainly over the next five years we're obliged to do a lot more work on the possible role of these carbohydrate-binding proteins in the blood and the, and the lungs in terms of resistance to infection and certain allergies.

MB Ken, perhaps you'll come back then in five years, to find out where all that went. But for now, for today thank you very much.

KR Okay, thank you.