



## Australian Academy of Science - Science education Interview with Professor Mollie Holman

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Professor Mollie Holman, physiologist and former vice-president of the Australian Academy of Science, was interviewed for the Australian Academy of Science's *Video Histories of Australian Scientists* program in March 1998. The interview was conducted by Dr Max Blythe of the Medical Sciences Video-archive of the Royal College of Physicians and Oxford Brookes University in the United Kingdom. Here is an edited transcript.

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*Professor Mollie Holman*

### The roots of a 40-year passion

*Mollie, your work has been a passion of 40 years, two-thirds of a lifetime. You have said that it was really about the dialogue between the autonomic nervous system and smooth muscle, which before you started nobody had got into very well.*

Well, not at the cellular level. Quite a bit was known about it from the

descriptive point of view, but nobody had really looked at the nuts and bolts of it. I guess it turned me on because of such a variety of things happening in different tissues.

*This is everything apart from voluntary movement of the body – all the movement of the intestine, blood vessels, ureters – an immense field of activity.*

Yes, including the heart, skin, sweat glands, and going on all the time without any conscious involvement. I started reading about this in a longish literature survey as part of my Masters degree in Melbourne, and I was very fascinated. It seemed as though there were different nerves operating by different transmitters throughout the body, compared with the rather simple pattern of innervation of skeletal muscle.

*You set out from that point in the early 1950s, and ever since you've been working to chart the performance of the autonomic nervous system in relation to smooth muscle. Let's now go right back to the beginning, to Tasmania in 1930.*

That's the year I was born, so I don't really know much about it!

*But your parents were established there. Your father was a doctor.*

My father did medicine at Melbourne University and worked with one of the early Australian pioneers in radiology. He did a year at the Royal Melbourne as a resident. Then the main surgeon in northern Tasmania, John (later Sir John) Ramsay, was looking for somebody to set up X-rays in his private hospital in Launceston. Dad met my mother, Mollie Bain, in Launceston – I think through the Launceston Players, the local dramatic society. He had started acting in Ormond College, with the Ormond Dramatic Society, and he was keen on drama for the whole of his life.

*You have told me that he really had a good feel for research and building apparatus. Was he essentially a hospital doctor when he came to Tasmania, working with the surgical team?*

Oh yes. He probably made the X-ray apparatus work for Sir John Ramsay.

*Your mother was a beautiful woman.*

Mum was a very attractive lady. Those days were very different for women, especially in a small town like Launceston. She didn't go to work. She never had a job but she did raise four children, all girls.

*Did they become scientists, like you?*

No. My next sister, Jill, did arts and was a schoolteacher for many years. The

next one did social work. She's still doing it on a voluntary basis, but social workers are born and not made. And the youngest didn't do a university degree.

### **School by day, physics by night**

*You didn't get a chance to go to school very early, because your father was rather strongly anti-kindergarten. Can you explain that to me?*

I started school when I was 7½, actually, at the beginning of 1938. War clouds were already well and truly looming up by then and there was certainly an anti-German feeling, including against the kindergarten idea. But the girls' grammar school, Broadland House, went right through from kindergarten up to when the girls finished school and left, so we were all in the same school. Launceston was a lovely place to be, because although it was a small town it was big enough to attract quite a few interesting visitors to Tasmania.

*Was that school a good place to be?*

Yes and no. We were a smallish group and were very happy, even though these were war years. We were very protected, I think. I went as far as Intermediate there.

*It was a traditional education, with lots of the three Rs but not much science?*

Languages, but no science at all.

*You got to the top of the class quite early on, didn't you?*

Because I started at school so late I was behind the eight ball a bit, but by the time I was about 11 or 12 I had got to the top of the class. Then I went down and was beaten into third. But I had a lot of extracurricular activities as an early teenager. I was very fond of roller-skating.

*While still at school, at the age of 14 or 15, you had the unusual experience of going to an evening school, with senior people, to do the physics that your remarkable father thought you should be doing.*

The others were mostly apprentices and young people a little bit older than I was. I did the equivalent of Intermediate physics. The Intermediate exam was the public exam that you took in school before you went on to do University Entrance or Matriculation, or Leaving. The course was in fact called Introduction to Science and Engineering, so quite a few of the people in the class probably would have been apprentice engineers. I absolutely loved it: it all seemed very logical and satisfactory.

*Were you building apparatus for the first time?*

Oh, just doing very simple-minded experiments that our teacher had set me.

*That would be getting towards the end of the war years. What was the war like in Launceston? Or did it pass you by?*

There were definitely clouds. My mother's brother Jim was in the Army throughout, in the Middle East and later in New Guinea. He was very close to action a lot of the time and we were always worried for him. My mother's elder brother Tom was in the Navy, as was her younger brother Bob. So I had three close relations very much involved in the war. Dad did quite a lot of work for the Army as well, in looking after people, examining people wanting to join up and so on.

### **To Melbourne and an extra year in science**

*You later moved to Melbourne. I think that again was your father's idea. He must have been a potent source of ideas.*

Yes, he was. That was 1945, and I did my last three years of schooling in Melbourne.

*Weren't you going to see a gran – your father's mother – who lived in Melbourne?*

Yes. She had never seen any of the children.

*And your father knew a head teacher there.*

Dorothy Ross was the headmistress of Merton Hall, the Melbourne Church of England Grammar School. Dad had a great admiration for her, as I think a lot of people did. She was an amazing woman, an Australian, who had done a degree in psychology. Also, Dad had an assistant called Jean Hill – a doctor and an outstanding person – who had been to Merton Hall.

*Was boarding a bit of a culture shock?*

Well, it was. I had a network of friends in Tasmania, and we'd had lots of wonderful parties in Launceston to celebrate the end of the war. Leaving there was a bit of a shock to the system. However, as boarders at Merton Hall we were treated like adults, really. It was amazing, and a wonderful school.

*Did you do science there?*

Yes, plus a few other things as well. I was editress of the school magazine in my last year at school. I wouldn't say I was exactly sporty – quite the reverse – but I did play basketball. Not hockey, as it was quite apparent by then that I

was somewhat shortsighted. Playing in glasses with a hockey ball would have been a bit dangerous.

*When did the idea dawn that you were going to have a scientific career? Was that earlier when you did the physics in Launceston?*

Pretty much throughout my career I was never sure what exactly I wanted to do, but I kept my options open because that meant doing things that later didn't limit the direction in which I could go. From Broadland on, I knew it would be something to do with science, but just what I didn't really know.

*As you got towards the upper grades, you must have had a wide base. Was there a lot of sport? Were you a swot, were you a reader, were you highly focused?*

There was not that much sport. I always enjoyed studying, for some unknown reason, so it was never an effort. I always read a lot, and at Merton Hall I did one year of Greek and Roman history, which I absolutely loved and still do.

*Tell me about the decision to go to Melbourne University.*

No choice about that in those days. If you were doing science for your University Entrance and did well enough, you went to Melbourne University. At Merton Hall, after Intermediate you did first of all a Leaving Certificate, and then you had a choice. You could do one more year at school and then University Entrance. But Miss Ross liked people to have an extra year, which she called the honours year, in between Leaving and Matric. You could pick up some additional subjects or, if you really were keen to do a science, you could have an extra year of science to improve your chances of getting good marks at University Entrance.

*Were there any teachers who particularly switched you on in science?*

Oh, my chemistry teacher, Miss Irving, was wonderful. She was extremely enthusiastic.

### **A science undergraduate at Melbourne University**

*To me, your first year at Melbourne University sounded unusual.*

Yes. It was a wonderful first year. After the war, Melbourne University set up a branch at Mildura, in an old Air Force base. It was there really to take care of the bulge of people returning from the war and wanting to enrol, especially in engineering, dentistry and medicine. They also took a small number of people who were enrolled in science. At that stage I wasn't sure whether I wanted to go to med eventually, stay with science or what, so I did first year medicine plus engineering maths, which gave me again a wide base that meant I could

go in a number of directions later on. That was great fun but very hard work, because engineering maths was not easy.

*That was when you decided not to do more medicine but to stay wide-based in your second year.*

That's right. I did chemistry and maths, even though in first year I'd done best in biology. Then, because I wasn't good enough at mathematics to do that and I only liked parts of chemistry – I liked physical chemistry but I found organic rather boring – it was physics for final year. In those days you did honours in science after a three-year course. I graduated at the end of 1951.

*Who were the people who made an impact, Mollie, in those undergraduate years? You must have been packed in with many other students.*

Well, there wasn't an enormous number of people doing physics by the time we reached third year, probably only 20 or 30 of us. There was just one other girl, and she and I were partners in doing our experiments. Sadly, there were no tutors to parallel the chemistry teacher I'd had at school.

### **Frog skin and membrane potentials**

*Did you go on right away to do an MSc?*

I got a 2A – by the skin of my teeth, I'm sure, because of my maths – so I could go on and do a Masters degree. I had a Melbourne University scholarship and I thought about physics, but I felt it would have been rather boring to do the experiments that were going on in the Physics Department at that time. My father was a great friend of the Professor of Physiology, Roy Douglas Wright, otherwise known as Panzy Wright. Whether through Dad's influence or Panzy's, I was allowed to take my scholarship with the Department of Physiology and Pharmacology, and to go ahead with research in biophysics, as we called it.

*This interest in biophysics had a little bit of fatherly influence as well, I think: he had introduced you to some of Schroedinger's writing. Did that have real impact?*

It did, although at that time I didn't know enough about biology to grasp precisely what he was getting at.

*But that was what precipitated the move?*

Yes, the idea that physics would have an enormous amount of input into biology – and Dad probably planted the idea in my mind.

*Panzy Wright handed you on to Frank Shaw. That was an interesting*

*encounter.*

Frank was interested in experiments which you would think of more as biophysics than some of the straight physiology work going on at that time. He was looking at why the ionic environment – the ions that are present in the solution inside cells – is so utterly different from the composition of the fluid in the body in which those cells live (the extracellular environment). Frank's real interest was in what forces there were inside living cells to give them this extraordinary difference in ionic content from the solution bathing the outside of the cells.

*So in those early days he was looking at the cell membrane mechanism?*

Yes. And he was interested in how drugs might perhaps alter the ionic gradients.

*What kind of investigative work was this? Was he actually taking cells apart, releasing their ionic contents? It would be difficult to manipulate the cells.*

He was mostly trying to look at what the ionic content was, mainly in frog muscles.

*And you joined him in this work?*

Well no, because I knew very little about biology in those days, having only done first year medical biology. But in his reading he had come across a very interesting preparation of frog skin which had been worked on by Danish workers. It's very hard for frogs to get enough ions into their body to function normally without some active process to soak up any sodium that's around in their watery environment, so in their skins they have a sodium pump. Frank thought that would be a nice model for the same kind of pump that's in all other living cells, so I had to set up an arrangement to measure the voltage generated by this active transport of sodium across the frog skin.

*By developing electrodes, and moving in and measuring cross-surface resistance?*

That's right. That was quite my cup of tea. I learnt an awful lot about what you had to do to make measurements of membrane potentials – which were quite complicated. People knew about them from the old physical chemists, like Guggenheim, but there was a lot of work to be done.

*It was a good place to start, but I think you were put out into a rather lonely room and left a lot to your own devices, making your own stuff away from the herd.*

Yes. Later on, Frank asked me to set up an apparatus measuring the voltage

across frog muscles, rather than frog skin, associated with these very large ionic gradients between the inside and the outside of the cell. It was not easy.

*I think you have said, 'But I was a bit pig-headed and I just was going to do it anyway.' You certainly got some interesting results.*

Other people had been doing it, but not so much in Australia at that time, I don't think. There was a lot of work going on in the UK, especially at University College, and of course we all knew and followed with great interest the work that Hodgkin and Huxley had been doing, and Katz, in relation to voltage clamping squid axons and learning a lot about what caused these voltage differences across the cell membrane.

*Was there a high spot of that work with Frank Shaw?*

I think the highest spot was when I finished my Masters thesis. That had dragged on and on, partly because after about a year on the scholarship I took on a university demonstratorship and was then part-time. It ended up as volume 1 and volume 2.

### **Turning to neuromuscular transmission**

*Were both these massive parts of your thesis about looking at cross-membrane situations with a range of ionic exteriors?*

That was what I was doing, but I decided to write my literature survey on something totally different – neuromuscular transmission – because I was very much interested in the work that had been going on in the UK. And that was why it went on and on. I wrote a review of the work that had been done by Sir Bernard Katz and his colleagues at University College, but I also read a lot about a different kind of neuromuscular transmission: the transmission that goes on at sites in the body other than in the brain and spinal cord, and from nerve to skeletal muscle. That's where I came to read about the autonomic nervous system and the innervation of smooth muscle and glands – in fact, the innervation of everything in the body other than skeletal striated muscles.

*You were deeply immersed in it by then, and looking to do a PhD?*

Yes. In those days people nearly always went overseas to do a PhD. I think one of the earliest PhDs in Australia was done in the Department of Physics at Melbourne University in 1948, but in general, and especially in biological sciences, to become involved in research mostly meant going overseas after a Masters degree.

*Your first inclination was to go to Bernard Katz in University College but you were talked out of it by Jack Eccles. How did you come to be in touch with him?*

Eccles came from Dunedin in New Zealand to head up the Department of Physiology at the Australian National University in the early '50s. He immediately had an influence on all the people working in Australia on neurosciences, as we'd call it now with hindsight, because he not only set up a wonderful department at ANU but also came along to scientific meetings and was a great encouragement to everyone. Whenever he had somebody important visiting ANU from overseas, he always arranged for that person to go to the provinces, as you might say, and give lectures to the medical students.

*He was a great sponsor of information dispersal?*

He was a great sponsor, and one way or another he looked after everybody.

*Had physiology actually started at this time?*

No, but we had a very active physiology segment within ANZAAS, which was like AAAS or the British Society for the Advancement of Science.

*Did you get to know Eccles personally very well? He was supposed to be something of an ogre.*

I got to know him but not very well. He wasn't an ogre at all, in my view. I think people who worked with him found him a bit dominating because he was so incredibly energetic and he was so hardworking.

*Mollie, did you ever see him work at the bench?*

I don't believe I did – not actually sitting over an animal and doing an experiment.

*I've been told that his mind would work ahead, adapting experiments, and however many hours were required, he would just go on. The mind would still stay as bright as ever, perfectly adaptable.*

Yes, that's absolutely right. He was very strong physically too. But a wonderful benchworker, undoubtedly. He had worked on smooth muscle when he was at Oxford, with Sherrington. He suggested that I should think about doing a DPhil at Oxford with Edith Bülbring, in this new area that nobody much was working in. Why not go and do something a bit new and different, rather than just go on with skeletal neuromuscular transmission as everybody was doing in those days?

**Deciding to study smooth muscle, not cardiac**

*Edith Bülbring had just started to research smooth muscle, hadn't she. She*

*was a pharmacologist, and although the smooth muscle bath had become the great tool of the pharmacologists, they knew precious little about it.*

Absolutely. Edith had dabbled in the biochemistry of smooth muscle, and people were working on mechanisms for contraction and so on, but she thought that to be able to record the membrane potentials in smooth muscle might just give another handle on how drugs worked. She herself said on many occasions that really she went into it blind, because being a medico she didn't know anything about physics or chemistry.

*And you came in about 1955 to join her, pretty blind, but recommended by Jack.*

Yes. I have found a letter I wrote to Edith, asking whether she could give me a place in the lab and saying, 'I would like to work on smooth muscle or cardiac muscle.'

*There was cardiac muscle work going on at that time, with Miles Vaughan Williams, in the lab where you were to work, in effect.*

Yes, next door. It was really only after I got to Oxford, or while I was corresponding with Edith, during 1955, that we homed in on the smooth muscle project.

*Was Edith a demanding supervisor?*

No, I wouldn't say she was a terribly demanding supervisor. I'd been working pretty much independently during my Masters period in Melbourne, and by the time I got to Oxford I was able to build my own apparatus and I was fairly happy with the simple electronics as we knew it in those days.

*She was not an easy lady at times. Did you form a good relationship with her?*

Well, it was a bit dicey at times. We had our little arguments.

## **Getting to Oxford**

*Before we talk more about your work with Edith Bülbring, let's look at your long journey to Oxford and what you found there.*

I left Australia on the *Strathnaver* in, I think, April 1955, with five other females in a six-berth cabin. We had a wonderful time of course on the ship going to England. After we had settled down for a while in London, several of us went off on the usual round-the-Continent trip that everyone did in those days.

*You'd already learnt to ski – another personal interest of some strength, I*

*know. Then you went back to Oxford. Did you become one of the ladies of Lady Margaret Hall?*

I didn't actually live in Lady Margaret Hall. I was very fortunate, actually. Stephen Toulmin, who was in History and Philosophy of Science, had been at Melbourne University as a visiting professor or on sabbatical, and I met him through mutual friends. He told me that his mother, in north Oxford, took in a boarder. So I lived in her house rather than in Lady Margaret Hall, but as it was very close I ate in hall quite frequently, for nothing.

*The last of the Bloomsbury set?*

Mmm, yes. Iris Murdoch used to eat there fairly regularly. Oxford pharmacology in those days was absolutely marvellous, like a mini United Nations. There were Germans and a man from Iceland, an Austrian – a great international community of people, most of whom had already done a PhD and were post-docs. It was a really international community, and although we were very poor and had no money we managed to have a wonderful time.

*I think there was terrific collaboration within that unit. You all sparked each other, with lunchtime chats and so on.*

Yes, indeed. The professor, Josh Burn, was very worried whether we all had enough to eat, so he employed a cook and we had a kitchen in the department. We had a proper sit-down lunch every day, with the whole department sitting round the table. That made for a lot of friendship between all the young people in the department.

*Was Josh Burn an influential figure?*

Not for me so much. Although I have worked so much in pharmacology departments, I never really became a card-carrying pharmacologist.

### **Action potentials: something funny going on**

*You've always stayed a physiologist. In Oxford you applied that physiology very quickly to looking at the smooth muscle and got an astounding result, quite early on.*

Oh yes. Techniques do change and improve, but Edith was quite right, she wasn't a physicist. In recording the membrane potentials in smooth muscles – such as muscles in the wall of your gastrointestinal tract – she found she was recording funny little signals. By comparison with the signals generated by skeletal muscles or even cardiac muscle these were very slow and sloppy, and very much smaller in magnitude. I thought, 'There's something very funny going on here,' but when I started I also got records of funny little signals coming from smooth muscles.

*What were you actually recording with? What kind of electrodes were you using?*

They evolved from traditional methods. We made a very micro-micro-micro-pipette: we would take capillary tubing, put it in the flame and get it all white hot and then yank it, so we got quite small pieces of capillary.

*It sounds very imprecise. You did develop skill at it, and at drawing out the glass?*

Yes. We had a very archaic kind of microelectrode puller, which had a spring attached to it. We had to take a little flame, move it up to heat one of the bits of glass, and when the glass got sufficiently molten the puller would automatically go boing! and hopefully we would pull a very, very fine tip, which was still patent. And then that had to be filled with potassium chloride as a conducting solution.

*Did you look at the tips under the microscope to check the dimensions?*

They're so small, if they're working properly, you can't even see them under an ordinary microscope. They're a fraction – probably a hundredth – of a micron, and you just suck and see. Anyway, I started off using Edith's electrodes and got these funny little recordings.

*Weren't they about 10 millivolts?*

Yes, or even less. They vary in amplitude.

*Normal skeletal muscles produce about 70 to 100, but you weren't getting anywhere near that. So you made some more electrodes, some more apparatus?*

We made some more electrodes but we were still recording only about 5 millivolts. Eventually one day I popped into a cell and instead of just getting a few millivolts I suddenly got something getting bigger and bigger, and then it turned out a little later on that they weren't 5 millivolts, 10 millivolts, they were 40, 50, 60 and so on. And in the second paper that I published on this from Oxford I think you'll find they're very much bigger.

*I think you went to 100 millivolts, Mollie.*

Not quite. But it was very gratifying: it meant that smooth muscle wasn't all that way out and peculiar – probably not much different from cardiac muscle, skeletal muscles.

*With the same kind of dimension of action potential after all?*

Yes. Logically, it had to be. That was fun, but there are still many puzzles.

*You told me once that when you got this wonderful result, when suddenly there was a big action spike, Edith Bülbring wasn't all that delighted.*

No!

*Thwarted, more than delighted. Would it be fair to say that?*

It's hard for me to put myself into her position and think what she must have felt like. Later she was pleased. And there were still some small ones that you'd get and sometimes quite weird shapes, so that really it took us a while to sort out exactly what was the basis of the action potentials in smooth muscle.

*So, very early on, smooth muscle – intestinal pieces – set a lot of questions for you.*

Yes, such as what mechanisms generate these spikes or action potentials, these very fast changes in membrane potential, that occur spontaneously in some smooth muscles but can be generated by an electrical stimulus in other smooth muscles. I wondered what exactly were the ions that were moving to make that very rapid change in membrane potential which we call an action potential.

*I think you went back to the Frank Shaw methods, changing the ionic background.*

Exactly. I did quite a lot of experiments that nudged me in the direction of discovering what was going on, but I was not the first person to say, 'These action potentials are associated with a change in membrane resistance for calcium ions' – not sodium ions, which until then had been studied as the cause of action potentials. I should have had enough sense to realise it, and I was very close, but it didn't dawn on me at that stage because I was so much influenced by the importance of the established sodium model.

### **The practicalities of research**

*During those Oxford years, you took only two years to write quite a significant thesis.*

Writing my Masters thesis had dragged on and on. I got the message, and was able to write this thesis up pretty quickly. It was entitled something like *The effects of changes in ionic environment on the electrical activity of smooth muscle*.

*Your performance must have been incredibly focused, once the European*

*travel was out of the way. You spent a lot of time at the bench – and did quite a lot of night work.*

One of the problems about being able to put a microelectrode inside a cell, especially a very small cell like a smooth muscle cell, is vibrations. These very fine-tipped electrodes are very subject to wobbling about if there's any sort of vibration in the system. Nowadays people use most sophisticated anti-vibration tables but in Oxford it was a big problem, and when a car or a lorry would go by in Parks Road that would often be the end of it. So I did a lot of work at night when things were quiet, with nobody else around in the lab. I remember clearly that when I was writing my thesis, I used to work from about 11 o'clock in the morning until about 3 o'clock the following night, have just a few hours' sleep and then get back to writing the thesis. And I tell my current lot of PhD students that's the way to do it. You don't want to waste too much time writing a PhD thesis: you're only going to write one in your life and the best thing is to get it out of the way as quickly as possible.

*Was it in the Oxford years that you found how focused you could be?*

Oh, I think I was fairly focused for most of the time after I settled down in my last year at school. I really enjoy studying. It wasn't a bad chore for me.

### **New opportunities and wonderful collaboration**

*This whole field that was opening up was an immense joy to you.*

Yes, very gratifying. But I felt that I couldn't really go much further on the particular muscle I'd been using, which Edith had developed: a strip of smooth muscle where the cells are in a longitudinal direction. These strips of muscle, called taeniae coli, go along the caecum, the large intestine, and they're very spontaneously active. They wriggle about all over the place and it was very difficult to keep a microelectrode in. It was very difficult to understand what was causing the spontaneous activity. In fact, we still really don't know the cause. So I thought that, given the opportunity, I would like to work on a smooth muscle that wasn't spontaneously active.

*Why didn't you stay on in Oxford? You would have been asked to.*

Well, I did have a Wellcome Trust scholarship for the last few months I was in Oxford. But at the same time I was offered a job as a lecturer back in Melbourne, in Physiology again.

*You loved home and you must have missed your family while you were in Oxford.*

Yes, although my parents did visit me there, for a wonderful time. Anyway, partly because I had family in Australia and lots of ties and friends, I decided

to come back to Australia, to Panzy Wright's department in Melbourne. I wanted to understand what caused the action potentials, why they sometimes cropped up spontaneously, to look at the whole question of excitation of smooth muscle. There are so many different kinds of smooth muscle in the body; there's quite a lot of work to be done.

*When you got back to Melbourne, the dignity of the Oxford years was to some extent submerged. You were put into rather limited circumstances.*

Yes. My laboratory was the university paint store. Although the paint tins had actually gone, it wasn't much of a place. There was a sink, which you'd normally have in a paint store, and some power points. But I had to mount my own table – hopefully, more or less vibration-free, because the paint store was right next door to one of the main thoroughfares, Swanston Street. Melbourne University is full of vibrations.

With some help from David Dewhurst, who was in the Physiology Department, and with funding from somewhere, I put together some apparatus. In those days we recorded signals from living cells on a cathode-ray oscilloscope, but I had to borrow one when I got back to Melbourne because we couldn't have afforded it at that stage. It took a year before I got a grant from the National Health and Medical Research Council to buy more sophisticated stuff.

*Mollie, you came from a golden Oxford laboratory back to an impoverished start. Was that a culture shock?*

Well, it wasn't that golden at Oxford. Just after the war there wasn't a lot of money round for medical research. But I did have a cathode-ray oscilloscope in Oxford and my laboratory wasn't a paint store! Among other things, the paint store leaked. I had some wonderful collaboration during that time at Melbourne University, particularly with people like Geoff Burnstock and Mike Rand.

*Wasn't it Michael White who recommended that Geoff Burnstock come out?*

Michael White, who was the chairman of Zoology at that time, was looking for new staff. Geoff had done his PhD with J Z Young, so he really was a zoologist by background, and had gone to the States on a Rockefeller fellowship from Oxford. Geoff and I first met up in Oxford, where we worked together and published a paper.

*Were you part of the invitation deal for him to come to Melbourne?*

To Zoology, yes. We both were looking forward to further collaboration, I must admit, because it had been very good for that short period in Oxford.

## **Just what was being stimulated: cells or nerves?**

*Let's talk now about your collaboration with Geoff Burnstock in Melbourne in the late 1950s and the early '60s. Those golden years produced an enormous output.*

We did have a lot of fun, yes.

*Geoff arrived in about 1959 to join you in the paint store, and your commitment was now to looking at a non-spontaneously mobile smooth muscle.*

That's right. I'd tried several. I'd started off on the ureter, the tubes that carry the urine from the kidneys to the bladder.

*With nice peristaltic waves.*

Yes, a very nice large action with an interesting shape. But they didn't behave very well in response to electrical stimulation. You could only stimulate them electrically if you waited a long time between individual stimuli. We did publish a bit of work on the ureters, but another tube among the pelvic viscera which was clearly not spontaneously active did give a nice twitch in response to an electrical stimulus. That was the vas deferens.

In the guinea pig the vas deferens was not spontaneously active at all, but gave a very reliable twitch response to a brief electrical stimulus. We thought at first that we were probably stimulating the smooth muscle cells directly with our electrical stimulus, but we found out we were wrong. One day we had a visit in the lab from Michael Rand, who had been at Oxford at the same time as Geoff and I, working with Professor Burn, and was visiting Australia. He asked me what preparation I was working on and then said that a researcher in Oxford had just developed a very nice, isolated nerve, smooth muscle preparation of the guinea pig vas deferens, which meant that you could put your stimulating electrodes on the nerve rather than muscle itself and get a nice twitch response.

Very soon we found out that when we were stimulating the vas deferens with an electrical stimulus we were in fact stimulating the nerves to the vas deferens, not the smooth muscle directly. So we now had a chance to study transmission from an autonomic nerve to smooth muscle of the vas deferens. We had a nice innervated smooth muscle preparation in the bath.

*This was the hypogastric nerve. Did Michael Rand help you with the early dissection?*

He showed us how to dissect a hypogastric nerve!

*So he, a present from Oxford, really got you moving.*

Yes. That was great fun.

*Vas deferens tissue was to go on to prove a major model.*

That turned out to be one of the most densely innervated smooth muscles anywhere in the body. There were masses of nerves mingling with the smooth muscle cells. When you stimulate those nerves you get a little signal, a change in membrane potential once again. Unlike the action potential, these are very much smaller signals, which have to sum together to reach the threshold for generating an action potential. So we had a model very much like the skeletal neuromuscular junction – and it turned out to be a model for quite a number of other situations in the body as well.

*So there was a summation sequence?*

Yes. We looked at the signals we got in the smooth muscle when we stimulated the hypogastric nerve, and we saw the small movements of the membrane, in the same direction as action potential but very much smaller – you could grade them with the strength of stimulation. You had electrodes on the hypogastric nerve and you'd stimulate: at first nothing happened and then you increased the strength. Gradually you would come up to a point where you saw a very small change in membrane potential; with a stronger stimulus it would get bigger and bigger, and then you would get an action potential. So we now had a nice handle on what was going on in neuromuscular transmission in smooth muscle. That was good.

### **Wondering about neurotransmitters**

*Eventually you got onto transmitters, didn't you?*

Yes. Perhaps I should explain a bit about the nerves that go to smooth muscle and the other tissues in the body. The skeletal muscles are innervated by nerves whose cell bodies lie in the brain or the spinal cord and send out what we call an axon. That goes out to the skeletal muscle fibre, and at its terminal in the skeletal muscle it releases a substance called acetylcholine, which causes a change in membrane potential similar to but much larger than I described for the vas.

But in the autonomic nervous system – the heart, blood vessels, guts, the whole lot – although the nerve cells send out an axon which releases acetylcholine at its terminal in exactly the same way, that acetylcholine is released onto another nerve cell. It does not go directly to the muscle fibre: instead, there's a relay in the system, with the synapse. And the cells which are activated by acetylcholine coming out of the preganglionic fibre can release different transmitters. Some of them release acetylcholine when they go out to the periphery; some release noradrenalin; some probably release other substances

as well.

So the vas deferens is innervated by sympathetic nerves, and we thought we were looking there at responses to stimulating nerves that worked through the release of noradrenalin. But quite early on in the piece the pharmacology, the way drugs acted on that neurotransmission process, made us wonder whether it really was noradrenalin that was causing the change in membrane potential.

*Are you saying that if you blocked noradrenalin, you still got a response?*

That's exactly right. One of the traditional drugs used to block the actions of noradrenalin and adrenalin on smooth muscle was phenoxybenzamine, which actually made those sub-threshold responses, the ones which were not big enough to be an action potential, bigger than in the control. So it was a bit of a puzzle, something new.

*At that stage very little was known about neurotransmission and transmitters. I remember studying the standard number of transmitters – acetylcholine and nora but not a big field at all. But all of a sudden you were saying, 'There's got to be more.' You were rewriting the texts.*

Yes. I felt for a long time that it could be a question of the noradrenalin acting on a different kind of receptor from any of the receptors that were known to latch on to it. I think most people nowadays believe that it is a different transmitter, and this was Geoff's baby: a little bit later on, he had the idea that the transmitter might be ATP, adenosine triphosphate.

*Why did he come to that conclusion?*

As a result of bits and pieces in the literature. There was a suggestion by Sidney Hilton, I think, that ATP might be a vasodilator. Possibly Graham Campbell had the idea – he was another collaborator of Geoff's and mine, a great reader of literature who had an excellent memory. It's very hard to attribute an idea like that to an individual, but Geoff certainly persuaded a lot of people that it was the explanation and I think most people nowadays would feel it was well and truly established.

*You're not one who presents it.*

Well no, just because you cannot readily mimic the exact changes in membrane properties that are caused by applying ATP to the bath with the changes that occur when ATP comes out of nerves. But it's an interesting story and I think most people would nowadays agree that ATP is a neurotransmitter.

*As Geoff called it, purenergic. So you were then into purenergic transmission. Was this about the stage when Max Bennett also got involved?*

Oh yes. Max had helped me quite early on in the piece, in setting up my lab at Melbourne. Then he came and finished this part-time while he was finishing his engineering course, after which he decided to do a PhD with Geoff Burnstock.

*And you got involved with him in all kinds of electrode work, such as gastrointestinal tract work?*

Yes. As well, he did some nice work on the ureter in my lab, because Geoff didn't have what he needed for that. At that stage of the game, I think, Max put together an intracellular set-up in Zoology, but when he first came into my lab it was the only place that was set up to do intracellular recording.

*Let's sum up this idea of dual transmission, that there might be two transmitters.*

There is no doubt that noradrenalin comes out of those nerve terminals in the vas deferens and in blood vessels, and elsewhere in the body where there's something a little odd about the transmission process. I think Geoff must take credit for promoting the idea of dual transmission, but it is very hard to know where the idea came from in the first place.

### **Inhibitory junction potentials**

*You and Geoff were talking to each other all the time while the idea of dual transmission was in gestation. You must have felt on top of a cloud, being so far into a subject that had been so neglected.*

Well, by then we'd got onto other situations in the body where you get transmission from autonomic nerves to smooth muscle. In fact, Max's PhD was to do not with the excitation of smooth muscle we've talked about up till now, but with the other thing that autonomic nerves can do: inhibit smooth muscle. He had been working on the electrical correlates, if you like, of what happens when you stimulate a nerve to gut muscle and it stops spontaneous activity, rather than excites it.

*This suggests peristalsis, wavelike movements of constriction, pushing material down a tube such as the gastrointestinal tract. I had realised there must be a relaxation, in that everything goes back after a major activity, but here we have a positive process. Were you the first to investigate the relaxation that preceded a contraction?*

Yes. The muscle couldn't move anything on if it didn't relax. We found a lovely little electrical correlate that went with the relaxation, and called it an inhibitory junction potential. Max did a lot of the basic work to establish that it really was so. And again we're not yet 100 per cent sure of what the neurotransmitter is. For a while people thought it might be ATP, but I don't

think there's 100 per cent very good evidence. We can block the fast inhibition that you get from stimulating inhibitory nerves which are present in the gut wall with a substance called apamine, but that doesn't work on the receptor. It works on the ion channel that is affected when the receptor is activated.

*That Burnstock–Holman period was wonderful. You were great collaborators, and you've stayed in contact over all the years – a great ongoing partnership, in a way.*

Oh yes, indeed. And it was great fun, right from the work for our first paper on the vas, which we published in *Nature* in 1960.

### **Sidestepping the sidelines**

*Geoff Burnstock was to go back to England in due course, and you were to go on to a new university. Had you found it difficult to follow your science career? You talked earlier of Edith Bülbring, but it wasn't a wild arena for women researchers. Sometimes you must have felt slightly sidelined.*

At the time I would have said probably it wasn't really very difficult, but looking back, I think it was perhaps a little difficult at times. I was probably patronised a bit, and certainly most of the graduate students that were around in those days were male and didn't really particularly like the idea of being supervised by a woman. I think that's part of the Australian way. On the other hand, there were benefits, because people were very nice to me and polite and so on. I think I've been very lucky.

*Was Panzy Wright kind to you? Was he a great supporter?*

He was a great supporter, although we fell out a little bit towards the end, in the 1960s. Panzy was very much involved with the setting up of the Florey Institute in Melbourne with Derek Denton. Because the Florey people were very much into salivary excretion I did a bit of work with them, measuring potentials from salivary glands, but I didn't want to give up smooth muscle just to work on salivary glands. I wanted to do my own thing rather than be part of the Florey scheme of things.

*You were again kept to a sideline whilst that major development was preoccupying people?*

That's right, yes.

*You needed to sidestep and move somewhere else, so in 1963 you went to the new Monash University – 15 miles from the centre of Melbourne.*

Yes. It had been set up in 1961, in the spot where people were predicting the most rapidly increasing population in Melbourne. Demographically that's still

an area where Melbourne's growing fastest. The first Professor of Physiology, Archie McIntyre, was actually a colleague of Eccles, also from Dunedin. He was very well known in neuroscience, whereas there really wasn't any neuroscience going on in physiology. And there were many other advantages in going to Monash: money, for instance, to buy apparatus and to get a good lab set-up.

*So you got a decent deal. You were going to a job of similar rank, as a senior lecturer, and with money to set up laboratories! I think you were getting more and more into vas deferens work.*

Well, we still were doing a bit on the vas deferens, but I was still working on the inhibitory side of things. It took me a while to get my lab set up, and I did this simple-minded pharmacology at the time.

### **The great orchestra of the ganglia**

After I'd been at Monash about a year, in 1964, I was very lucky – and probably Archie helped – in that I got a Chafer lectureship to go to Otago, in New Zealand, to work with Gary Blackman. He had done some work earlier, I think as a post-doc, on recording from the ganglion cells we talked about earlier. But he had done work on frog ganglia and there was enough around to suggest that mammalian ganglia were probably very different from amphibian. I knew about the nice little clumps of ganglion cells innervating the vas deferens in the pelvis, so I went with the main purpose of using Gary's expertise and mine to do some recordings from the ganglia of the hypogastric nerve.

*Ganglia are like little connective tissue capsules, full of a whole range of inter-networking nerve cells. They are absolutely fascinating, but not enough work had been done on any ganglion structure.*

That's right. Eccles' daughter Rose had done a little bit of work but not recording intracellularly, not actually recording membrane potential directly. Gary and I were successful: it turned out to be a very nice little preparation. When I came back to Australia I was very keen to continue working on the peripheral nerve cells or ganglion cells.

*So those four months generated the real beginnings of ganglion work. Just give me the germ of that. Did you actually see transmitter situations?*

We saw a transmission process very similar to what goes on from these cholinergic nerves to the skeletal muscle, but there were other interesting things in ganglia. They have a great orchestra: there are slow changes in membrane potential which modify their excitability; some of the inputs are very strong and it's almost just like a direct relay; other ganglia have weaker synaptic inputs – a lot of interesting things.

*We're talking about the synapsing, the linking together of nerves and the very delicate interrelationships at the ends of axons. Looking at the transmitters in these very fine areas, were you finding dual transmission in ganglia?*

No, not in those early times. But important dual transmission is more likely in the nerve cells in the wall of the gut, another place where you find these nerve cells outside the central nervous system. Towards the end of the '60s and in the early '70s, I was very keen to make records from those nerve cells that are in the gut wall, because I thought that if you could record from ganglia you should be able to record from those enteric neurones.

*You've got to get electrodes into enteric neurones, impale them?*

That was the ambition. It was a very interesting period, because by then I had a bit of a reputation and I had quite a few post-docs and other people coming through the lab. One of the interesting sidelines that we got onto was to look at some very strange reflexes mediated through some of those hypogastric ganglia and other ganglia, like the inferior mesenteric ganglion. To make a long story short: we found evidence that if you take a preparation of the inferior mesenteric ganglion and put it in an isolated organ bath with a bit of the large bowel, there's continuous synaptic input coming from the large bowel backwards towards the central nervous system. We had a great bit of fun investigating that for a while, because we felt that it might give us a window into what those enteric neurones in the wall of the gut were doing, by simply recording in the ganglion cell that they were connected to. People are still working on those reflexes through some of the sympathetic ganglia in the pelvic area.

*There's a vast amount of ganglionic transmission in the intestine to be charted.*

Yes. Sorting out what goes on in the enteric nervous system is another vast area. In Australia we're ahead of anywhere in the world, I'd say, in that exercise, and in the early '70s I was lucky enough to be in on the very early stages of that too.

*We're talking about a wonderful kind of longitudinal muscle, circular muscle, and two incredible networks that have a lot of independence from the rest of the nervous system but have outside influence imposed on them as well.*

That's right, from the sympathetic nerves and the cholinergic nerves.

*And the nerves coming in actually have a big effect on secretion and on absorption?*

Yes, and on motility. The enteric nervous system itself does very complicated things without being connected to the central nervous system at all, like that

peristaltic reflex that you mentioned, and coordinates motility with secretion and absorption.

*Did you find more than dual transmission situations in that work?*

First of all, the enteric neurones have to be sensory neurones, otherwise you couldn't have a nervously regulated motility or secretion. So there are classes of sensory neurones, there are classes of what we call inter-neurones, that connect the sensory neurones to other neurones, and then there are excitatory nerves and inhibitory nerves. And they're polarised: some go up, some go down, some go round. It looks as though every different class of those nerves has its own special chemistry or neurochemistry, a different cocktail of neuropeptides and more classical transmitters, and they do seem to be chemically coded. If you see one that you've made visible using histo-fluorescence – fluorescent histochemistry – you can pretty much predict what that neurone might be going to do. A lot of work in this area is still going on in Australia.

*And you got into looking at this incredible array of transmitter opportunities, with all kinds of subtle divisions and outcrops.*

It's still a very exciting field – and it's a very nice model of the neural network, so people who work on neural network theory are also very interested in the gut plexuses.

### **Links and inspiration**

*Your work has covered so much: in our talk we've only just reached the 1970s. The excitement with this intestinal network system went through the '80s and I believe you're still involved in it.*

Yes, I am. We're still going strong. A student who worked with one of my colleagues, Bob Bywater, has just done a lovely PhD on some of the complexities of the patterns of activity in segments of mouse large bowel. We've still got an awful lot to learn.

*From 1970, when you got the chair, all through the '70s and '80s, you had many PhD students joining you in that field.*

Yes, but not an enormous number. I've always worked with a small group. I've never really enjoyed working with a large group, just one or two colleagues.

*You became the hub of quite an interest in Australia. You'd started off almost as an individual, in virtually a new field, and suddenly, by the '80s, Australia had become a central region for autonomic nervous system, smooth muscle research.*

Yes. We had the first meeting of the International Society for Autonomic Neuroscience in Cairns, Queensland in late 1997. It was great fun.

*In 1970, also, you became a Fellow of the Australian Academy of Science. And you became a member of the Biological Sciences Panel.*

Yes. I was on Council for a while. I've been a pretty regular attendant at Academy functions.

*And became the Vice-President. You also developed a lot of international collaboration, partly through Geoff going back to the UK but also because in the 1970s you went to London and worked with Bernard Katz – with whom you might have worked a good deal earlier, but for Jack Eccles.*

Yes. But one of the really nice things about science, as I'm sure you will have heard often, is that you make lots of friends right round the world. On average, since I came back to Australia, probably more than once every two years I've been able to attend some kind of a conference somewhere in Europe or North America.

*Perhaps we could take in 1971–72 in London with Katz, at University College.*

It was just a few months, actually, over the summer. It was a very exciting time. He had some wonderful people working in his lab then. Ricardo Miledi was still there, Bert Sakmann was there, and a number of people who've made a big difference to neurosciences – a really inspiring lot. It was wonderful meeting these people.

*Swapping ideas and being able to move ahead technologically?*

Yes, although from my point of view of science, it wasn't much good. Katz's people wanted to make records with a very low noise level, so all their work required the use of electrodes that had a very low resistance, whereas I wanted high resistance electrodes. It was a bit frustrating, in that I had to wander all over University College trying to find a puller that would make a high resistance microelectrode.

### **Tidying up loose ends**

*Just to return to the years at Monash and your work on intestinal plexuses: you had a chance early on to start teaching medical students. That played a big part, and you did some work then on blood vessels. I think you looked at the portal vessel.*

Yes. The transmission situation in the portal vein is very different from the one I talked about in the vas deferens.

*Every new territory has its new subtleties. It's an enormous excitement, isn't it? It's like finding new constellations of transmission, just astronomical.*

Yes, yes, especially when you get to the enteric nervous system.

*You can't let your mind come away from it – it's still so full of questions. But in the early '90s you did let your mind wander to the adrenal gland. That's a big trip.*

Oh yes. When I think about what I've done, I like to think I've tried quite a lot to tidy up loose ends, to solve problems that were sitting there waiting to be looked at. The medulla, the central part of the adrenal gland, is made up of cells which are rather similar in their development to ganglion cells. But nobody had ever made very satisfactory records from neurotransmission to these chromatin cells or knew much at all about the way they functioned. In the last few years I've had quite a bit to do with looking at neurotransmission and some of the other cellular mechanisms important for the release of noradrenalin and adrenalin from these cells into the blood stream.

*So the adrenal medulla is still a focus of great interest to you. You have written of the cells being in rather elegant clusters anatomically, histologically, and numbers of nerve roots coming into clusters. Is there a whole range, then, of subtle possibilities for transmission?*

Well, probably not a great deal, because most of the cells that we've looked at so far in rats and in guinea pigs have at least one synaptic input coming onto them, which releases wads and wads of acetylcholine. So if you stimulate that nerve you can be sure that you're going to get that chromatin cell to undergo an action potential and release a packet or several packets of catecholamine. There is probably not very much by way of subtle modifications of transmitter release in the adrenal chromatin cells.

### **Into retirement a bit**

*You're supposed to be into retirement a bit now, Mollie, since the end of 1995, yet you're still deeply involved. But you can enjoy the luxury of networking worldwide with the many people you've formed close associations with, and travel a bit. What other excitements do you have planned?*

I do enjoy travelling. Also, I'm having great fun at the moment: I've been lucky enough throughout my life to have had a secretary, so I've never actually had to learn to type. I decided that I really would have to find out something about computers, so I've just completed a very elementary computer course, with word processing – except my typing's appalling. I'm just at the point now of going out and spending a large amount of money setting myself up with a personal computer. Perhaps it will make me a better correspondent!

*Mollie, for sharing so much of your career with me and giving me so much detail, my immense gratitude.*

Thank you. I've very much enjoyed it, in fact.

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