An interview with Charles Michel

Conducted by Rod Levick and David Miller at Hodgkin Huxley House on 12th February 2015

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This is the transcript of an interview of the Oral Histories Project for The Society's History & Archives Committee. The original digital sound recording is lodged with The Society and will be placed in its archive at The Wellcome Library.

The Physiological Society

Charles Michel in conversation (photo by David Miller)

This interview with Charles Michel (CM) was conducted by Rod Levick (RL) and David Miller (DM) at Hodgkin Huxley House on 12th February 2015. The transcript has been edited and annotated [with some explanatory details given in square brackets].

DM: **It's the 12th February and we're in Hodgkin Huxley House. So, this is David Miller and we are here to make a recording for the Oral History project with Charles Michel. And the person you'll hear after me will be Rod Levick, who will be conducting most of the interview with Charles. So Rod ...**

RL: **Okay, I'm Rodney Levick, I'm the interviewer.**

CM: I'm Charles Michel, I'm the interviewee.

RL: **Okay, Charles. Charles, you're a Northern lad. Tell us about your Leeds background and your school days.**

CM: Well, I'm a third-generation Yorkshireman, that is my grandfather, my father and I, were all born in Yorkshire and lived there. That is my father and grandfather lived their entire lives in Yorkshire, I just lived the first 18 years of my life full time in Yorkshire. My great grandfather, however, was born in India because he was the son of a soldier in the Indian army, so he was born in the Coolies Bazaar in Calcutta. He was an interesting character because he kept a family bible and his first entries were when he was a soldier on St Helena, round about 1820. And I was really rather pleased about this because, as a family which came as refugees from France, to be actually in the guard where Napoleon was exiled, strikes me as rather a good thing. [Laughter]

RL: Revenge.

CM: But my real background is in Yorkshire, yes. So my father was a Yorkshireman, my mother was also born in Leeds. Her father was born in Ireland, he was an artist and in fact made a living as a stained-glass artist, he had a studio and he did that.

RL: This is why you can do those very nice little [scientific] sketches, Charles. [laughter] That explains it.

CM: Yes, he was, he was actually quite a good water colourist as well. He died when I was six but he made quite a deep impression on me because he was a great storyteller, great romantic, and I can still remember sort of wonderful stories he told, which would involve of course the adventures of Sir Richard, his name was Richard, and his page who was called Christopher, my first name is Christopher. I learnt a lot actually from my maternal grandmother about life in the late 19th century and early 20th century. She had three boys and last of all a daughter, who was my mother. I can remember the Second World War really quite clearly. I can remember my third birthday, which would be 1941, quite clearly. I should say I was born on one side of the Headingly Cricket Ground, which is known outside Yorkshire, and we lived in a terraced house on the other side of Headingly Cricket Ground. During the Second World War the cricket ground was used largely by the services and I remember very vividly the build-up of vehicles before the 1944 invasion…

RL: Really?

CM: That was one place they were stored prior to going down south.

RL: You were [aged] - how old then – in 1945?

CM: 1945, I'd be seven, in 1944 I was six. And also, I remember VE Day and VJ Day very clearly indeed. Leeds was actually quite fortunate, it wasn't bombed like Manchester or Liverpool…

RL: Or Sheffield?

CM: Or Sheffield, yes. We were relatively fortunate. There was some bombing, which I also remember quite well, and there was obviously one occasion [laughs] where my parents tell me there was bombing during the night and I'd heard it and they'd not, they'd slept through it. I think they'd been up with the air raid warnings several nights in succession and were particularly tired. I'm rambling a bit. I went to the local primary school and the thing that I think is of considerable interest is that the Labour Party at the moment, heading for the election, are saying that they won't allow classes of more than 30. I was in a class of 65 and I remember this very clearly because when I got into the junior school the form mistress, to check that we were all there, she gave us all numbers and in the morning we would go in and when we were sat down, we would start. "Right, we'll take the register..." and we shout out our numbers.

RL: What number were you, Charles?

CM: I can't remember but she took the boys first and the girls then followed and the girl who was first in the alphabetical order said she was 45 and that was a mistake because she should have been 35, and the teacher said, "Now, that's fine because we might get some more children, more boys before the end of the year." So, if there were roughly equal

numbers of boys and girls, there must have been probably 70, approaching those sorts of numbers.

RL: Presumably there was an 11+ [examination for grammar school admission] in your day, Charles?

CM: Yes, I didn't actually take the 11+ because I left the school. My parents rather hoped I would get a scholarship to the grammar school, Leeds Grammar School, which at that stage was going through an independent phase and so I went to the junior school of Leeds Grammar School. I didn't get a scholarship. There was only one internal scholarship and I didn't get that, so they had to pay for me.

RL: It must have been a very bright boy that did get the scholarship.

CM: Yes, he probably was. When many years later we took the entrance, the Scholarship Exam at Oxford, he came up with me but he didn't get a scholarship. [laughter] We exchanged places.

RL: So you were late developer, Charles?

CM: Not really because I was going to say one of the advantages of going at that time, I was quite, I wasn't particularly interested in academic things, you see the great thing for me was in 1945/46 Headingly Ground stopped being used by the military and they started playing rugby league during the winter and cricket during the summer. My father and his younger brother and his father, (my grandfather), used to go and watch rugby league matches on a Saturday and I was taken along. And I became terrifically keen on rugby and then in the summer there were the county cricket matches. And, actually, Leeds had quite a good club cricket team at that time. And rugby and cricket were the dominant interest of my mind, as I remember, until I was a little older.

RL: So, when did you start getting interested in science. You got interested in science at school at some point?

CM: Well, that's interesting, you see to keep us quiet at the primary school, paper was very, very scarce but a special treat we were given a clean, blank, piece of paper and allowed to draw on them. And we would draw aeroplanes and ships and motor cars and that sort of thing, and I became very keen on designing planes and ships, you know, as small boys do. And as a small child I was fairly clear what I wanted to do, even though it changed every six months [laughs]. By the time I was eight I had said several times that I wanted to be a ship designer, that's what I wanted to do. Then it became much broader, my interest, it was largely drawing these things, I wanted to be a sort of inventor. And then when I was 10, by this stage I'd got rather ahead of myself at school and I was 18 months – two years ahead of the average age in the form, something that turned out to be very useful later. I had the first science lessons, and sort of very elementary physics, and I was tremendously excited. And we did practicals and I can still remember very vividly, tracing a ray of light through a block of glass and seeing you've got the refraction, following the refraction path through the glass by placing pins in various places. And also the demonstrations done by the master who taught us, he was very enthusiastic, very old fashioned. Even by that stage he was … I imagined him teaching before the First World War. He nevertheless was very enthusiastic and so I decided I wanted to be a scientist. I didn't really know what a scientist did except

that they kept on getting locked up for being atomic spies, that's right [laughter]. Spies. It seemed rather a important subject and they were obviously rather precious people.

DM: Did you have any of that from your family, from your parents? You haven't really mentioned what they did. They didn't bring that to you at all?

CM: No, not at all. My father encouraged me but he was a schoolmaster but his interest had always been English and history and those sort of interests. So, in spite of being more interested in rugby and cricket at the age of I suppose 12, I moved into what was the A stream of the middle school of Leeds Grammar school. Unfortunately, the A stream was the classics stream and so I did Latin and Greek.

RL: It was usual in those days, wasn't it? Bright children did Classics.

CM: We had one lesson of science a week. And then in the Third Form we had Chemistry, one lesson a week, it may have been two, but it was very few, that was… In the Fourth Form we may have had a lesson of Physics but I seem to remember Chemistry again then and certainly in the Fifth Form it was Chemistry. And the classicists didn't do Physics and Chemistry and certainly not Biology at O Level. They did Physics with Chemistry. Anyway, when I got to the Fifth Form, O levels had come in the year before and they had an age limit. You weren't allowed to sit O levels until you were 16. Summer 1952, at the end of my Fifth Form year, I was 14 so I went up into the Sixth Form without doing O levels. And then the examining boards relented and you could take O levels when you were under 16 and so I took three O levels in my First Year Six. Now I should say although I disliked the Classics, I disliked Latin and Greek and [laughs] there were other things which Roz my wife said was I going to mention when I was here. There was one master, well there was one in particular. A rather brutal classics master in whose form I was. I think anyone who came across him would remember him. He left a mark on everyone's career, one way or the other. He was…

RL: And on the person as well?

CM: Oh, many marks on all the people in his sets and forms. And I think the one, the only one I really resent, was that I was Form Captain of cricket and [laughs] I got beaten on one occasion because the form lost to Lower Four [laughter]. So, you can imagine the man he was.

RL: Yes.

CM: Anyway, I managed to persuade the classicists that I would be much happier or much better doing science.

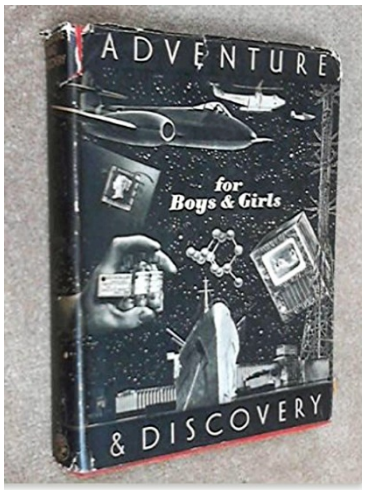
RL: Just before you go onto the science, [regarding the] Latin that you did, do you regret that subsequently or was it ever useful during later life?

CM: I'm very bad at languages and so I don't have the advantage of being able to translate Latin quotations and so on. The one thing I did learn from Latin was how to interrogate English sentences. And that really I am grateful for, yes. I think it's very important. I remember actually, I never had any doubts, or no one ever disputed anything grammatically with me until you and I wrote our first paper together [laughs]. And I remember a really fierce debate in the lab with you over…

RL: **- Use of English -**

CM: Yes, Use of English. [laughs]

RL: **Anyway, sorry, I distracted you, Charles. You were going onto science and you'd decided you didn't want to be a classicist.**



No, but I think before I went into the classical form I wanted to be a scientist and then it just increased. So, I then started actually outside school taking an interest in scientific things, largely sort of childish things. And the, I told my family I wanted to be a scientist and of course they said, 'Yes, yes.' But an uncle, around about 1950, bought me a book which was called *Adventure and Discovery*, I think it's probably *Adventure and Discovery for Boys*. [Likely to have been: '*Adventure and Discovery for Boys & Girls*' Introduced by Kenneth Lindsay (Publ. Jonathan Cape, London, 1946]. And it had a series of articles about, largely about developments which had occurred during the war like radar, the atomic bomb, but it also had two or three articles on medicine of which two really excited me. One was about corneal transplantation and I was really absolutely taken by this, it seemed a beautiful, skilled, operation which, from reading the account, it seemed to involve careful measurement and accuracy and so on. And I was very taken by this indeed. There was another article on antibiotics and sulphonamides and antibiotics, gave a sort of brief history. It had two photographs that I remember very vividly. One was of Sir Alexander Fleming at St Mary's Hospital Medical School and the other was of Sir Howard Florey.

RL: **- who, just for the record, was later Provost of The Queen's College, Oxford [where CCM was later elected a Fellow]**

CM: Well, I was going to say he was the first person to give me a permanent job. And reading those articles made me start to think about the possibility of doing medicine. I still wanted to do science. There was also another thing in my background. In 1947, which was my first year at the grammar school, Leeds Grammar School, 1947, winter was a famously cold winter. And it was a time when there wasn't much heating and my mother was ill, quite seriously ill. And when she recovered, she obviously didn't recover properly and she had multiple sclerosis essentially. She had a downhill course from there. And she died when I was 16, whilst I was doing A levels. But anyway, as I say, I went into Sixth Form, I did biology, which I found exciting, very exciting.

DM: **I was wondering, you had this accelerated route into Sixth Form, so then you had specific subjects that you were following?**

CM: Yes, well I had to get my O levels in the Sixth Form. O levels had just introduced with the rule that you couldn't enter for them until you were 16 When I went into the sixth form I thought I was going to have to do my O levels and A levels together and then fortunately the age limit came off during my first year in the Sixth so I was able to take three O levels, which were English, Maths and Latin, because I was much better at Latin, which is more a bookworm language than I was at French, which you have to speak and understand.

RL: **- in a funny voice!**

CM: Anyway, I did reasonably well in the First Year Sixth, and I was aiming to go to Leeds medical school to do medicine. And then in the second term of the second year in the Sixth, we had a new headmaster, and our form master came round and said, 'The new headmaster would like to talk to people who might be interested in going to Oxford and Cambridge and I suggested that you might be interested.' I wasn't interested at all and thought I would go to Leeds medical school because it was the best medical school in the country that I knew. And being a good Yorkshireman, you know, why would I go down to the south? [laughs]

RL: You thought Sheffield was too far south?

CM: [laughs] And anyway, there were three of us who it was suggested we should go and talk to the Headmaster. And the other two were both a year older than me, who were actually very close friends. So, I went along and suddenly this idea of going to Oxford or Cambridge came up. Well, I did my A levels that summer at 16 and I didn't do brilliantly at all, and as I say, my mother died at the time, which is not terribly good.

RL: And it's very young to do A levels. I mean most people are 18 when they do A levels.

CM: Yes. But anyway the next year my two friends, both Brian **[??]** who is a physicist, he got into Cambridge and Ian Chisholm, who is a biologist, he got into Queen's. He did the Hastings Scholarship and got into Queen's.

RL: Queen's College in Oxford?

CM: This is Queen's College in Oxford. So, Christmas came around and, or I should say after Christmas, the form master came around to me and said, 'Well, you know, I know you're a bit young but Oxford have a scholarship exam in March, how about giving it a go?' I thought, you know, I didn't feel prepared for it at all but I went along on the sort of understanding that I either got a scholarship or nothing. I had always thought one ought to go to Cambridge to study science, but I thought medicine was perhaps supposed to be quite good at Oxford and so I thought, 'Well, I'll try Oxford.' So, I went along and was absolutely stunned by how beautiful it was, the sort of atmosphere, the way in which a Northern lad was treated by the people who interview you.

RL: [One interviewer would] have been Cyril Carter, the physiology tutor [at Queens], was it?

CM: No, I went to Brasenose actually.

RL: Oh, this wasn't [for admission to] Queens?

CM: No. And I didn't get a scholarship to Brasenose but the College wrote a very nice letter to the school about me. And so it actually put pressure on me because everyone expected me to get a scholarship the next year, which fortunately I did and also a state scholarship when I took A levels again, changing the A levels slightly. So, I did Zoology, Botany and Chemistry. I should say I had scraped through Physics largely by my own devices. Physics was the thing that had excited me initially about science. When I went into the sixth form we were taught by somebody who was completely unsympathetic to the people doing Biology. 'Oh, you've got to do A Level Maths to do A level Physics,' was very much his attitude. I got into the second year sixth having struggled with Physics in the first year but probably better than most biologists. And then we had a physics master who was excellent and I really began to get a feel for doing Physics in the first term of that second year Then the master had a very

severe heart attack which really finished him as a schoolmaster. We had two terms without Physics instruction and I looked at the syllabus for A level and in those days for me it was the NUJMB [Northern Universities Joint Matriculation Board] A level syllabus to…

RL: **No, we did Oxford & Cambridge [A level syllabus].**

CM: Ah.

DM: **It was London for me.**

CM: Northern Universities Joint Matriculation Board. The physics A level paper had general questions and questions on more advanced subjects. I think you had to answer three or four general questions and then you had to answer two or three advanced questions. So, I concentrated on three advanced subjects and just hoped I'd know enough to get through the rest and that actually worked. It got me through but it meant I really didn't know half the A Level Physics syllabus. And after I got a scholarship to Oxford in those days you used to take Natural Science Prelims before you came up if you were a scholar.

RL: **Sorry, I'm a bit confused now, Charles. You told me about a Hastings scholarship to Queen's College [Oxford].**

CM: Oh yes, sorry, I didn't fill that in. So I scraped through Physics A level. Then, the next year, when I tried for a scholarship at Brasenose and didn't get it and that summer I did A levels in Chemistry, Zoology and Botany. Then the following November I got the Hastings Scholarship. In those days the Hastings was done before the main open scholarships.

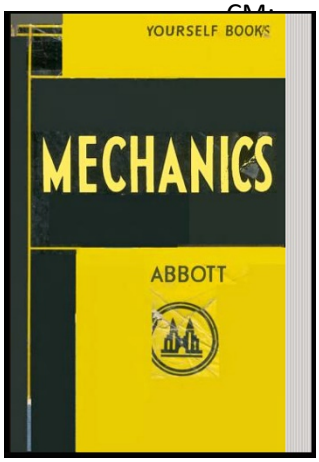
RL: **Yes, yes, as it was in my day.**

CM: As it still was in your day, yes. And I got into into Queen's.

RL: **Queen's option, Yes. [***Explanatory comment by RL:* Perhaps at back of my mind was fact that these scholarships, set up by Lady Hastings, were intended for Northern Grammar School boys, so Queen's was a frequent option for bright Northern boys.**]**

CM: And then Carter wrote to me and said, first of all I had to get another second language because I'd only got one language. So, fortunately the Oxford exam, 'Responsions' it was called which was the sort of qualification you had to have to matriculate, the Oxford French exam didn't have an oral paper so [laughter] I was quite happy to do French.

RL: **Right.**



CM: Scraped through that. But Cyril Carter, who tutored both of us, he wrote to me and said, 'Well, Michel, you know, you're a scholar, you ought to do the Natural Science Prelims before you come up.' So I had to do another physics exam at the end of my schooldays, And inevitably I failed. And that was one of the best things that happened to me because I did actually worry about it, did quite a lot of reading over that summer. There were some books you could buy called 'Teach Yourself' series, and I got a book called '*Teach Yourself Mechanics*'. I'd never had any real instruction in mechanics, even though I had A Level Physics, would you believe it. I've still got the book at home, largely for sentimental reasons… [laughs]

RL: **Is it yellow , yellow and black? I had a '*Teach Yourself Botany*' book. [laughter]**

CM: And so I slogged away at that over the summer before I went up. During my first term at Oxford, I had tutorials from a first-year research student, somebody who had just done their finals in the Honours School of Physics. And I had a tutorial, one tutorial a week with him, and I got really switched on by the physics, really enthusiastic. By the time I took the exam, I had no problems. You know, I could almost have given up doing medicine to do physics at that stage…

RL: **Well, you can switch at Oxford can't you, often, at an early stage? Did you consider switching?**

CM: Yes, I didn't have A-level maths and that was necessary really.

DM: **So, were you also given lectures or labs in physics, or was it just tutorials?**

CM: I didn't have time to do that. I just had the tutorials.

RL: **Well, one of my questions Charles, was going to have been - you've more or less answered it - was why did you do Natural Sciences? And I guess is the answer that you went into Oxford to do Medicine, and in Oxford you do Natural Sciences as a precursor to Medicine?**

CM: Yes, yes, but I was quite keen to do natural sciences because I still thought I'd like to do some sort of research and there was more of an opportunity to do research. And also I suppose through my mother's illness I'd seen that it was great being a doctor. But there were a lot of diseases you couldn't treat, and I could sense the sort of helplessness you might feel with a patient you wanted to help and you had no idea what was going on. And certainly multiple sclerosis was a disease in that camp at that time. So, I'd thought in terms of, well if I did anything, I'd work on the nervous system and I thought that neuropathology, something like that, would be the way to go.

RL: **Yes, I guess you're now answering the next question that I'd got in mind, which is why you interrupted your medical course to do research, to do an Oxford DPhil? And you've sort of given us a reason for that, [or] reasons. But you actually didn't do it in neurology or neurophysiology, you did it in respiratory physiology, didn't you, your PhD, your DPhil rather. So why did you opt for research in respiratory physiology?**

CM: I think I saw pretty quickly, quite wrongly actually in some ways, that neuroscience was very interesting: I enjoyed it. I thought doing neurophysiology, particularly in my third year, I enjoyed it. I enjoyed it actually in my second year preparing for the BM examinations but there was not very much you could do in medicine with neurology at that time. You could make diagnoses but that was about all, a few treatable diseases. You know about the best thing you could do was diagnose a slipped disk in the neck and give someone a collar. [laughs] It was pretty limited.

RL: **Yes.**

CM: Whereas not only could you do things in other areas of applied physiology but there seemed much more opportunity to do more than had already been achieved, so it seemed a much more, so I suppose that influenced me. There was another reason and that was my idea of anatomy and physiology when I started was really anatomy. I was quite interested

in anatomy and comparative anatomy, just doing zoology at school. I got very disenchanted by anatomy because shortly after I started we started, as you probably did, did you have to dissect the whole body?

RL: **Yes, the entire body, yes.**

CM: That's right. Well, we started with the upper limb.

RL: **Yes.**

CM: And so after we'd learned the bones, all the numbers and names of the bones in the hand and that sort of thing, we did the shoulder joint. I found this fascinating. I'd never thought of it before, that you had this joint and a simple movement like raising your arm like that, how many muscles were involved in stabilising the joint. And so after I'd learnt the names of the various muscles, also the origins and assertions, my enthusiasm for the physics which was quite fresh at this stage, took over and I started working out the moments around the shoulder joint for very simple movements, lifting the arm, like that [demonstrates], being one of them. And so I wrote out some of these things. And I was also struck by how inefficient the musculoskeletal system is and has to be in order to work at all, that is the principle of the level operates against you in most limbs…it had never come home to me actually.

DM: **Because the muscle can only a shorten a relatively small amount, so the leverage has to…**

CM: So it's attached.

RL: **That's right.**

CM: So close to the fulcrum. I mean in fact you could say one of the few sets of muscles which operate at a more mechanical advantage are those which move the fingers because they're not actually in the hand. Most of them are in the forearm.

RL: **I'm going to come on to ask you about [your] use of maths in physiology but was that in fact the first time you wrote down some equations for a little bit of physiology?**

CM: Well, these were sort of, you know, cosines and sines and things like that.

RL: **So that was you first venture into mathematics in physiology?**

CM: Well, in a way. I never thought of myself as being good at maths, I wasn't for my generation particularly good at arithmetic. At school I was actually very good at trigonometry. Geometry and algebra less so, but trigonometry I could do, I suspect it was because I could see the practical side of it, and you know it made much more sense, whereas occasionally with a geometrical problem you couldn't make head nor tail of it [laughs]. But anyway…

RL: **So, anyway, you decide to do a DPhil?**

CM: Yes, but before that, I should say that I started physiology and I saw it in terms of functional anatomy but I realised there was something else that I was missing, and I think during the first vacation I was at home I discovered in the public library a book by A V Hill, which was a series of Christmas Lectures and it was called *Living Machinery*. And I read that book and I was absolutely hooked on physiology. It was very quantitative in a simple way… and it had quite an impact on doing practical experiments. I became terribly enthusiastic doing the

frog experiments, the sort of ancient frog nerve muscle prep. I say ancient because they were the sort of experiments done with pre-First World War equipment (the Lucas rheotome) and [laughs], but I got tremendous interest and pleasure out of doing them. So that I think was the first thing. Then I really enjoyed doing physiology - I tried to understand the works which had just quite recently been done on nerve membrane potential, action potential, and so on by Hodgkin and Huxley. It wasn't until my third year I really began to understand it properly. By that time, I'd also become more interested in cardiovascular, renal, respiratory physiology.

RL: Right.

CM: And then the idea that Cyril Carter had, our tutor had–and I think most tutors had at that time–was that you should have a full life during term in Oxford but you should read a lot in the vacations. And during the summer vacation between my second and third year, he gave us several books to read which included Haldane's book on respiration and just recently published book by Heymans and Neil on reflexogenic areas of the cardiovascular system. And Barcroft's book, Joseph Barcroft's book, on the *Architecture & Physiological Function* and Henry Barcroft's book on the sympathetic control of blood vessels, the first of the Physiological Society monographs.

RL: All of which I remember you [later], I think, recommended that we read as students [laughter].

CM: Well, I thought they were…

RL: And they were excellent, yes.

CM: And I think there were other things there. Haldane and Barcroft's books really focussed my mind on respiratory physiology and Heymans and Neil indicated, the Neil chapters at least on respiration, that Dan Cunningham [Daniel Cunningham, 1920-1996] was a rising star in respiratory physiology.

RL: Ah.

CM: And so I thought, 'Well, I could perhaps do a BSc' as people did, a one year research, additional research. The BSc became an MSc, thus it's people who got the BSc like John [Tooke] for example. He now has MSc after his name, the same thing, it's just…

DM: An MA and MSc.

CM: He has an MA as well, that comes with the first…

DM: With respiratory, yes?

CM: So, I was thinking in those terms when I went into the Third Year and I shared digs with a chap who was keen to do research and he said, 'There's a scholarship called the Christopher Welsh scholarship, which is for biological scientists.' You had to do the Honours School of biological sciences and in those days physiology which we were doing, was part of the school of biological sciences. So, he said, 'You ought to do it.' I did the sums and yes, a research scholarship for three years. I thought, 'Well, I'll probably never get it.' You were up against all the botanists and zoologists and the other chap, Richard Haslam, he was very much more knowledgeable than me, you know. He wanted to work with Krebs [Hans Krebs, Professor of Biochemistry in Oxford at the time], he was dead serious chap... Anyway, I

agreed that I'd have a go at this thing and amazingly I got it that year. The first year for a long time it had gone to a physiologist and I think the previous physiologist to hold it was J F Fulton [John Farquhar Fulton, 1899-1960]

RL: **Uh huh. Fulton. Yes.**

DM: **And the basis for getting the scholarship was…?**

CM: Well, you took a written exam at the end of your penultimate term, . Let me think, your eighth term so it was the Easter of your third year .and then you had a very long interview on what you wanted to do research on. Before then, I had talked to Dan Cunningham about the possibility of doing a research with him and he said, 'Okay, get a First in Schools and we will talk again...' [laughter]

RL: **Encouraging!**

CM: So, anyway, I got this scholarship and I suddenly had three years research. I was slightly uneasy because you know the clinical part of the medical course was another three and a half years. But everyone was supportive and my father was supportive. And I was actually quite keen to do a DPhil really. So I did a DPhil.

RL: **And I think, wasn't it Brian Lloyd was a co-supervisor, along with Dan Cunningham?**

CM: Yes. I was going to say that I was extremely lucky because Dan was my supervisor, official supervisor, but he and Brian worked very closely together, in fact they collaborated all the time. And I think another factor in making me want to do respiratory physiology was a paper by Cunningham and Lloyd, it was Lloyd, Jukes and Cunningham, which was a mathematical description of human responses to hypoxia and CO_2, and this did involve a little bit of mathematics - it was very simple linear algebra but described the responses in terms of linear equations which struck me as - you know clear thinking. It got one out of all these problems such when you assume you are stimulating breathing with hypoxia you inevitably change the CO_2 stimulus. Dan Cunningham had previously done a very beautiful experiment in which he managed to keep the CO_2, the alveolar CO_2 constant whilst hypoxia is used as a stimulus so that you got the pure hypoxic stimulus in the presence of constant CO_2. But the Lloyd-Cunningham analysis meant that you could do it actually in a different way, which was actually a nice way of thinking about things. It sort of clarified your thoughts.

RL: **I'm seeing an interesting parallel here, Charles, in the way later on you looked at the effect of osmotic pressure on fluid exchange in capillaries and how the flow [fluid exchange] itself changes osmotic pressure [the osmotic pressure difference across capillaries]. So you got a similar sort of problem, haven't you, there, in some respects?**

CM: That's very true, yes, yes. Yes. So, anyway, I had two years, I had potentially three years research looked after by the university, fees paid. It was even better because, as an undergraduate I had a very small grant and I had a college scholarship of course, which paid fees and so on, which people don't enjoy these days, but when I became a graduate I suddenly had £300 a year in three instalments. [laughter] It was probably £340, I dare say, but it was some substantial sum, it seemed to me at that stage. And I was paid in three instalments at the beginning of each term. So, the beginning of the summer term I was

absolutely flush. [laughter] I had a full year's grant in six months, you see. I never had so much money.

RL: Spend, spend, spend. [laughter]

CM: So that was, and also I had the security. I didn't have to worry about anything. You know as far as immediate things. My research project was about regulation of breathing but I should say I'd become very interested in the exchange of gases in the lung and also in the tissues, not much was known about exchange of gases in between the blood and the tissues. But my project was on the regulation of respiration, at least at the beginning, and we were looking at the interactions of metabolic acidosis and respiratory acidosis and hypoxia. And my task really was to get pH measurements, blood gas measurements going. Because really all the measurements they had made up till then in the Oxford respiratory lab (since JS Haldane's time), apart from a few measurements my predecessor, Donald Shaw, had been based on alveolar CO_2 & PO_2 measurements. And they'd just bought got this thing (electrometer) called the Vibron which was a potentiometer that had almost zero drift, compared with the higher resistance potentiometers that had been available before, so was able to measure small potential differences with very little drift and so was adapted for using with glass electrodes (for measuring pH). Previously pH measurements had an accuracy of 0.02pH. The thing was to make it comparable with our alveolar PCO_2 measurements, or 0.2 of a millimetre of mercury so we wanted the reproducibility of blood (plasma) pH measurements down to be 0.002 pH units. I found I wasn't a particularly good person to pick up a technique and just make it work, as you are [laughs] ... and had certainly not as my predecessor had been, Donald Shaw, he was very good at doing that. So, I'd been keen on physics as I've described, and even more so perhaps with more success in physical chemistry. And so I wanted to find out how gas electrodes really worked and I spent a lot of my first year reading up physical chemistry, pH, and electrolyte solutions and trying to understand it. I think it paid off in the end and eventually I built an arrangement which really did give reproducible pH measurements to about 0.002 or plus or minus 0.001.

RL: Wow.

CM: But really I didn't make much progress until I got this thing working. It took 12 months to get it to go.

RL: Yes.

CM: And then things just whipped away and by this stage -

RL: Sorry to interrupt again, but there is [was] a bit of a pattern in those days, wasn't there? When you did a PhD or a DPhil, you spent a long time building your apparatus, your particular kit, and then at the end if you were lucky you got some results. [laughs] It was sort of a frequent pattern, wasn't it?

CM: Yes, very much so. I should say I'd been given, before I'd really got into the pH thing, I was told to calibrate a CO_2 meter which was based on, was it based on chemical absorption from flowing gas. You divided the flow of gas and had a CO_2 absorber on one side and a control compartment on the other and you measured the pressure difference between the two gases as they emerged from the two pathways. And what was it called? The flow bridge analyser- we didn't have an infrared analyser – let alone a mass spectrometer.

DM: Were you using human subjects, by the way?

CM: Yes, this was all done on human subjects. I should say I was also attracted to human physiology because I was struck by the ingeniousness of several of the methods that were used. I remember particularly Roughton's [Francis John Worsley Roughton FRS, 1899-1972]

calculation of the time that a red cell spends in a pulmonary capillary. And actually the Kroghs' [Schack August Steenberg Krogh,1874-1949] measurement of diffusing capacity I thought was very clever.

RL: We should probably move on a little bit, Charles.

CM: I'm sorry, yes.

…

RL: Yes, we ought to move on and get slightly further into your career.

CM: Yes.

RL: Charles, you were actually my first tutor - sorry, you taught me at my first year at Queen's and you were still a final year medical student at that time.

CM: Yes.

RL: And I know you then qualified in medicine but then you gave it up and became a physiologist. And that I think is always a precarious step, isn't it, giving up a secure career like medicine for a potentially hazardous research career with all its insecurities?

CM: Well, it would be nowadays [laughter] but of course then I was quite sure that was what I wanted to do and once you had a job it was alright. And I was very fortunate…

RL: And what job did you have?

CM: Well, I should say that, and I'm afraid I must go back here to being a research student. I said in my, as a research student, once I got the apparatus working, things just sailed away. I should say that earlier, before I got the apparatus working, we had made quite a significant observation which was that when you had a human subject breathing CO_2, the changes in PCO_2 and pH that occurred in blood, the arterial blood, didn't follow the CO_2 dissociation curve. And we worked out, Brian Lloyd and I worked out a theory for the CO_2 dissociation curve, so that from a single sample, of blood, you could you could calculate how the CO_2 dissociation curve would behave in vitro. And we could show that there was a deviation. You got what appeared to be a non-respiratory acidosis, a metabolic acidosis accompanying the respiratory acidosis, and we were going to follow this up. This became the thesis subject rather than the control of breathing, and I did quite a bit of work on the control of breathing as well, some of which went into the thesis, but this was the principal thing for me and this (the changes in pH and PCO_2 in blood) was the thing I was really interested in. And what I realised was, funnily enough, during a holiday walking in the Yorkshire Dales, I realised that there was a very simple explanation for it - that was the distribution of bicarbonate between the plasma and the interstitial space. And that in effect you have a haemoglobin concentration in the body which should really be expressed in terms of the volume of the plasma and the interstitial fluid, whereas in vitro you have a haemoglobin concentration which is in the red cell's fluid, the red cells and the plasma only.

RL: You haven't got the buffering effect of a huge interstitial volume?

CM: Well, it's a diluting effect.

RL: I used the word buffering [in a non-chemical sense].

CM: So you have a steeper dissociation curve.

RL: Yes.

CM: I say CO_2 dissociation curve, you have less buffering of the CO_2 by the haemoglobin. And so really, apart from that my thesis was a bit thin on experiments, I did quite a lot of in vitro experiments as well. By the end of my summer term in my second year I could see my thesis finishing and that turned out to be incredibly fortunate because that year Lloyd and Cunningham organised the Haldane Centenary Symposium and I was a sort of boy who ran around with a notice board, met people at Oxford station coming up from London and put them on a bus taking them to University College where they were staying. Probably one of the best things was to meet Haldane, J B S Haldane, off the train. And I had this stick with a notice on the top saying 'Haldane' and he came to me and said, "I'm Haldane." [laughter] And he was incredibly nice actually, he was very nice indeed, very bright. He impressed me very much at the meeting, his participation in the discussions. Anyway during the meeting I sort of ushered people around but I was allowed to go in to hear the papers and be involved in the discussions. At the end of the meeting Fred Kao came up to me and said, "Hi Charles, I've got a post-doc going, could you come and work for me next year?" So I said, "Well, you know, this, that and the other." Anyhow…

RL: We should point out for the record that that was said in an American accent [laughter]. It's not going to translate when it's typed. [laughter]

CM: Anyway, it was completely out of the blue, of course. I then explained to him that I'd not written my thesis, and I'd got to do that and I was going on to do medicine. "So well, you think about it, and if you could let me know by Monday morning." This was Friday night. "Let me know by Monday morning. We're taking a bus down to Heathrow airport at such and such a time, I'll meet you in the bus station." Something like that.

RL: Yes.

CM: Anyway I talked to Dan Cunningham on Saturday about it, and the Saturday lunchtime I thought I'd better go and tell my father because I'd more or less decided I was going to go. So I got the train up to Yorkshire, came back, told my father and my father seemed happy. [Laughs]. Came back to Oxford and said I'd go. Another thing I'd just like to say, Dan thought I ought to talk to G L Brown [Sir Lindor Brown -Waynflete Professor of Physiology], who was the head of department of Physiology. G L Brown was going away immediately after the Haldane symposium and he rang me up in the lab from Heathrow airport with the initial command of, "Charles, write down this number immediately, I'm running out of money." [laughter] And he, so I wrote down his number and dialled back from the lab phone to Heathrow call box and he advised me, he said, "No, I think you ought to go and do medicine, qualify, get your medical degree and then come and talk to me about doing more physiology." Anyway I decided to go and when "GL" came back from his business overseas I went along and saw him and I said, "You know, thank you very much for your advice but I'm afraid I'm going to go." And he said, "Well done." And he was really so positive about it, he

was a great guy. And when I came back from the States, he was equally supportive. I had a great time in the States and I felt independent, to some extent, although Fred was the boss - it was a good relationship.

DM: Was that a big lab in the States at that time? Were there a lot of people there?

CM: No, it was not. Four or five of us. And - it's just amazing how much experimenting we did.

RL: But these were live animal experiments, weren't they? They were transfusion from one animal to another, weren't they?

CM: Yes, these were cross-circulation experiments on anaesthetised dogs. Not the sort of experiments that one would consider doing today.

RL: Yes. But it did mean - correct me if I'm wrong - but it was the first time you'd really moved away from human physiology into animal physiology, would that be right?

CM: Yes, I mean there was a mammalian class actually which we did in the third year of the honours school, so we learnt how to…

RL: Yes, but in terms of research, it moved away from the human somewhat.

CM: Yes. So when I came back from America I was quiet clear I wanted to be a physiologist and I thought if I couldn't get a job in England, I would go and work in America. I knew I could get a job, I was pretty confident I could get a job. It might seem presumptuous but it was quite possible at that time.

RL: Yes.

CM: I also, I had other plans. I thought what I'd do, when I did qualify in medicine. What I wanted to do was learn more physics and chemistry. And Sandy Ogston, who taught me in my final year, I say taught me, he'd given lectures in my final year, he had impressed me enormously and I thought it would be a good idea to go and work with him. He was, at this stage, in Canberra at the ANU (Australian National University), and he used to come over from time to time to Oxford and I'd talk to him about this possibility and seemed quite happy with the idea. So that was the aim. But Cyril Carter retired, was due to retire, in 1965. And I had a call, yes I had a telephone call from the provost's secretary at Queens, the Provost being Florey, and she said that the Provost would like to have a word with me, could I make such and such a time. And well, yes of course I could [laughs] and I went along and met him. I remember it was an entirely informal meeting between him and me and he just chatted to me about research I wanted to do and then he said, "As you know, Dr Carter is going to retire in two years' time," or 18 months, whatever it was, and "I can't offer you a research job, it's a teaching job" "Would you be interested?" So I said, "Yes, I would be." [laughs] And he said, "Well, I have to get the governing body to agree to it." So he said, "I've talked to Brown, (GL), and he says he'll give you a job in his department" It's the first I'd heard of it [laughs]. Not quite. GL had said to me, "When you get your medical degree come and talk to me." But up till then I thought of going to Australia to work with Sandy Ogston. So by the time I taught you, when Carter was taken ill in his last year, I was already lined up to succeed him.

RL: So really you decided at that point not to proceed with medicine but to make a career of research?

CM: My intention was to be a physiologist and…

RL: Was it doing the DPhil that clinched the matter for you?

CM: Yes. I mean, I'd like to have done it in any case but I, you know, it just gave me the confidence and I think also I'd wanted to do research and I really was hooked on doing research in physiology after doing the DPhil, or whilst I was doing the DPhil.

DM: It's interesting how the career sounds like this. I was thinking from the point of view of medicine. You haven't mentioned whether you had any mentor who looked after you as a potential medic? It sounds as though that all just didn't happen.

CM: No.

DM: …whereas various people picked you up on the physiology side, clearly, and were concerned about you and were lining bits of your career up without you even knowing about it [laughs].

CM: Well, no, I'd said I went to GL when I came back from America, I wanted to be a physiologist. In fact I did consider giving up being a clinical student I was so fed up with clinical medicine when I started that I thought, 'Why not cut my losses and go and try and go over and try to get a fellowship to work with Ogston.

RL: When you did start up your own lab, Charles…

CM: Yes.

RL: You started it up, if I remember rightly, with a project to study capillary permeability and that's a big switch. At least on the face of it it's a bit switch from blood gases and respiratory physiology.

CM: Well, yes, it seems a big switch certainly from the regulation of breathing but I was interested in exchange of gases in tissues.

RL: But the subject was pretty dead at the time, wasn't it? There was very little going on in the 1960s, wasn't there?

CM: Well, there wasn't , virtually nothing had been done for some time. Well, that seemed to be a good thing for me to do, something no one else had done recently. But the thing that I think really got me was, in human physiology and mammalian physiology, one was constantly developing models which involved simple ideas about microvascular exchange. And there was no real solid background from which to work. In fact there was a bit more than I thought at the time, but I only came to appreciate that when I really got into the literature of microvascular permeability.

RL: Yes.

CM: I had thought, when I was with Fred Kao, that I could use the techniques that I learnt in his lab, to do organ perfusion and limb perfusions as Pappenheimer had done.

RL: Yes.

CM: That's how I was thinking at that stage. But…

RL: **There were whole organ methods pioneered by Pappenheimer and Renkin and also David Yudilevich**

CM: Well, Crone and Yudilevich.

RL: **Crone and Yudilevich.**

CM: Renkin, Crone and Yudilevich, they are very much linked together.

RL: **So having decided to study capillary permeability and organ supply, why didn't you adopt those approaches? Because what you actually did was you went for the classic…**

CM: Well, because I had been well trained as a respiratory physiologist, and I was very much aware of the effects of non-uniformity. The big fault that I saw in all of those techniques was that you were dealing with a population of capillaries, so if you wanted to know anything about permeability, you were dealing with populations and the averaging was probably muddying the picture.

RL: **Right.**

CM: And very early on I'd worked out some of the effects as I began to learn more about how to calculate blood tissue clearances, using the sort of Renkin, Crone, Yudilevich approach. Once you got a population, or even if all capillaries had the same permeability but different blood flows, the ratio of blood flow to surface area is different in the different vessels. Then in fact you average your data over a linear relationship whereas in fact the true relationship is a highly non-linear and the more so with extremes of perfusion, that is under perfusion and over perfusion the worse this becomes. And so I thought, "If I want to understand how permeability works, I have to work on single capillaries."

RL: **And that meant going back to the Landis method of cannulating single capillaries and that involved the frog mesentery because the capillaries are a little bit larger than mammalian ones. Was that your reason?**

CM: That's true. I tried to avoid having to calculate single capillaries at first and I tried close injections through the arterial system whilst visualising the mesentery, and discovered that you really can't get a step change in concentration that way. It's surprising though how the dye just fades in, as opposed to fades out.

DM: **Just in passing though, Charles, you're mentioning the need for a level of microscopy that you won't have encountered before. I mean, you're talking about live tissue, visualising it in a living state. And hence you're now going for the thin membranes that are available with [a prominent] capillary supply and that's the best you can do. But did you have to do a lot of work on the microscopy side or could you just pick that up, more-or-less 'off the shelf'?**

CM: That wasn't too difficult, actually.

DM: **Okay.**

CM: I went to talk to Sanders in pathology, and he was reasonably helpful. He didn't really tell me very much but he gave me the idea of building a sort of tray for trans-illuminating tissue and he showed me his method, he had a rabbit with an ear chamber and he showed that to me.

RL: Where did you learn how to make the micropipettes?

CM: Oh, well a lot of people were making micro-electrodes in the lab and Simon Miller was actually doing what I'd just done, that is he was a clinical student but he was coming into the lab and trying to work at weekends and evenings. And he had a design for a simple, micro-electrode puller, and so I built that myself and I built the base of the rig that we used. I think you added some other things more professionally [laughs].

RL: I doubt it very much, Charles, I doubt it.

CM: And then when I realised I'd got to learn how to cannulate single capillaries, I just sat down two or three afternoons a week with a micropipette and eventually found I could do it. And I only just managed to do it regularly before you started as a research student and you learnt about it quite quickly.

RL: I know, and I became a little bit better by the time I finished [laughter]. I mean, moving on Charles, that early work was with dye perfusion as you hinted then and we looked at this story, didn't we, together, of small pores and large pores, and whether dyes were bound to albumin or not, and so on. But just moving on a little from there, when I gave up medicine and returned to physiology, and you very generously supported me in the lab while I was waiting to get going on synovial fluid - -

CM: We got some money from the -

RL: - Arthritis and Rheumatism Council. While we were waiting, you and I investigated capillary pressure in human fingers and toes, in fact our own. And our results differed in some important ways from those of Landis [Eugene M Landis, 1901-1987] in the 1930s.

CM: Yes, well Landis, 1930.

RL: Yes, published in 1930. And virtually every textbook account in those days, and I think probably mostly still today, were based on Landis' results.

CM: Yes.

RL: And you were concerned about this and wrote to Landis, who was by then retired, I think.

CM: Oh yes.

RL: Can you tell us about that?

CM: Yes, well actually I'd already told Landis about your first research because, if you remember, it was following up his last research. Well, it wasn't his very last research, but his last research at Harvard and that was looking at the effect passage of dyes through individually perfused capillaries and trying to find evidence for large pores, as they were called. And so we had corresponded from then onwards and of course I'd met him and talked to him at the Benzon symposium and he was very supportive of what we were doing. But no, his measurements had suggested in humans and also in a range of animals that the capillary pressure and the colloid osmotic pressure of the plasma, were more or less the same. And you and I found that, in ourselves, when we were warm, [laughs], the…

RL: - and [hand or foot] at heart level.

CM: And we went to great pains to get things right-at heart level, our pressures were a few centimetres of water higher than his consistently. And we'd also looked at the effects of skin temperature on capillary pressure and shown that there was a more or less linear relationship, as the skin warmed up the capillary pressure went up with skin temperature. And we suggested in the paper that perhaps it was because laboratories were warmer in the 1970s than they had been in the 1920s and 30s. But there was something else: Landis' paper was published in 1930 and I suspected he'd done the work in the winter in '29-'30 and my father had told me he was in college that winter and it was a terribly cold winter, and he [my father] used to have a basin in his bedroom to wash and shave from and it would freeze overnight.

RL: Gosh [laughs].

CM: And [laughs] remembering what my father had told me about the winter of 1929, I wrote to Landis and asked him about it, and he wrote back and I think we can read out what he said, because I brought a copy. "You're quite right in thinking that my 1929/30 measurements were made at colder temperatures. I did all of that study in November/December/January after teatime when Sir Thomas Lewis ended our collaborative day in his lab, and at night after dinner. During that winter, as an economy measure I suppose, all lab heating was turned off at or before teatime. By evening my subjects told to be extremely quiet, often had to have blankets to keep them from shivering and moving their fingers.

RL: It's amazing that [most] textbooks drawing of fluid exchange are based on – [over talk 1:21:43]

CM: - on cold skin. [laughter] Yes, but Landis and I corresponded, you know, I'd send him reprints and that sort of thing, but after this initial correspondence where there was a real conflict between his work and ours, (we corresponded once or twice a year) he was very reasonable and very supportive.

RL: I need to just…

[brief interval]

…

RL: Can we sort of change direction just slightly?

CM: Yes, of course.

RL: And can I ask you about your involvement with the Physiological Society and also the British Microcirculation Society? Tell us about that aspect of your career.

CM: Well, I mean Phys Soc was very much a big thing from the word go. That is, it was the forum for presentation of your research. And it was rather an exclusive sort of society at the time I first attended it as a research student.

RL: Exclusive or distinguished? I mean, what do you mean by exclusive?

CM: Well, exclusive. I mean to be a member you had to be somebody [laughs], very much so, you know, you were put up for membership and you could be black-balled and it was rather like a gentlemen's club in some ways.

RL: Yes, that's true, yes.

CM: ***{{Video clip of this comment BEGINS}}*** In fact, if you held a permanent academic post in physiology then you were elected, I don't think there was ever any problem there. If, on the other hand, you held an academic post which wasn't in physiology there would still be discussion about whether you would be elected or not. I regard the Physiological Society, certainly in the sixties, when I really came to know it first, as an absolutely splendid organisation and once you were attending the meetings you were accepted. Again, GL Brown was tremendous at engaging with young attendees. When I was a research student, at a meeting at University College, I remember he was there with a crowd of people around him and he saw me in the distance hovering on the edge of the group and he waved me over and said, "Now then, Charles, Alan," speaking to Alan Hodgkin, "you know Charles Michel, don't you?" [laughter] ***{{Video clip of this comment ENDS}}*** Of course Hodgkin had no idea of who this research student was. [laughter] That was a wonderful sort of way of dealing with things. I also remember a marvellous occasion after I'd just become a member. I took Simon Miller who had given me his design for a microelectrode puller. And we went to the dinner and we'd been talking to various people and we were among the last to arrive at the tables so of course we couldn't sit together, nearly all the seats were taken up, there was one gap and it was next to Henry Barcroft [1904-1998], and there was another one on the other side, and I sat next to Henry. And he turned to me and said, "I know you, don't I? Weren't you in Oxford with Cunningham [Dan Cunningham 1920-1996]?" So I said, "Yes" and we talked and I was actually very pleased to sit next to him because I'd just finished doing clinical medicine and I'd been very puzzled by the mechanism of ischaemic pain. I just couldn't understand what the mechanism was, nor do I understand it now actually. And so I asked him about it and we had an extremely good discussion and then he turned to the chap on the other side of him and said, "You know, what do you do?" And he was a very brash American, I think he was rather famous actually, subsequently, I think he was working as a post-doc with Andrew Huxley at the time and…

DM: Yes, perhaps it was [Lincoln] Ford, yes.

CM: And he said, after he'd finished he turned to Henry and said, "What do you do, then?". [laughter] And Henry, Henry just said, "Well, you know, I'm very interested in blood flow in muscle and particular at the moment I'm concerned at the way in which the different adrenergic systems operate on the peripheral blood vessels." And he explained it beautifully to him and it was, and there was that lovely sort of atmosphere which existed between the old and the young.

And of course, in contrast to this extremely friendly atmosphere, there were incredibly fierce debates at meetings, as you know.

DM: After presentations and abstracts.

RL: Voting on the acceptance of the abstract for publication. Yes.

CM: Yes. So, when, in 1974, I was asked if I might be put up for the Committee, I agreed and so I went on the Committee of The Society until 1978, and then, much to my surprise at the end

of ’79, Denis Noble came around, (he’d become Meetings’ Secretary the same time I’d gone on the Committee) he was the Committee Secretary then. He came round and said, ‘We’d like to propose you as the next Meetings' Secretary. Would you agree to be proposed?’ So, well I was a bit overcome with the idea at first, and also I knew how much time it would involve and I didn’t think I would be very good at it, but I enjoyed it immensely.

DM: That was still on the old system … you ran everything from your office with a temporary PA, basically.

CM: That’s right. In fact, essentially The Society was run by three people, the Treasurer and the two Secretaries.

RL: Yes.

DM: Who was Treasurer at the time you were…?

CM: Ron Linden [1920-2010]. He succeeded Robert Comline [Robert Semple Comline, 1919–1998]

DM: Yes.

CM: So Ron was Treasurer and Tim Biscoe, who had been the Meetings' Secretary became the Committee Secretary. And we talked a lot about the commitment and the way in which things were changing in the university system, and I said I thought six years was too long. I enjoyed being the Meetings' Secretary, particularly as one saw the whole of physiology as Meeting Secretary, I enjoyed that very much. I’ve always believed physiology, different areas of physiology, can stimulate each other.

RL: Which isn’t the case so much these days because the meetings are all specialised.

CM: Yes, that’s the way it is, yes. I wasn’t terribly keen on being the committee secretary and sort of wielding power and manipulating committees and that sort of thing.

RL: But you did then go on and become a member of an International Physiological Society Committee, didn’t you?

CM: When we had the Glasgow IUPS Congress, I was asked to be the chairman of the Programme Committee, so that was another four to five years, and that was again, more or less dealing with the science changing.

RL: I seem to remember you telling me a story about how you had to go to Russia once and the state of the roads. In what capacity was that?

CM: That was actually very interesting. It was of course all about the time of glasnost, you see. Russia was still the Soviet Union and we wanted to be able to see if we could do a deal with them, that’s it, with the Russians or the Soviets as they were then, because the 1993 congress was in Glasgow and the 1997 congress was scheduled for Moscow. St Petersburg, it became, yes. St Petersburg. And so three of us (Julian Jack, Ian McGrath and myself) went over to talk to the Russian physiologists about this idea (of subsidizing the attendance of Soviet physiologists in Glasgow for a reciprocal arrangement in St Petersburg) and it was very interesting. [laughter] A very interesting trip. Yes, the roads were appalling.

RL: But you weren't just important in the Phys Soc committee, you were also very important in the British Microcirculation Society.

CM: [laughs]

RL: Tell us about your role in the BMS.

CM: Well, I joined the BMS soon after I became a member of the Physiological Society largely through Terence Ryan -

RL: - a dermatologist -

CM: - a dermatologist, who had taught me, he was a senior registrar in dermatology when I was a clinical student and he was interested in the microcirculation and he had told me about this, about the microcirculation society. And so I went on to a meeting. There was a mixture of people there, the first meeting I went to, of engineers and clinicians, mainly, I say mainly dermatologists, there seemed a lot of dermatologists in the society. And obviously they were speaking two languages but I felt I could see the relevance of what the engineers were saying and the clinicians actually, said, quite a lot of interesting things there but their analysis of what was going on seemed not terribly scientific, should we say? I went to one or two more of these meetings and finally I just gave up because the number of engineers attending dwindled to zero and the clinicians gave anecdotal papers. And then there was a revival by a series of people we know, including Laurence.

RL: Lawrence Youlten?

CM: Laurence Smaje and Lawrence Youlten.

RL: Lawrence Youlten, yes.

CM: And they organised, or Laurence Youlten organised, the meeting which I went to and supported. And then a chap whose name I've forgotten at the ARC Institute, it used to be the Arthritis & Rheumatism Council [now Arthritis Research Campaign] Institute, somewhere in the Charing Cross area.

RL: There was, yes, the Kennedy Institute.

CM: The Kennedy Institute, that's right, yes.

RL: I'm not sure who would be at…

CM: There was one that was organised there.

RL: Right.

CM: And then we started going regularly and presenting things at that meeting. Previously there had been a meeting in Oxford which was run by the plastic surgeon, Patterson, and Terence Ryan and that actually was quite…. You and I did a demonstration of cannulating capillaries.

RL: Yes, yes, we had the frog dying just as the first person came through the door. [laughter]

CM: Well, certainly it was…

RL: But it was a very small society when you first joined. A tiny society.

CM: It was a very small society.

RL: **Now it's got a membership of, I'm not sure, well over 200, I think.**

CM: I think more than that now.

RL: **Probably a lot more, yes**

CM: Well…

RL: **And you became President…**

CM: Yes.

RL: **…did you not?]**

CM: But I think the growth of The Society was largely due to, Yes, now I can say the indiscreet things [laughs] One of the things that I objected to about the society, it was run by a Cambridge anatomist called Munro [Peter Alexander George Monro, 1919-2005] who was a sort of control freak and I think he wanted to run everything in the society and control it, it seems.

RL: **[laughs]**

CM: And Laurence Smaje sacrificed himself by going onto the committee of the society and proposing that Munro, who had been the Permanent Secretary of the society should actually become the President. And he [Laurence Smaje] volunteered to become the Secretary and I think that was the great thing because there was a shift in the….

RL: **The whole emphasis and focus of the society. Yes, it became much more scientific.**

CM: It became much more scientific.

RL: **Yes.**

CM: And, well, he hosted a meeting I remember quite well and you hosted a meeting at St George's once.

RL: **Charles, time is flying and we still haven't got onto really hard science. We've touched on some hard science but your life's work has barely been touched on so far.**

CM: Oh, well, that's alright [laughter]

RL: **I mean, just to put it in focus, I've always said that the ability of molecules to permeate through the capillary wall is a fundamental necessity of life in all vertebrates. It's a very important topic. So what do you see as your main contribution, or your lab's main contribution if you're too modest to acknowledge it as being yours, in this area?**

CM: Well, I'd like to think the working of single capillaries was an important step and though a lot of people still regard measurements on single capillaries as being dubious.

RL: **Do they?**

CM: Oh, I read something where it suggested that experiments on single capillaries, one couldn't really be sure that one wasn't damaging the tissue.

RL: **As opposed to growing cells in culture? [laughs]**

CM: Whereas in fact you and I showed, right at the beginning, and this was a crucial thing, that the permeability to macromolecules is as good as if you hadn't cannulated and perfused the capillary, provided it's done carefully. But obviously if you're sloppy with your preparation you do get an inflamed microcirculation. So I think making quantitative measurements of permeability on the single vessels was a contribution. Then the very small things, our experiments on measuring human capillary pressures was a significant contribution. Returning to the single capillary story though, I think the general approach that our group had of combining quantitative measurements of permeability with ultrastructure was something which I dreamed of and which happened actually relatively quickly. And so we were able to do it over a large number - over 30 years. That was quite good. But perhaps the thing that recently appears to be most successful and one that you've drawn attention to very much is the development of ideas of fluid exchange, the extension of the Starling Principle which really arose because we used measurements of fluid exchange as a basic technique for investigating permeability. And in the 1970s, when we got the red cell technique running very smoothly indeed, so that one could make lots and lots of measurements on different capillaries quite repeatedly, then it became obvious there were certain things which didn't fit the classical picture – for example - something that you later explored in *Joints,* namely that if you put macromolecules on the outside of capillaries they had less of an effect than if you had macromolecules of the inside of the capillary wall. And I had to give a lecture, around about 1976 (it would be, because you were still in the lab at that time) you were doing your, finishing off your…

RL: It was the year we got married, yes, so I was just finishing off.

CM: Not you and I got married. [laughter]

RL: No.

DM: No, just to make that clear.

RL: 'We' being Angie and myself.

CM: I had to give a lecture on Starling [Ernest Henry Starling, 1866-1927], I say I had to, I'd agreed to give a lecture, to some cardiologists in the European Cardiology meeting . I was asked, 'Could I give a lecture on Starling's hypothesis?' I know I sort of…I had two tutorials in college one evening and they were both cancelled and I had two hours. I sat down and started thinking about it. I knew about all these odd things we'd noticed and I suddenly realised it was just moving towards a steady state position where the colloid osmotic pressure in the interstitial fluid immediately surrounding the capillary was determined by the filtration rate and so I did a rough analysis, graphical analysis essentially–very similar to the one you did in your review in 1991–just drawing curves for the washout of the peri-capillary space by different levels of filtration and looked at the consequences of that and discovered that there was quite a different sort of relationship, between filtration rate and pressure. And the absorption couldn't occur in a steady state, undermining the classical Starling view. And I sort of stewed over that afterwards. I actually wrote it up, a private sort of little paper, but I didn't do anything with it and almost immediately afterwards, that is within a year, Gene Renkin asked me if I'd be prepared to edit the *American Handbook of Physiology* volume on microcirculation with him, and he said, 'Okay, which chapter do you want to write?' And I saw an opportunity to write this out there and to analyse data using this steady state analysis. And it, of course, eventually appeared, in 1984 that volume. And

for that I thought I had to produce a proper algebraic statement, which I did, for that review.

RL: Yes.

CM: Gene Renkin included it in his review, in his Wiggers lecture the following year but he had a cartoon of the evolution of Starling's hypothesis.

RL: Dinosaurs.

CM: Which he had nice, simple, Starling equations followed up by this expression of mine....

RL: It started with *Amoeba* didn't it?

CM: It started off with Amoeba, went on to frog, then it had these…

RL: Dinosaurs.

CM: Tremendous dinosaurs, which had lined up against my equation [laughter], which I thought was one way to put people off. [laughter]

RL: But in the 1980s you took this one stage further, Charles. You've not mentioned fibre matrix yet. That was a further layer of biological importance as well as complexity, isn't it?

CM: Yes, well I mean the pore model was the model everyone used–and I still use it. It's extremely useful. But in terms of reality, this combination of electron microscopy and quantitative measurements, there were no pores of the size that you needed to predict the correct permeability coefficients. On the other hand there was this fuzzy stuff on the inner surface of the capillary. And right from the beginning I'd backed this as probably the molecular sieve. And then, in the late 70s, I collaborated with Sandy Ogston [Alexander George (Sandy) Ogston, 1911–1996], who had now come back to Oxford as President of Trinity College. We wrote a paper on irreversible thermodynamics, which is…one or two people have read but I think that's probably all [laughs]. I did see it…

RL: I confess I did try to read it once. I gave up after a while. [laughs]

CM: I did see it referred to actually relatively recently, I was quite chuffed about that.

RL: Oh right.

CM: But he of course was the expert on diffusion through gels, so I talked to him about it then. And he was very helpful and I read some of his papers and it was there that I came across the Kozeny equation [Kozeny-Carman Equation named after Josef Kozeny (1889–1967) and Philip C. Carman], and that was really the lead into the fibre matrix hypothesis. I suggested it qualitatively the one year and the next year I went over and I discovered [Fitz-]Roy Curry had been thinking about it also. And as a well-trained chemical engineer in his first academic appearance, he knew because he knew the Kozeny equation, Carman-Kozeny function, and he'd used it. So we then talked about it at the 1979 conferences we went to, and I wrote, drafted, the paper as soon as I got back from Canada and sent it to him, and it got published the following summer.

RL: Along with Roy Curry and others, you've always adopted this very rigorous mathematical approach to physiology, haven't you?

CM: [laughs]

RL: Do you think this is a sort of, this quantitative approach to science, often with writing down your quantitative approach as an equation using theory, do you think that should be more generally applicable in physiology? Do you think we're still birdwatchers too much in physiology?

CM: Well, I don't know that people are bird watchers…

RL: In some fields?

CM: Well, I mean I'm now in retirement.

RL: You *are* a bird watcher. [laughter] [Charles studies the puffin population on Alderney, his retirement home. And of course he has developed a few equations to describe puffin population dynamics!]

CM: I'm in a Department of Bioengineering. And I feel the bioengineers have taken over where, sadly, in many areas of physiology, the quantitative aspects seem have been abandoned and the bioengineers are taking over. But I mean biology has got a lot of what is real science still going for it. It's not all qualitative, by any means, but it lacks that appeal which I think it had for me. And I think I would have been attracted by bioengineering if I'd been a schoolboy now.

RL: A lot of research now is along the lines, 'Oh, protein kinase A affects molecule B which affects molecule C.' Do you think we should be moving into a phase where you write an equation for the rates of the reaction and try and tie the whole thing up in a more quantitative way ?

CM: I think if you've going to understand dynamics, you've got to. Yes, you had to write out the rate constants, but it is very complicated and I think one of the great things of course in the last 20 years, has been the development of computing. I say 20 years, really it's 20 years where computing has gone, developed so rapidly, that now there's, I won't say anyone can solve any equation numerically but you can solve equations numerically in a way which has never been possible before.

DM: I was, for example, modelling calcium movements in muscle. The way I was doing it, using the diffusion equation, you know at a level that say A V Hill would have dreamed of.

CM: Yes.

DM: We used to be able to integrate over the whole fibre for any period of time and the curves would come out. But one thing this quantitative approach struck me with, something you've raised a couple of times in what you've said, Charles, is that without this kind of rigorous modelling you don't know what's going to emerge. It's the predictive power, isn't it? You find things that you imagine are going to be vaguely linear and when you really set to, you find they're not. And there is then a property that emerges. That's my experience, and clearly yours, from the equations and the curves generated. And the last thing is you find an experimental angle that means if this is so then the *difference* can be tested. And that's the beauty of it, that the description–if the description's adequate–then you can reveal it.

CM: Yes. I think I can say two things very briefly. One is a quotation from Rutherford, not Rutherford, Lord Kelvin.

DM: Yes. RE: stamp collecting?

CM: No, that was Rutherford.

DM: That *was* Rutherford. [laughter]

CM: Kelvin said, 'If you know something about something and you can measure it and express it in numbers, you know something about it. If you know something, but can't measure it and can't express it in numbers, you have a knowledge of a certain kind.' I can't remember the wording exactly, but he said, 'You can't–you can hardly call this science.'.

RL: Yes.

CM: You can hardly reach a stage of calling it science.

RL: For the transcript we have got that quotation.

DM: We'll find it, yes. [**"**When you can measure what you are speaking about, and express it in numbers, you know something about it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science.**"** *Lecture on 'Electrical Units of Measurement'* (3 May 1883), published in *Popular Lectures* Vol. I, p. 73**]**

CM: The other thing, what was I going to say? Oh yes, I find writing an equation clears my thoughts. I know what the assumptions are, I know I can follow the errors in reasoning, which, as I solved the equation incorrectly, when I look back at it I can see those errors. [laughs] Whereas if I write something down in prose, there's always a level of argument about it that I find I'm uneasy about.

RL: I can testify to the fact that that's the way you work, Charles, because when I've written down an equation and sent it to you, you've immediately said, "Oh, I see that at the beginning here you're making the implicit assumption that…" [laughter]

CM: Well, I'm not a mathematician, I'm afraid, but I'd like to have been a mathematician, I suppose, retrospectively but I never knew it at the time.

RL: We're running out of time, Charles, and there's a speculative final question I want to ask you, which is: what do you think are the challenges to up and coming capillary scientists? How do you think things might develop in the years to come? What's going to be important?

CM: Well, I don't know, is the simple answer. I imagine that people will begin to understand the detailed mechanisms of inflammation which is one of the big, big topics. And also probably the ways in which the endothelial cell plays and important role in the development of organs and tissues. But these are all areas I have intuitions about but no real knowledge.

RL: No, it's a speculative question but…

CM: An area which I feel sadly is lacking at the moment–and it's linked to the quantitative approach–and that is that I became interested, and started working on, microvascular exchange because I thought it was important in so many different departments of

physiology, to so many different areas of physiology. And I still believe that quite strongly. And I would like to see it taking on a more important role in endocrinology for example. It has a considerable role in renal physiology, gastrointestinal physiology. Ten years ago, I published a paper with Pappenheimer [John Richard Pappenheimer, 1915-2007) on glucose absorption where we made use of this linking between an epithelial secretion and endothelial exchange coupling. And I think, the microcirculation which I'm interested in is present in all mammalian tissues and it has a role there which needs to be understood and integrated in understanding the dynamics of metabolism and the other functions of these tissues.

RL: **Hm. That's probably a good place to stop…**

CM: Okay.

RL: **But just quickly, we don't have to transcribe every moment, I thought you might have said, 'Oh well I think the fibre matrix concept might prove to be very important in the regulation of capillary permeability.'**

CM: Well, I think it is [laughter]. It's become very fashionable. I don't think many people use our theory or elements of it, that is the mathematical theory, but the sort of rather loose, woolly concept, the fuzzy layer concept.

RL: **But there's all kinds of directions it could go in, aren't there? I mean, what regulates its secretion and properties, and can they be manipulated, and would this affect capillary permeability in a beneficial way? I mean there's all kinds of possibilities in the future.**

CM: Well, I mean I thought that in inflammation you would see changes in the glycocalyx and the early experiments, which Geraldine Clough and Mary Philips and I did, much to our astonishment, we found there was apparently a great increase in the fuzzy layer. And of course it's now recognised that the glycocalyx is shed during inflammation. It's a major sort of thing.

RL: **Yes.**

CM: Well, people don't look at *Journal of Physiology* 1978 but there are the first pictures.

RL: **I know the pictures you mean.**

CM: Shedding. I was very disturbed by that and I thought, 'Well, it must involve thinning of the matrix.' I mean I would like to see the architecture, the molecular architecture, of the matrix worked out and of course I've been working on that with John Squire really ever since I retired.

RL: **Yes. I remember a British Microcirculation Society meeting where a chap got up and he gave a long talk, which was all about thixotropy and how the fibre matrix theory couldn't possibly be right because of thixotropy. And it was [laughs], it was terrible science, really. He got a lot of flak from various members of the audience and then in the end Charles, I think, was invited to say something. Charles got up and this is the most damning comment I've ever heard Charles make [laughter]. He said, 'Well, I have no special regard for the fibre matrix theory but I do have a special regard for the scientific method.'**

DM: **Ooh…. Nobody comes back from that. [laughter]**

RL: **It's the most aggressive thing I've ever heard you say, Charles, at any meeting. [laughs]**

CM: I have been rude to people at meetings.

RL: **Well, no… [laughter] I mean the guy had been talking nonsense for about 20 minutes.**

CM: Well, when I was secretary to the Phys Soc I remember Ron Linden coming to me and saying to me, 'You know Charles, I always thought you were a nice chap until I heard you interrogating that poor chap from Cardiff.' [laughter] Oh dear.

RL: **Well, I think you were, always have been, a nice chap, Charles [laughter]**

CM: You daren't say anything else!

RL: **No, no, I think the science always takes precedence with you.**

CM: Yes, I think it does. I mean I don't think I hesitate to tell people that they're wrong. I try and do it as politely as possible.

RL: **Exactly.**

CM: Yes, and I think actually a person who could be very aggressive and very unpleasant but who could be, or seemingly, unpleasant but had no intention of being so, was Andrew Huxley.

DM: **Yes. [laughter]**

RL: **He attacked us when we gave our first paper on capillary permeability, yes.**

CM: He attacked you and I was actually rather cross because he didn't let me intervene. I remember he referred to the Langmuir isotherm.

RL: **He did, yes.**

CM: And you…

RL: **As a junior research student I'd never heard of the Langmuir isotherm , so it was difficult to respond.**

CM: Well, fortunately I had heard of it, I had heard of it and I knew what he was talking about and it was somewhat…it's a very similar relationship to the binding of T1824 [Evans Blue] to albumin. But it was different, it was a different sort of relationship. And also his analysis of it was incorrect in this particular context.

RL: **He simply hadn't appreciated that the binding co-efficient was very, very high. The affinity coefficient was very, very high. So … he was looking for a curve, wasn't he?**

CM: Andrew Huxley showed his worth to me, because afterwards he came out and we discussed it and at the next meeting he came up to me and I was giving a demonstration, I think you were away on holiday, you usually were in the summer [laughter]

RL: **…Off climbing**

CM: And he came up to me and said, "Well, I was very silly about that, sorry I…" and he was very, very supportive actually afterwards.

RL: **That was little consolation. I refused to give any more Phys Soc communications for years. [laughter]**

DM: **A proper baptism of fire… Okay well, shall we finish the official record and—officially—thanks very much, Charles. It's gone fantastically well. And to you too Rod for steering us along. It's been really good.**

Charles Michel (right) and Rod Levick (left), February 2015 (photo by David Miller)

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