The Royal College of Physicians and Oxford Brookes University
Medical Sciences Video Archive MSVA 124

Professor Max Bennett FAA in interview with Dr Max Blythe
Sydney, 27 March 1996

MB Professor Max Bennett, it's a great pleasure to be talking to you this afternoon here in the Royal College of Physicians in Sydney. You were born in Melbourne in 1939 to fascinating parents.

MB My father was a Jew who was very interested in engineering and was very dedicated to the religious side of his family, and my mother was of Irish descent so, as I said to you earlier, I really feel like Bloom out of Ulysses, that I have both those kinds of rather interesting heritages which I was taught to live up to and found slightly contradictory.

MB It must have been a fascinating family with that strong Catholic...

MB It was.

MB But with that Jewish pressure as your father was a strong figure.

MB Well, he was a very strong figure because he was fascinated in engineering, although he wasn't able to practise much himself because he went away to the Second World War and that really broke up his career prospects, but he was quite determined that his son would be an engineer. He was also a person of great philosophical depth and a very spiritual man, a religious man, so I think both those influences had a tremendous effect on me in my early childhood.

MB Max, just going a little further back, how did they come to be in Australia? Had both their parents been Australians?

MB Yes, well my mother's parents came from County Cork and my father's parents came from a place called Glansk, which is just on the border between Russia and Romania and depending on how the pogroms were going, you either said that you were a Russian or you were a Romanian if you were of Jewish descent in that particular area of the world.

MB So, they hightailed it out here. So, that was your background? Fascinating.

MB That's right, and during the war when my father was away – I was only about three or four – my mother had to send me to a school and she, naturally enough being of Irish descent, sent me to the nearest school to our neighbourhood and that was a Catholic school.

MB She snuck you into a Catholic school?

MB Yes, and here I was the only Jew in a Catholic school of several hundred and that was an interesting kind of experience because I kept winning the religious prize and they didn't quite know what to do with me because they didn't think it was appropriate for a Jewish boy to go up on the stage and receive the prize from the then Archbishop of Melbourne, it was Archbishop Mannix.

MB A Jewish boy, so that was a fascinating kind of conflict, in a way.

MB Well, that went on even after my father returned, my mother demanded that I continue my Catholic education.

MB So, she was powerful?

MB She was very strong, yes, and he rather anticipated her mood and rather insisted that I didn't but, in the end, I went on to a Catholic school.

MB So, she won. What kind of a war did he have? Was he a significant...

MB Well, he was first of all stationed in Australia and then he went to New Guinea, which was a very tough area in the Second World War with the Dakota Trail and areas of that kind, which were very hard in terms of the death rate to Australians. So he came back to Melbourne after the war, somewhat I think shattered a bit by his experiences there, and as a consequence perhaps of that he became much more centred in the spiritual life and he started to read a lot of Eastern philosophy and Eastern religion and effectively became a Buddhist which he really practised for the next forty-five years of his life until he died last year, just on eighty-five years of age. So, he lived in isolation for nearly forty-five years effectively as a Buddhist monk.

MB It's a fascinating background.

MB That philosophical bent of his plus the engineering side of things was what interested me very much.

MB Yes, those were the early tides that you swam with.

MB Which have more or less dominated my own thinking in the last twenty-five years or so.

MB When did school begin to mean – apart from getting into the prize-winning arena in that early school – where did you go for secondary school?

MB I went to secondary school, to another Catholic school, which was nearby, Christian Brothers School, and in that school when I was about fourteen, I came across or was very lucky to have a teacher who subsequently became head of Catholic education in Victoria, a chap called Brother Kilmartin. And he had a tremendous influence on me in terms of really being unsatisfied with any really, I think, facile answer to reasonably penetrating questions and so, I think, he really lit the light of inquiry as to how things operate, and particularly the larger questions concerned with questions of cosmology and questions of related...

MB He fired you up.

MB He fired me up.

MB Did you get close to him? Was he a person you talked to?

MB No, he wasn't easy to get close to. I don't think someone in a religious order is, so he wasn't in that sense close, but he would give me books to read and instilled – he really did instil in me, only for a short period, about eighteen months – a real, I think, fascination with the world around me.

MB So, that was one of the key paths you crossed?

MB That's right. He would be one of the key, certainly the key figure after my father, that I had in the first twenty years of my life.

MB You also had a brother, by the way.

MB Yes, he was very interested in pursuing engineering himself, but he had rather a bad accident when he was quite young, a physical accident, and that really de-railed him from any career, so he's had to really take a back seat.

MB Sounds like rather a tragic episode in your family life?

MB Yes, it did. It didn't actually dismantle his physical well-being entirely, but it didn't make him...

MB It cut him down.

MB It made it difficult. Yes, it cut him down, that's right.

MB So, from Father Kilmartin – that was an exciting stage. You began to read quite interesting philosophical works.

MB Well, I did. The influence of my father on the spiritual side and Kilmartin on the religious side for some reason had channelled me into the general direction of reading a lot of Plato. So, I read a lot of Plato's early dialogues and then I went on to read Descartes and (?) and some of the philosophers around the 17th and 16th centuries ...

MB Mind and body philosophy.

MB Mind and body philosophy, and somehow the mixture of that with engineering really set me going on trying to think through an analytical approach to solving some kind of problem associated with how the brain works in terms of its development of consciousness, and that became a dominating, I think, string of my life when I was about eighteen, which I have pursued ever since.

MB But, you went off to university to do engineering. You might have done a number of other things, but you went off to do engineering.

MB Well, I did engineering because of the influence of my father, but also I found that that didn't divert me from my philosophical interests because I spent most of my time as an undergraduate doing philosophy and not doing engineering at all. There I came across Cameron Jackson who'd worked with Wittgenstein, who you will know about, and Cameron Jackson introduced me to Wittgenstein and to Wittgenstein's great works, The Philosophical Tractatus and Philosophical Investigations, which I got heavily involved in and we formed a group of undergraduate philosophers called the Athenean Society and we all got together. Every Friday we would read philosophy, mostly from Wittgenstein, but also from another Cambridge philosopher, much earlier than Wittgenstein, called Alfred North Whitehead, who mixed mathematics with philosophical investigations and was the mentor of Bertrand Russell, just the same as Bertrand Russell was the mentor of Wittgenstein.

MB So, Whitehead was a figure in that time?

MB He was a very strong figure. He had ten years previously retired as professor of philosophy at Harvard, having been professor of mathematics at University College, London.

MB A powerful figure.

MB Very extraordinary figure.

MB He weighed on your life at that stage. We should say you were in Melbourne University.

MB I was in Melbourne University, but when I finished engineering – just towards the end of engineering – I decided the only way to really tackle the problem of how the mind arises from the brain was not to sit down doing philosophy, but to actually tackle questions in neurophysiology. So, I went across to the medical school as a vacation student in my fourth year of engineering and, as a consequence of that, got to know some of the good neuroscientists on campus and I was lucky enough to discover two people, Molly Holman and Geoff Burnstock, who were really, by far and away, the best neuroscientists of their generation in Australia, although I didn't realise that at the time. They gave me some simple experiments to try out and that really electrified me because at last I was doing something which I didn't know would be a major turn-on and that is, with my own hands, investigating nature and getting a buzz out of discovering things that no-one else had ever discovered before.

MB Just teasing that back, at school you had done biological sciences a bit.

MB No, at a Catholic school, you don't do biological sciences, not in those days.

MB Right, I needed to make that clear.

MB Because, in fact, if you open up a text-book on biology, you might find out something about the reproductive tract and that might get you asking questions which would embarrass people. So that kind of biology is completely missing, at that stage at any rate, in a Catholic education, which was a great shame because it meant you either went down the stream of law or sociology or went down the stream of the physical sciences, leaving aside what is undoubtedly the greatest growth industry in natural philosophy at the end of the 20th century, and that is biology.

MB Max, I'm getting this picture, and it's a phenomenal picture – no biological education, go to university heavily on the engineering side but desperately keen on philosophy and a whole range of philosophical issues, and somehow with a holiday job you break into a biological arena.

MB Yes, well I might add I've been professor of physiology for many years now at Sydney University, but I've never done any biology in my life of a formal nature. I've never done a subject in biology, I've never taken any undergraduate degrees, but I think the most incredible thing that happened was that just as I'd finished my engineering course and, in fact, before I went to the graduation ceremony, Geoff Burnstock, my mentor by that stage, said to me, 'Why don't you come on and do a higher degree in Biology?' without my ever having done any biology as an undergraduate. And I said, 'Well, that would be interesting, but I really want to do philosophy'. And he went away for a vacation for four or five weeks as he was want to do in those days and he still does now, some thirty or forty years later, he goes to New Zealand for his annual leave, and while he was away, I started to actually do some experiments which turned out had never been done before on the gastro-intestinal tract. What I did I could actually show on this white board. What I did was I took a piece of the gastro-intestinal tract which we can just indicate here as a tube, as indicated there, and I started to place recording electrodes on either side of the muscle of the tract, so these electrodes here will record the electrical activity in the muscle of the tract here. Then, the one move I made which had never been made before was, I put a series of electrodes for stimulating the intrinsic nerves within the gasto-intestinal tract, so within the muscle there are nerves...

MB A plexus...

MB Yes, there's a plexus there, precisely, Max, and that plexus is responsible for the phenomenon of peristalsis, that is the movement of food down the gut. You will remember in your Julius Caesar that the soothsayers used to take out the entrails after they killed the animals and eight hours later the entrails would still be moving and they would actually use them to make forecasts about the future. The reason why those entrails are moving is because the enteric neurones here, this plexus, is still alive and is still causing peristalsis, even though the creature is dead.

MB So, there's a kind of rhythmicity in the whole of that.

MB The rhythmicity of the gastro-intestinal tract is controlled by this plexus of nerve cells. Now, as it turned out, those nerve cells had not been stimulated in this way before. What people had done before is they'd stimulated the extrinsic nerves

coming in to the gastro-intestinal tract from the spinal cord, but they hadn't actually stimulated...

MB You directly went and stimulated the...

MB And when I did that, what I recorded here for the first time was a potential change which had this particular shape. That's called an increase in potential, an increase in negative potential. Now, the standard theory was that if you ever recorded such a potential, it would be due to a substance called noradrenaline which is released from nerve terminals and that idea had been around for nearly a hundred years, from work that was done at the turn of the century by Langley. So, I stimulated this, recorded this potential, and expected it to be due to noradrenaline being released from nerves. So, I put on a substance which would block noradrenaline and what happened when I put on that substance, was that this potential remained exactly the same, so the implication was that the main control system which was producing relaxation of the gastro-intestinal tract and was responsible for the movement of food down the gastro-intestinal tract, was not due to noradrenaline at all. But, the concept that noradrenaline was the transmitter being released from these nerves here had won two Nobel Prizes. The first Nobel Prize went to Otto Loewi and Sir Henry Dale[1] who claimed that these nerves here, which are called sympathetic nerves, that those nerves were releasing a substance called adrenaline, which is actually found in the adrenal medulla above the kidney. Now, subsequently, von Euler discovered that it was not adrenaline at all, but it was something very close to it, noradrenaline, and he won the Nobel Prize, together with Bernard Katz and Axelrod.[2] Now, what I had come across was the fact that the gastro-intestinal tract, this major component of the nervous control, was not due to this substance at all. So, the question was what was it due to, and there was only one other substance which was supposed to be acting to control the internal organs and that substance was acetylcholine. Now, acetylcholine was known to produce the opposite effect to adrenaline, it was supposed to produce a potential change which went up, not a potential change which went down. But, nevertheless, I tried to block acetylcholine which I did successfully, and that didn't affect this at all. So, what we'd done is we'd discovered that there were nerves in the controlling internal organs which were neither acetylcholine nor noradrenaline…

MB So, a new transmission.

MB A new transmission but not, as it turns out, a new transmission that controls the gastro-intestinal tract but, as it turns out, it controls most of the viscera and vasculature. The transmitter substance which is responsible for this event which was not blocked when we tried to block noradrenaline and acetylcholine is a substance which looks like its controlling, for example, the contraction of your urinary bladder or the actual contraction of a muscle in the eye called the nictitating membrane which is found in many animals, or the bronchi of your lungs. So, this transmitter, as it's turned out over the last thirty or forty years, is widespread and is a major component

[1] Sir Henry Dale and Otto Loewi were awarded the Nobel Prize for Physiology or Medicine in 1936 for their discoveries relating to chemical transmission of nerve impulses.

[2] Sir Bernard Katz, Ulf von Euler and Julius Axelrod were awarded the Nobel Prize for Physiology or Medicine in 1970 for their discoveries concerning the humoral transmittors in the nerve terminals and the mechanism for their storage, release and inactivation.

of the control of your internal organs. Now, that experiment was done before I graduated in electrical engineering.

MB You weren't quite twenty-four?

MB I wasn't twenty-four, I was twenty-three, yes, so it was an extraordinary stroke of luck.

MB And you hadn't even decided to go into this department, you hadn't even decided...

MB No, I hadn't made a commitment at all, but I was very lucky that six or eight months earlier, before I actually saw this potential, I was in Burnstock's office doing some wiring for him as a technician at that stage while I was still finishing off my engineering, and in walks Sir John Eccles, who had just finished writing his major treatise on the synapse, that is on the region of apposition between a nerve and a muscle and how that operates, and before it had gone to press, he gave Geoff a copy of the work which was in proof, and Geoff gave it to me that night, so I read it. It was a work then of about two hundred printed pages. It subsequently became a major book called *The Physiology of the Synapse* and in that book I came across the fact that there were these potential changes in parts of the nervous system which were called inhibitory potentials, that is they inhibited the on-going activity of the nervous system, so they were called inhibitory potentials. So, when I saw this come up on the oscilloscope screen when I stimulated the nerves as I've just explained to you, I realised that I'd come across an inhibitory potential which was, as I've just mentioned, not due to either acetylcholine or noradrenaline.

MB What do you do with a discovery like that? I mean, did you realise the significance of it?

MB Well, I didn't quite take in the significance of it, but my colleague who was doing the PhD at the same time, Graeme Campbell, who had done biology and had taken exhibitions on biology at Melbourne University – he realised straightaway that this was big in the sense that we'd come across something in this recording which was contradictory to the standard paradigm that had been in place for nearly eighty years at that stage. But, I didn't quite take in the full significance of it. But I did, by the time we'd sent the paper off to *Nature* which was published very shortly after this work, because the pharmacological and physiological community in Great Britain were aghast, because they were dominated by the paradigm which Sir Henry Dale had set in place – who had been President of the Royal Society and won the Nobel Prize in 1938 and was really the father of modern pharmacology, that is pharmacology of the 20th century – and he'd set in place, in concrete, the fact that these transmitters were the only ones that operate to control the internal organs. And since most people are in hospital, not because there's something wrong between their Adam's apple and the top of their skull, that is with their brain, but because there's something wrong between their Adam's apple and their pelvis, that is there's something wrong with their heart or their gastro-intestinal tract or they've got emphysema or something like that, then the discovery of new transmitter substances for the control of the internal organs was, as it turned out, of some significance.

MB So, you went on with Burnstock?

MB We had to actually work very hard against the British community to convince themselves that we had actually overturned the standard paradigm, but matters got worse for me because six months after this discovery, I learnt how to put electrodes inside cells. These are very fine electrodes which you can now push inside an individual cell. Now, these cells are only three thousandths of a millimetre in diameter, so it's very difficult to get electrodes into them, plus the fact that in the case of the gastro-intestinal tract, it's moving up and down, and you're trying to get an electrode into something which is one three thousandth of a millimetre which is moving a few centimetres. So, it wasn't very easy, but when I got it in, the first experiment I decided to do was one which I'd been really, I think, inspired to do because Alan Hodgkin had just won the Nobel Prize that year, 1963, for his discovery of the fact that the influx of sodium ions into a cell was responsible for the rising phase of the action potential which is the whole basis of communication between one nerve and another. So the very first thing I did when I put an electrode inside a smooth muscle cell was to record the action potential and here it is there, a large transient potential change, and of course, the first experiment I did was just to try and find out or to show, really, that Alan Hodgkin was dead right, that what he'd shown for the squid giant axon held for the mammalian autonomic nervous system. So I took all the sodium ions out of the medium surrounding this piece of smooth muscle tissue to show that what would happen is that the action potential would get smaller and then gradually collapse, and what happened when I took all the sodium ions out was nothing. The action potential remained perfectly normal, so I'd discovered an action potential which was not due to the influx of sodium ions.

MB Another ion in the story.

MB It was another ion story in the sense that the only ion that I could change which would greatly modulate this potential was calcium. And that was the discovery of the first calcium action potential in the nervous system, so I sent that off also to the British physiological community and they were copping this about twelve months after copping this lot, here, and they were not very pleased that the idea...

MB You were checking all the stones that had come down the mountain...

MB Yes, but this was quite accidental. It didn't require any great analytical power at all, it was just, in a sense, partly because we had an engineer bumbling into the area, and without any pre-conceived ideas, was doing experiments which seemed fairly simple on organs and tissues which hadn't been looked at before, but were technically difficult to deal with. And it was taken for granted that they would act in the way that all the other tissues would act, namely, for example, the way Hodgkin showed the squid giant axon worked because the action potential was due to an influx of sodium ions. Well, it wasn't true. It turns out that all the internal organs, with the exception perhaps of the heart, work by means of a calcium action potential and not sodium at all. So '63 was a great year for me.

MB Vintage year. Has it ever been better? Can't have been.

MB I don't think it's ever been better than that. Might have been almost equal, but never better.

MB That was a powerful year. How did you get the technique of actually putting the electrodes in? Was that finnicky?

MB I was meant to learn the technique from Molly Holman who was in the Physiology Department at Monash University. She is the most brilliant woman scientist in Australia, and she had learnt the technique at the time of its invention in Oxford some years earlier, she learnt it in about 1957, and I went over to Monash to learn the technique, but in the six months I worked with her, she never succeeded in getting an electrode inside a cell. I remember vividly the week that I left her, not having actually succeeded in the task I set myself, because it was the week the Nobel Prize was announced in which Alan Hodgkin, together with Jack Eccles, who was then in Canberra, won the Nobel Prize,[3] so that was a cause for a great celebration. So, I went back to Melbourne University and re-invented, if you like, this technique of putting electrodes into these very small cells. So, it was a great period of trying to work this out. I suppose the main interesting point that remains is what is the substance which produces these potential changes and which is causing the control of many of the internal organs outside of the system which releases noradrenaline and acetylcholine? And one of the main substances which is causing these potentials is adenosine triphosphate, ATP. Now, that wasn't due to me, that was due to my colleague in the laboratory, Graeme Campbell, together with Geoff Burnstock, my mentor.

MB But was he sparked by this particular bit of work?

MB My discovery of that meant that he… the fact that we discovered that it wasn't blocked by the standard transmitter substances blocking agents, that really set the task for him to try and find out what it was.

MB How long did that take, to get to ATP as an answer? Was that done in your PhD time?

MB The idea – it was done just after my PhD time, about four years after this was originally discovered. But it took, I think, around about thirty-five years to be accepted. It wasn't accepted, I don't think, until about two or three years ago, that this was the case for several reasons: one, we were overturning such a well-held paradigm and secondly, adenosine triphosphate, ATP, is such a ubiquitous substance – it's found in all cells, it's the main source of all energy, of course, in cells – and the idea that that substance which is everywhere could be used specifically as a transmitter was a no-no. But, now it's known to be a transmitter of the central nervous system in the brain as well, so it's a real growth industry, strangely enough, nearly forty years after this whole event was first thought of.

[3] Sir John Eccles, Alan Hodgkin and Andrew Huxley were awarded the Nobel Prize in Physiology or Medicine in 1963 for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane.

MB Catching on.

MB So, this block of work here which took me about four or five years altogether, was really my first introduction to biology and I was extremely lucky to have stumbled across all this without having done any formal biology at all.

MB You mentioned Jack Eccles. I just want to come back to – Jack, obviously, had a profound effect on anyone working in this field. Did you have a chance to meet Eccles in those early years?

MB Yes, I met him on a couple of occasions and, rather interestingly, the longest conversations I've had with him have been the last two years while he's in his nineties. Those conversations have been associated with his early research life and why he was subjected to such cruel derision as a consequence of his idea back in the early '30s that nerves like these, in fact, nerves right throughout the peripheral nervous system, don't work by releasing a transmitter substance, such as noradrenaline or acetylcholine which then acts on a muscle, but they work by imposing an electrical pulse onto the cell that the nerves end on. This is the concept of electrical transmission. Now, the reason why Eccles was led to that is very much tied up with this story that I've just elucidated, because what Eccles did when he first started to record the electrical signs of what happens when you stimulate nerves to, for example, tissues such as the smooth muscle of your micturating bladder or the muscle in the nictitating membrane of the eye. When he first recorded these electrical potentials, he discovered that he couldn't block them with the standard blocking agents that Sir Henry Dale had said must block them, because Dale had shown independently that these nerves going to the nictitating membrane and the bladder were releasing noradrenaline in this case and acetylcholine in this case. Now, Eccles stood up with the logic and said 'I've recorded electrical pulses which are due to transmission. They are not blocked by the agents which Dale says should block chemical transmission, therefore, transmission should be electrical and not chemical at all.' Now, Dale's reply to all this, which was very influential because at that stage it was known he would win the Nobel Prize within a few years, which he did in 1938 – this is about 1931 we're talking about. Dale said 'That's a lot of nonsense. What is almost certainly happening here is that the nerves are coming down and they're forming a synapse indicated by a terminal by that bulb there, and there's a muscle on which they're terminating and the transmitter which is released here, which we might say is noradrenaline, that transmitter is released and is immediately of such high concentrations in the region there between the nerve terminal and the muscle, that the blocking agents that you're introducing from outside can't block it in there. And what you're recording is an electrical pulse which is due to the action of this transmitter acting on those receptors there on that muscle, but it's not blocked by my agents. But, the main reason why this substance works is not because of what it does there, but because it diffuses out from there and acts on parts of the muscle which don't give rise to an electrical pulse at all and, therefore, you don't record the effects of the chemical transmission, and you're not getting any block of your chemical transmission because the concentration of the substance is too high for the blocking substances to act. Now, Dale, because of his authority, carried the day on that issue and what Eccles and I have been discussing in the last eighteen months is that the real reason is that the

transmitter substance wasn't noradrenaline in this case and in the case of the micturating bladder it wasn't acetylcholine, it was in effect, adenosine triphosphate. So, they were both wrong.

MB That was a ding-dong debate in the early '30s. It got quite acrimonious, I think?

MB Very acrimonious. It used to lead to tremendously, I think, difficult periods for meetings of the Physiological Society of Great Britain, where Eccles and Dale would enter into quite vitriolic kind of argumentative conditions and their respective students were pitted against each other. But, in fact, the real explanation was certainly that we were dealing with a different transmitter. So, the paradigm that Dale had in place was not correct, and I don't suppose Eccles' was either, but the nice thing about Eccles is that the logic of his argument was true, whereas I think Dale's argument, really, is slight of hand. He had to bring in another variable, namely, that the concentration of his transmitter was too high for the blocking agents to act on. He stuck with that argument almost to the end of his life.

MB You've written about that. I just want to put that on the map.

MB Yes, I've written about that in an introduction to a Nobel symposium on the negatives of a transmitter release on the synapse.

MB We're just going to fade down and change a reel at this stage, Max. That's got us wound into the story nicely.

MB Max, talking about Eccles really leads us into a fascinating part of your interests, the history of this, kind of, field of neuroscience and we can't really leave it at Eccles because he went to Oxford to team up with [Charles] Sherrington. And, before that, the story got even more exciting, which you've written about, so perhaps we could talk about your interests in that background.

MB Well, Eccles went as a Rhodes scholar to Oxford to work with Sherrington, who was then in his seventies, and remained working actively until he was about seventy-six when he retired as head of the department of physiology there. Sherrington, himself, would be regarded, I think, as the major conceptualising figure of the 20th century on how the central nervous system works. He wrote the greatest…

MB It has to be – monumental.

MB Which I think sets the whole of, certainly Eccles', main contributions to science, that is he followed the Sherringtonian paradigm. Now, Sherrington himself was introduced to neuroscience by John Langley, who was a professor of physiology at Cambridge and, for me, is the gigantic figure in this whole story that I'm enumerating. Because Langley was a real genius who I don't think has been quite recognised for the enormous impact he's had – on the one hand, his school, I think, was primarily responsible for the idea of chemical transmission at all in the nervous system and, also, he developed a whole new line of research on what we now call the plasticity of the nervous system. That is, to what extent can nerves grow in a mature

person and make new connections. Clearly, during events such as memorising something, that is when you are laying down new memories in the hippocampus of your brain, there must be changes to the synapses that are going on which are responsible for this and this general area of the plasticity of nerve connections was begun by Langley, and it was reading Langley's...

MB 1890s 'ish?

MB Langley introduced Sherrington to neurophysiology in 1888. They published their first paper together and, at that stage, Langley was the head of physiology at Cambridge, just having taken over from Michael Foster. So we're talking about, in the case of Langley, 1880s and then when he started working on what we call the plasticity, that is the extent to which nerves can change their connections, we were now talking about the 1900s. And it was reading his work on the autonomic nervous system, which is the system that I've just been enumerating on here in relationship to my first work, that I stumbled across these great papers of his on this phenomenon of plasticity; and the great question which it seemed to me as if Langley had left up in the air was, to what extent can, in a mature animal, a nerve terminal, once it's been lesioned in some way, re-grow and find its right connection again. So, I thought at the end of the 1960s when I'd finished this first block of work on the autonomic nervous system, that I would set up a laboratory to examine this phenomenon of plasticity, and the laboratory that was offered to me was at Sydney University. So, I left Melbourne and set up my own lab in laboratories which I've been occupying now for nearly thirty years. I still work in the same lab that I did when I first began there, and the block of work that I started to do was essentially described as follows. I went not to the autonomic nervous system that controls the internal organs, but the nervous system that controls the muscles which we have locomotary control over, such as our forelimbs and our hindlimbs, and these muscles consist of individual muscle fibres, each of which has a nerve coming down and forming a discreet single ending on it, in a very specialised region which is referred to as the motor end-plate. So, the first question I set myself was why – which some people had worked on since Langley, but very controversial opinions had been derived as to what happens when you sever the axon there – now, when you do that, all this remaining part of the axon which is not connected to the cell body of the neurone back here, degenerates. And you get formed here a growth cone, a bulbous protusion of the axon, where it's been cut and it re-grows. Now, the question is, to what extent can it form a connection on this muscle, and the first thing I discovered was that if you don't cut the axon too far back from the muscle, the nerve will re-grow, and it will form connections only in the position on the muscle fibre that it was originally connected to.

MB So, that's how it was originally designated?

MB So, this site here must contain some information on the muscle fibre which stops this growth cone, if you like, from growing any longer, and then it anchors itself and it forms a normal terminal. So the first point was the concept that there are information molecules specifying where nerves make connections. The next question I asked was 'is this site already on the muscle fibre during very early embryonic development when the muscle fibres have never seen a nerve before?' Because what normally happens during development is, you put out your limbs, they gradually

develop muscle cells and then the nerves grow out from your spinal cord and they find the limb and they grow in there and they form connections on the muscle cells. So, the question I'm asking myself is, do those muscle cells have this information about where the nerves connect before the nerves come down, and what I discovered was, they don't. That is, in a virgin muscle cell which has never seen a nerve terminal in its life, the nerve comes down and it forms a synapse anywhere on the surface of a muscle cell, so there are no information molecules on the surface of the cell at all to delineate where the nerves should connect. And then the nerve imprints on the surface of the cell the information molecules which later in life will be used if the nerve is severed, to determine that that nerve when it re-grows, will form a connection only there. So, these two sets of experiments showed that, for the nervous system, excitable tissue like neurones and muscle, that is cells which can give rise to electrical pulses, have on their surface in mature cases, these little patches of information as to where nerves anchor – and if they're lesioned, then that's where the nerves can grow back to, but not anywhere else. But in early development, those sites aren't there and the nerve has to impress those sites on the muscle cell.

MB Very specific imprinted areas.

MB Very specifically imprinted, and there are two main problems associated with trying to get nerves to re-connect in a lesioned human being. For example, last night, anyone who watched the Hollywood presentation of the Academy Awards would have seen the tragic event of Christopher Reeves, the late Superman, sitting in his wheelchair. He has a lesion up here, round about C1, cervical level one, and so he's unable to move any voluntary muscles at all, from there down. Now, the question is two-fold about how to remedy that condition. The first question is how to get the axons to re-grow through the lesion and once you've got them through the lesion, the next question is how to get them to connect up to the right cells. So, this question of the identification of these molecules here which confer specificity on the nerve connection has to be delineated before we could ever be able to get those connections to actually mend, if you like, after a spinal cord lesion. So, there's a tremendous amount of interest now in neuroscience on one, trying to remove inhibitory factors which stop the nerve from re-growing through the lesion and, secondly, once it has, to make sure that the nerve connects up to the right informational molecules on the right cells so that the specificity that's delineated here is recapitulated.

MB Max, I just want to come in at this point and ask a couple of things to assist me. Were the experimental challenges of that quite daunting when you came to Sydney in '69? I mean, it doesn't seem to me quite – were they easy to do?

MB These experiments were not very difficult to do. I suppose, if there's any daunting side of it, it's actually in the way in which you go about during the dissections, and I had a PhD student working with me, Alan Pettigrew, who's now Vice-Chancellor of the University of Queensland, and he was superb at doing the actual dissecting work and the suturing work to actually set up this particular...

MB Using cat or ...

MB We were using mostly rabbits and rats and lower mammals like that, so the experiments were not all that difficult. The techniques available to us, like the electron microscope, were fairly well-established techniques. I think it was actually the way we designed the experiments which might have been helpful in establishing that this was the case, that these were the connections that were being made. So, I was asked to go to Harvard by Torston Wiesel and on to a meeting of the Cold Spring Harbor symposium in 1975 to talk about this work and it was a delight to do that because, at that stage, Torston Wiesel and David Hubel had shown that there was similar plasticity of this kind in the visual cortex, in the occipital lobe, at the back of the brain. And they showed that during early development, there is tremendous plasticity in which different connections can be made depending on the kind of visual experience you have in early development. Now, the aspect of this which they were particularly interested in was our discovery that during early development of the animal, when this imprinting process was occurring, a muscle cell didn't have just one terminal on it, as it does in a mature animal, but it had several terminals on it. So we have not just one neurone connecting to this muscle, that we do have in the normal mature case, but we have several terminals coming down here and that those terminals are competing with each other, and they're competing for the final connection with the muscle cell. And then what happens is that these terminals are eradicated, so that there's only one left. Now, it turned out that our description of that in muscle also held for the brain, that is, during normal development of the brain, there's a tremendous excess of connections between one neurone and another neurone and gradually they're downloaded and you remove a lot of them, and part of the removal process is conditional on your experience. So that your visual experience of the world, for example, has a condition on the visual cortex such, that this removal of terminals is either accelerated or not, and this fashions the extent to which the neurone conductivity, or in this case the visual cortex, can mediate your visual experience. For example, if you only saw vertical bars when you were a baby – a favourite thing in Victorian aristocratic families was to put their families into white nurseries; beautiful white nurseries with white curtains on the wall and the crib was in white, and the only thing that might be painted might be the vertical bars on the crib – well, the child is only seeing vertical bars and those vertical bars will give rise to them having a set of connections made in the visual cortex which will favour them seeing the vertical over them seeing the horizontal, because the elimination of these terminals in the visual cortex will be such, that the ones that are left in a strong condition are the ones subserving your vision of verticals.

MB The pattern is discriminating the vertical...

MB That's right. For the rest of your life, your vision is dominated by verticals, so a glass of water like this will consist mostly of vertical sides, but not of a top or a bottom at all. The horizontals are gone. So, the question of the elimination of these terminals, as a consequence of experience, is a very important one in terms of developing the mature, in this case...

MB And was this the way your work went, looking why those nerves backed down?

MB Well, it did. After we talked, at that stage in 1975, to Wiesel on the one hand and to some people that were working in those days on the development of these, connections in the peripheral nervous system, we decided to examine an idea which had just come up by a very great neuroscientist called Levi-Montalcini who won the Nobel Prize for this work.[4] What she did, she showed that in the peripheral nervous system, the nerves which released noradrenaline that I talked about in my previous presentation, those nerves will only stay alive during early development if they get a growth factor from the muscles on which they make their connection. So, if this is the muscle, in this case here, on which these nerves make connection – which for the sake of argument in this case, we'll say their connection involves the release of noradrenaline on to a muscle such as an internal organ muscle like the micturating bladder – then those nerves will only stay there if they receive, from this muscle, a growth factor. Now, if that growth factor is not supplied by the muscle, then the result is that growth factor will not be transported back up the nerve to the cell body which provides this nerve terminal with nutrient and, therefore, as a consequence of that, this growth factor doesn't get to the cell body nucleus and the cell body dies. So, during development of the sympathetic neurones connecting to your internal organs, there is a normal loss of these neurones, a lot of these neurones degenerate in a normal developing human being, as a consequence of the competition between these nerve terminals for this growth factor. Some of the nerve terminals get it and some of them fail to get it.

MB Is this because one early one, getting on well, forms a sink?

MB No, not necessarily at all. It could be that the earlier one that got there first loses out. Part of the reason why they're losing out might be they've made the wrong connection and they don't get access to this growth factor as easily as the ones that have made the right connection. And, therefore, this mechanism is one of eliminating incorrect connections and keeping the right ones.

MB What is a correct connection?

MB Well, a correct connection is one which, if this neurone cell body here, say, in the spinal cord receives an appropriate input for the motor cortex, then it will operate this particular muscle in a functionally useful way. So, the whole story unravels, that is – you've led me into my next question – and that is, in the central nervous system, does this paradigm work? That is, connections on to this neurone, which might be found in the spinal cord, do those connections remain intact because they've got a growth factor now from this neurone, not from the muscle, but from this neurone. That is, what we have here is that this neurone is providing a growth factor...

MB So, a cascade of growth factor?

MB So, it's a cascade of growth factor and that is effectively what we set out in our next block of work to try and see, and that is whether the brain also works in this paradigm that Levi-Montalcini had set up, the sympathetic nerves in the periphery.

[4] Rita Levi-Montalcini shared the Nobel Prize for Physiology or Medicine in 1986 with Stanley Cohen for their discoveries of growth factors.

Whether, in fact, nerves will stay alive in the brain because they get a growth factor. So, the new block of work that I was concerned with is really whether this concept of Levi-Montalcini's, that growth factors are supplied by target organs to nerve terminals, and if they're not, the neurone cell body which is supplying those nerve terminals to generate was one which I wanted to see was working in the central nervous system. The preparation that I chose for this, and which I worked on with a dear, close colleague of mine, Bolton Drayer, were the neurones in the eye that connect the eye to the brain. The reason for choosing these neurones is that we worked out a nice technique for isolating these neurones into a culture dish, which had the normal nutrients which keep cells alive, and the technique which we developed was to inject an enzyme into the part of the brain that the eye normally projects to. This enzyme is then taken up by the nerve terminals which are projecting from the eye to the brain, is transported back into the eye and, therefore, the only neurones in the eye which are labelled with this enzyme are the ones which project to the brain. All the other twenty or thirty other cell types in the eye, such as the photo-receptors that take in the photons, those are not labelled, so we could now disassociate the retina, even of young animals, foetuses if you like, and detect which were the ganglion cells, as they are called, which connect the retina to the brain. Now, that technique enabled us to do two things. The first thing was, we counted the number of neurones in the eye that connect the eye to the brain during normal development, and we found that about half the neurones which are present in your eye when you are quite young normally degenerate and are wiped out during the normal development of your eye's connections to the brain. And it's now known that that happens right throughout the brain. That is, you've got approximately half the number of neurones now in your brain, Max, than you had when you were about that big, that is, you lay down an excess of neurones. The second thing we were able to do was, since we could identify these neurones from the eye in this dish, we were then able to see what would keep these neurones alive, and the natural thing to do was to follow Levi-Montalcini's paradigm. She would say that what would keep them alive is a growth factor which is supplied by the normal cells back here in the brain that the retina connects to. So, what we did was to take out the visual centres of the brain that the eye connects to, we mashed them up into their individual molecules, and we put them into the plate with these neurones that we had that we were able to isolate from the eye, that connect the eye to the brain. And we showed that the only part of the brain that would keep these neurones alive, was the part of the brain that these neurones normally connected to and the other parts, like the cerebellum which doesn't get an input from the eye at all, these other parts did not contain a growth factor for these neurones. So, that opened up the paradigm that there are growth factors right throughout the central nervous system which are specific for the neurone classes that are actually projecting that part of the nervous system from which you've derived a growth factor. Most of the work I did in the eighties, was concerned with trying to isolate these growth factors for the specific parts of the brain, in particular the retinal ganglion cells which connect the retina to the brain. That work I had the great pleasure of presenting to Levi-Montalcini in a meeting of the Pontelli Academy in Rome in 1984 and it was shortly after that she won the Nobel Prize, because it was realised in the late eighties that the concepts that she developed in the sixties, concerning these sympathetic nerves which released noradrenaline into muscle, held for the entire nervous system. And now there is a tremendous amount of pharmaceutical work that is now done in isolating these various growth factors because they could be implicated in a whole range of diseases.

For example, Parkinsons disease involves the degeneration of neurones which release dopamine. These neurones are found in the substantia nigra and they might well degenerate because they don't get their normal growth factor from the regions of the brain they project to. In Alzheimer's disease, there is a loss of neurones in the parts of the brain concerned with memory and that's why old people gradually lose their memory because they have a form of dementia which involves the degeneration of these neurones. These neurones won't degenerate if you give them their normal growth factor. So, growth factors are very big in terms of trying to keep neurones alive.

MB Is that the work that you're still continuing?

MB No, it's not, no. What I've been doing in the last eight or nine years is I've gone back, now, to looking at the mechanism by which transmitter substances are released from nerve terminals on to muscle cells. The reason I did that is that we were able to develop techniques which will allow us to visualise a nerve terminal while it was sitting on a cell and while it was alive, so that we could bring down a microscope – here we have the barrel of an objective of a microscope – and we could actually look at the nerve terminal there while it was normally functioning, and this enabled us as a consequence of that to bring recording electrodes down to specific parts of the nerve terminal at our will. So, let me blow up that region there. What I've got here is a nerve terminal. Now, the nerve terminal has little bulbous regions in it, like so, and this is the entire nerve terminal I have here, and it's abutting on a muscle cell as shown there, and any of these little bulbs can release a packet of transmitter. That's one nerve terminal. Now, because of this technique of us being able to visualise these individual bouton or varicosities, as they're called, we were now able to bring electrodes up and record the release of transmitter from an individual element of the nerve terminal. And what we discovered when we did that, was that within a single synaptic arrangement on one nerve terminal, each of these bouton, or varicosities, has its own individuality. You cannot treat a nerve terminal as if it was a homogeneous structure. Each of these, for example, has quite a distinct capacity to release transmitter on the arrival of a nerve impulse down the axon.

MB Is it one transmitter or more?

MB It's more than one transmitter.

MB Like mixtures?

MB It's mixtures and that concept was due to my mentor, Geoff Burnstock, who argued against the establishment that the patterns of transmitter that come out don't just contain the classical transmitters, but they also contain lots of other things, such as neuropeptides. It's now known that all release of transmitter doesn't just involve a single transmitter, but there are what we call co-transmitters. So that, for example, nerve terminals on muscles that you use voluntarily, they not only release the classical transmitter, acetylcholine, but they also release substance P and calcitonin and gene-related peptide and adenosine triphosphate. So, there's a whole cocktail coming out. What emerged from those early days we did back in the sixties, with Burnstock and Campbell, was not only that we became interested in nerve terminals releasing

transmitter, that there were different transmitters being released at different terminals, but even the elaboration of the concept by Burnstock that within a single terminal, there's a cocktail of transmitters coming out, not just one or two transmitters. And that, as a consequence of our work recently, there is considerable heterogeneity within a single nerve terminal as to its capacity to release transmitter.

MB And a nerve terminal as well – bouton terminals are there in greater quantities than that as well, I think you were saying. You've shown five there. These are massive clusters of...

MB There are massive clusters, hundreds or thousands of bouton on a single nerve terminal.

MB And all behaving independently.

MB And all behaving in ways that are not homogeneous, that is, acting in one sense independently – in the sense that they have different properties for each transmitter – but they can interact with each other in different complex ways. Perhaps one important point I should make is that most of these are not doing anything at all, so you take a mature human being and you look in their brain, most of the nerve terminals in their brain are not doing anything. That, if you think about it, is a necessity, because if you're going to incorporate new information into, for example, the part of the brain concerned with memory, the hippocampus, then you have to up-regulate some of these terminals so that they become effective. Now, you can't have them suddenly being made effective if they're effective already.

MB There are great reserves.

MB There are great reserves. The concept that the nerve terminal is in-homogeneous like this, leads on to the fact that most of it isn't doing anything because you actually bring it into action as a consequence of needing it, such as in the laying down of our memory.

MB I just wanted to come round to that particular point. In this, you've actually turned full-circle. You've come back to transmitters, from the sixties you've come right back around again.

MB Yes, this work was greatly affected by Bernard Katz who, together with Eccles and Kuffler, have probably had more effect on me than any in neuroscience around - I would add in there Torston Wiesel and David Hubel. Stephen Kuffler was a great, I think, supporter of bringing new techniques in to open up scientific questions in neuroscience and, particularly, at this sort of level of analysis of the synapse. This would be the way he would go, and that I found very inspiring, and so we went down this track.

MB And so these were the gurus. How did Katz have a specific influence? We've not brought him into the story.

MB Well, Katz's influence was that, I think, he would be regarded as the genius of the synapse of the last half-century. The conceptual framework of the way in which we operate, in terms of understanding synapses, was really laid down by himself in the early fifties. And, I think, some of the first breaks with that tradition are, first of all, that the terminals he looked at and treated as if they were homogeneous are in-homogeneous – they're all different, these sub-components here of a single terminal – and, also, the concept that there are co-transmitters, that is, that they are releasing cocktails of transmitter. These are two main shifts in the paradigm which he put in place. It's very interesting to me, Max, to be talking to you sitting in the College of Physicians here, because the most famous photograph ever taken in the history of brain sciences was taken about two hundred metres from where we're sitting now in Maquarry Street in Sydney. That photograph was taken in 1940 and shows Eccles, Katz and Kuffler, who worked just opposite where we're sitting now, together in the Karamatzi Institute, and I have that inspiring photograph on my wall as many other neuroscientists do throughout the world.

MB This brings us to the end of reel two.

MB Max, we've taken a fascinating turn. We've looked at your career in a series of blocks which was helpful. It brought us to the bouton terminal and transmitters in incredible cocktails, and the versatility that's possible within the nerve terminals. Does that take you back to a philosophical route of thinking? Does that take you to think of memory and mind? Is this a further journey?

MB Well, I think that the dominating drive that I've had in the last forty years has been reading philosophy and also trying to get insights through neuroscience as to what might be the, if you like, the physical basis of consciousness. Up until about eight or ten years ago, I wouldn't have dared said that to you, Max, or to anybody else, because I would have been laughed at and I would have blushed considerably indeed and been regarded as someone who's gone senile. But, about ten or fifteen years ago, two gentlemen entered the field. One was Roger Penrose, the bald professor of mathematics at Oxford and the other was Francis Crick, who left molecular biology to enter neuroscience. Both of them considered neuroscience questions in the context of their main interest, which was what is the physiological basis of consciousness. As it's turned out, both of them have come to totally contradictory positions on the matter but, because one was regarded as one of the great mathematicians in the world, and the other one is commonly regarded as the greatest biologist since Darwin, it made the field respectable. That is, you can now talk about consciousness as much as you like at neuroscience meetings and it's only the very young ones, who don't know what the senior people are doing, that are embarrassed by what you're talking about. So, I feel much freer, now, about talking about the subject. This subject seemed to me to be best tackled, not by getting lost in the wiring diagram of the brain but, coming down to what's happening at the synapse, and my whole life has been dominated by an attempt to elucidate synaptic function, either in terms of natural function, in terms of transmitter release or in terms of what I term plasticity. Because I think, as Eccles does and, certainly, as Roger Penrose does, that the secret of how the brain operates to give rise to memory and consciousness, is certainly found in the way in which these terminals either increase their efficacy or decrease it or grow in different ways. So,

that's been, as it were, the experimental side of my life and it's been coloured by these sort of philosophical needs.

MB And where is the ball game now? I mean, you were mentioning, apart from some of the transmitters that were more traditionally known, and some of the ones that you looked at earlier on, that we got polypeptides into the ball-park. That could be a very sophisticated story of communication.

MB Well, there's no doubt, now, that the way in which the synapse operates is very complex, in as much as this cocktail of stuff coming out, the neuropeptides – like encephalin, substance P and others – they are acting back on the terminal to change its capacity to secrete transmitter as well as acting on the muscle cell of the neurone on which the terminal impinges, to change the capacity of the receptor molecules which grasp the transmitter after its release, and change their capacity to actually identify and interact with the transmitter. So we've got a very complex machine here, which requires, I think, quite a lot to actually elucidate.

MB But, is there a basic model for the formation of a unit of memory?

MB The theory about how memory is laid down is a rich theory, which involves changes in the capacity of these synapses to operate, and is, I think, fairly straightforward. I don't think there's many mysteries now about how memory is laid down. The mystery though is still, or the debating point, is the way in which consciousness arises. That's been helped along, not only by Penrose and Crick coming into the field but, also, Gerald Edelman, who won the Nobel Prize in immunology when he was about thirty-five in 1963, around that date, has also come into the field and is a major theorist also on what are the physiological bases of consciousness. So, the general area of 'how does consciousness arise from the brain' is one which is very respectable now and, therefore, I think I'm able to talk about it both publicly and in the...

MB You've written about it.

MB And I've written about. I've written about it for a number of journals in order to try and really give, I think, a kaleidoscope of some of the excitement that is now going on in philosophy, and in neuroscience, as we delve deeper into brain structure. And we can now use these non-invasive imaging techniques, such as positron emission tomography and functional electro-magnetic resonance imaging, to actually see the brain functioning as it is doing so, and as it is giving rise to conscious thoughts, so this is a field which is undoubtedly growing at a great pace.

MB And this is where your unit is, in Sydney, at present?

MB Our unit in Sydney is still centred on this aspect of synaptic function.

MB Yes, but using more imaging techniques and a whole range of...

MB We are using – the introduction of more, I think, high resolution imaging techniques is something which is at the forefront of the examination of how synaptic

function continues. But, besides that, I've had an on-going concern about, I suppose, the way in which research is supported in this country and...

MB And you have got a bit political in that. I mean, you have set up an action group.

MB Yes, in the eighties I chaired a group which set up the Federation of Australian Scientific and Technological Societies, which brought together the eighty scientific and technological societies in this country into a common forum, in order to proselytise before the government for appropriate funding for research. And I did that under the auspices of the Australian Academy, and that has been operating, I think, very effectively in the last twelve years, since 1984. In addition to that, I have more recently set up the International Society for Autonomic Neuroscience, which is an international society concerned with the study of the peripheral nervous system, that is, the study of those nerves which control the internal organs that I described in my first block presentation. This society is having its main congress next year in Queensland, in Cairns, and it's the sister organisation, we think, to the International Brain Research Organisation, which is the main umbrella group for the study of brain functions. ISAN, as we call it, that is an acronym for International Science and Autonomic Neuroscience, is for the neck down and IBRO is for the neck up, if you like. Then, more recently still, we have founded the Sydney Institute of Biomedical Research, which is the main institute for biomedical research in the Sydney region and it's situated at Sydney University. This brings together all the main researchers at Sydney University in that general field of research and, collectively, they make, in any objective criteria, the most powerful group, I think, of medical researchers in New South Wales and probably one of the two or three most powerful groups in the country. And that is really, I think, moving along quite excitingly because we've got a lot of new multi-disciplinary research going on as a consequence of bringing these groups together onto the campus of Sydney University. So, that's been quite exciting.

MB Max, on the political side, how far have you won progress for science in terms of government funding because in England, we have not gone forward, we have tended to have gone backwards?

MB Well, in Australia, we have a peculiar problem which is probably not found in any other OECD countries outside of Portugal and New Zealand, and that is that, for various historical reasons, there has been a complete lack of the funding of research and development in this country from the business side of the fence, so that all funding of research and development almost up until a few years ago, not all but a very high percentage, was done by government. In fact, the Australian government supports research and development and always has, virtually, since the First World War when CSRO was founded at a level comparable with that, or better, than most countries in the OECD. But because of this lack of funding from the business base, if you like, from the business community, Australia has an appalling tradition on the funding of research and development. It's not really the government's fault; it's really this historical malaise that's developed in the business community here that research and development is not something to put money into. That's turned around very dramatically in the last several years because of the introduction of a 150 per cent tax break on research and development, which the government has offered the business

community, and which the business community has had some alacrity in grabbing hold of, because it's a nice little bonus to them. And that has really moved ahead research and development quite fast, but it comes off such an extraordinarily low base, that we are still well down when you look at the collective funding of research and development in Australia from both government and business.

MB But, it's rising.

MB It's rising, it's rising very fast.

MB What of your philosophical writing. The philosophical kind of side of you that's stayed and never gone away from those early days in engineering and philosophy. What is the story of today in the nineties?

MB Well, I've just finished a work called 'The Idea of Consciousness,' and that work is really concerned with giving the various views which neuroscientists have of how the workings of the nervous system can give rise to consciousness. It's a somewhat didactic work, so it gives you the views of people like Gerald Edelman and Francis Crick and also Roger Penrose, so it gives you a kaleidoscope of opinions about what might be going on. What might be going on tends to be polarised into two separate camps now, not that it's necessary that either camp is right. One camp really derives from the work of Schroedinger, one of the co-inventors of quantum mechanics, together with Heisenberg. Schroedinger was a Fellow of Magdalen College at Oxford in the thirties, after he left Nazi Germany, left Austria, and a co-fellow at that college was John Eccles, before he left Oxford to come to Australia to work in Sydney in the Kanamatzi Institute. Schroedinger had a large affect on Eccles, and Eccles developed the idea, under Schroedinger, that there were quanta-mechanical phenomena going on between this nerve terminal and the neurone on which it impinges. And that, within the mysteries of quantum mechanics, one could tease out the basis of consciousness. So, the idea, I think, in its historical roots actually comes up through Schroedinger and I would say the greatest proselytiser of that idea at present is certainly Roger Penrose, who's written two major books on this particular area, and Eccles himself published a paper three years ago working with a quantum mechanicist from Germany, from one of the Max Planck Institutes. He published a paper, in his nineties, in *Proceedings of the National Academy*, on the way in which quantum mechanical ideas might be utilised to explain the way in which conscious phenomena might be derived from the workings of the synapse. The main argument against this idea – the standard omen against it – is that the brain is too hot to allow the interference phenomena that occur in quantum mechanics to occur and, therefore, for interesting in quantum mechanical phenomena to occur in this particular situation. But, there is certainly one part of the brain where quantum mechanical principles operate, and that is where there are captures of photons by the rods and cones of the eye, because photons are essentially a quantum mechanical particle and their interaction with the pigments in the eye must be a quantum mechanical phenomenon. But, nobody yet has been driven to use quantum mechanical methodology, if you like, to try and work out some phenomenon at the synapse. That is, at present, all the phenomena that we have been able to derive on the synapse, has been capable of being explained on classical ideas, using classical physics, effectively. But, you never know, as we delve in closer and closer, you know, in a totally reductionist way, you

never know what we'll come across. The other side of the coin takes advantage of the fact that nothing quantum mechanical in the way of analysis has ever had to be used to explain any brain phenomena whatsoever. That is the view which Francis Crick leads off with, particularly in his recent book *Astonishing Hypothesis* and it's generally supported by Gerald Edelman as well. That comes down to the fact, then, that it is the wiring of the brain essentially, and the way in which this wiring works, which gives rise to consciousness, and the reason we regard consciousness as mysterious, is because we are experiencing such an enormous range of extraordinary phenomena when we go through a stream of consciousness event, that it's hard for us to grasp that the 10^{15} synapses of the brain and ionic activity could give rise to this sort of phenomenon. So there Crick in his typical hard-headed fashion says 'It's the wiring that's doing the job'.

MB It's the tensions in the wiring.

MB Not the tensions in the wiring, it's actually the phenomenon which the wiring gives rise to in terms of us being able to use language, and hear the language through the auditory pathway, that phenomenon is itself capable of explaining anything we have to do about the origins of consciousness. And the main popular paradigm there at present, is one that comes out of the work of Wolf Singer. What Wolf Singer's work comes down to is really this, that there are different modules in the brain subserving different functions which we've known for a long while. There's a module concerned with audition, there's a module concerned with vision, there's a module concerned with smell, but when we see a beautiful woman pass by who's carrying a bunch of roses, we have an holistic experience. The smell and the vision, these come together as one phenomenon, so how is it that a module here concerned with language or concerned with smell and a module here concerned with vision give rise to an holistic experience in our consciousness.

MB A conscious experience.

MB Now, what Singer has shown, is that neurones in these disparate parts of the brain come into synchrony in their firing patterns, so that the neurones which are subserving your experience of an holistic event, out of all the neurones in the brain which are not, just those neurones which are subserving your holistic experience are in phase and are firing together at the same frequency. Whereas, the rest of the brain, the huge amount which is not experiencing or contributing to your holistic experience, but which may be taking note of a lot of other things going on, but the notes they are taking are not contributing to consciousness, they are not firing in phase with the same frequency. So, at present, the argument for the Cricks and the Edelmans of this world for the development of consciousness at any moment in your brain is that it is derived from those parts of the brain which are firing in this pattern and it's through the horizontal connections across the brain that they are brought into the synchrony of firing, and it's just that synchrony of these neurones which gives rise to this phenomenon, this holistic experience that you are having as you look at me now and listen to me talk.

MB Talking about roses and women walking across parks with perfume kind of affecting us, what about your private life and private interests? Was there marriage?

MB Yes, I married a woman who's a painter and she is a very successful painter of landscape and she does a lot of work concerned with the outback, and she goes on trips into the Bungle-bungles and areas like that which are very exotic areas in central Australia. She lives a life which, luckily enough for me, is really independent, I think, of my own life because I work a seven day week and my family life is very restricted as a consequence of that. So, Gillian, who I've been married to for thirty-one years, has been a phenomenal companion. Without her, no doubt, I couldn't have kept the pace up that I felt necessary in order to probe the questions that I've elucidated to you today.

MB I asked these questions about background, because I haven't had a chance to find out before. We were swept together into this meeting which is a great pleasure. Have I missed anything on the way, or any opportunities on the way of going through your story – anything that actually focuses on something?

MB The time that you've given me has been very generous and I thank you very much for letting me bash your ears about things which have excited me so much and have been such a great experience for me.

MB I've been riveted by it all. Thank you so much.