An interview with David Colquhoun

Conducted by Jonathan Ashmore
on 3 and 17 June 2014

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The Physiological Society

David Colquhoun photographed by Jonathan Ashmore, June 2014.

This interview with David Colquhoun (DC) was conducted by Jonathan Ashmore (JA) at University College London on 3 and 17 June 2014. (The transcript has been edited by David Miller.)

Student life

JA: I'm sitting surrounded by multiple files from David, computer screens and all sorts of interesting papers. David, I think the most useful thing is if we proceeded chronologically, so what I'd like to know first of all is how you got interested in science in the first place.

DC: I wasn't very interested in science at school; it was … a direct grant school but it tried to ape more expensive schools. The only thing that really mattered was sport there [laughs], and I did a bit of that but I just simply didn't take any interest at all in any academic subject. The pinnacle of my academic achievement was to fail O-Level geography three consecutive times, getting lower marks at each attempt. I was quite proud of that. No one had ever done it. So I left after the third attempt and went to Liverpool Technical College, as it was then called, probably university by now, and did my A-Levels there. And that was okay because you could concentrate on what you were doing while you spent every lunchtime in the billiards hall opposite. There was a particularly nice botanist; he took us to see his gardens in Ness. I never was interested in botany and still am not, but he was an interesting bloke. And I did well enough in A-Levels to get into Leeds University and then I suddenly got interested [laughs].

JA: What did you study at Leeds?

DC: They had a four year pharmacy degree. My father, who was a teacher, taught Harold Wilson [the former Prime Minister James Harold Wilson, 1916–1995]

and Steve Jones, among others. I think he was trying to steer me to something with which I could earn a living but pharmacy seemed the maximum intellectual thing I could cope with at the time. I did apply for medicine too; in fact I got offered a place, only one place, which was in Bristol oddly enough, which even then was fairly selective. But I decided not to do it. I thought that was a mistake but I think it probably wasn't actually. I would have hated clinical medicine; too much uncertainty, not enough maths.

JA: Do you remember thinking it was a mistake at the time?

DC: I thought it periodically afterwards, yes. But once I got into research then I was quite glad I hadn't done it because in Leeds we had, we got quite a bit of statistics one way and another and I got very interested in that.

JA: So how did you move into research from a pharmacy degree?

DC: Well, the fourth year was specialised in pharmacology. In fact there were 15 of us in the first three years and three in the final year. How things have changed. And there was no teaching at all actually in the final year; it was a bit of a rip-off except that I discovered in the library, quite by accident, papers by a chap called Katz [Sir Bernard Katz, 1911–2003]. And I thought, 'These are interesting'. I had no idea how famous he already was of course. As an undergraduate, our external examiner was Walter Perry [Walter Laing MacDonald Perry, Baron Perry of Walton 1921–2003], who founded the Open University shortly afterwards when they didn't give him the vice-chancellorship in Edinburgh, and he made a terrific job of that, of course; really wonderful. He was one of my supervisors. I hardly ever saw him except when he came into the lab between committee meetings for a cigarette: another thing that's changed. He had quite a bad stroke shortly afterwards but recovered from it entirely […].

JA: He of course was one of the people that G. L. Brown brought into the National Institute for Medical Research.

DC: Yes, he'd been director of biological standards. He had a terrible time there because of this faulty batch of polio vaccine occurred on his watch. But that had made him interested in statistics. In the oral exam in the end of the third year (he was our External Examiner) he asked me, 'What's the difference between confidence limits and fiducial limits?' which I thought was a fairly stiff question [laughs]. Of course nobody really knew; statisticians had been arguing about it then and ever since. But that set me off onto a quest to find out, so I spent a lot of my fourth year actually working on that, with advice from a chap called Welch who was famous for introducing the version of the *t*-test which works when variances are unequal. He'd given us our first year course in statistics. He had a very large blackboard, and he'd come in, stand with his back to the students writing on the blackboard in chalk and saying at the same time what he was writing. So he spoke very slowly as a consequence. Also the whole lecture was laid out. He would have failed any teaching test in history but I found this work wonderfully interesting so I actually wrote a paper from the *University of Leeds Medical Journal*, my very first paper, on statistical

inference, though of course I failed to sort out Perry's exceedingly subtle question. [Some of this history has appeared on my blog.] Oddly enough [55 years later] I've just written a paper just recently about the interpretation of *P*-values which is sort of 'first and last papers' on the same topic.

This was 1956–1960; that's when I was in Leeds. And I was two years older than average because I'd done an apprenticeship in a pharmacy in Grange Road, Birkenhead, homeopathic pharmacy, about the most humble start you can imagine.

JA: Would you say that again? Homeopathic pharmacy?

DC: Yes, Timothy Whites and Taylor's Homeopathic Chemists. We thought at the time that the Boots opposite was rather ethical because they didn't do homeopathy but in two years we had one single prescription for a homeopathic preparation which we made up with much laughing and not according to the rules though the old lady seemed quite happy about it. The subject was dead then. The resurgence of fantasy medicine only came in in the late 60s.

JA: So it was not a profitable line?

DC: No, it wasn't. They went out of business of course, actually [laughs].

JA: So once you got your pharmacy degree, how then did you decide to move onto further research?

DC: Walter Perry was also our external in the fourth year and in the meantime I had written this thing which I suppose must have impressed him a bit. I'd also started getting into matrix algebra and I'd bought Aitken's little book on 'Determinants and Matrices'. I couldn't get much help with that from the department but I recall asking an Argentinian PhD student, I can remember his name, Leo Becka (who was in the hall of residence where I was), what the difference was between a determinant and a matrix because I was in a bit of a fog when I picked up this book. He said, 'A determinant is a number and a matrix is a table.' And after that I just sailed through it. it was as simple as that. And I've been interested ever since. I actually went into the final fourth year exam viva with this book, with this book sticking out of my pocket; a shameless bit of one-upmanship [laughs], and I heard later from Bernard Ginsborg who was in the Edinburgh department (a wonderful bloke and a huge influence) that Walter Perry had come back and said, 'I've just been examining a bloke who likes determinants and matrices…' [laughs]. And so he offered me a PhD job which I immediately took, of course.

JA: Did any of your contemporaries also move into research, or into pharmacological areas?

DC: Two of them did. Both of the people I did in the third year, a lady called Stella Gregory, later Stella O'Donnell, who went to Australia [University of Queensland] and worked in a pharmacology department there. And there was Ed Abs, who was a very large Yorkshireman from the poorer bit of Leeds, I

think; a very jolly bloke. He chain smoked cigarettes; he died in his 40s unfortunately. I was the best man at his wedding and he went to Portsmouth Polytechnic straight as a senior lecturer after his PhD actually. He was earning far more than me initially.

PhD project

JA: So you've now got your Bachelor's degree and you move into the area of being a PhD student. How did that move on from there?

DC: It was okay. I picked the wrong supervisor, or I didn't pick him, he picked me really because he was interested in immunology and I was trying to do ligand binding experiments with antibodies, which is not quite my thing really but it went reasonably well. We did discover two different forms of guinea pig gamma globulins, one of which produced passive sensitization and one of which didn't. They were discovered more or less simultaneously by a chap called Benacerraf [Baruj Benacerraf, 1920–2011] who was a terribly famous immunologist so we never got much credit for that. It seemed like the perfect control but we couldn't detect any difference in their binding when radio labelled, so it was a bit of a flop really. There was just too much non-specific binding and also the equilibration was too slow; the tissue died before it had equilibrated. So it didn't produce any very startling results having been scooped on the gamma globulins and the binding stuff having failed. While I was there I recall going to a Pharmacological Society meeting. There was a talk given by Bill Paton [Sir William Drummond Macdonald Paton, 1917–1993] who was then Professor of Pharmacology in Oxford about the binding of atropine to smooth muscle. He said, 'I shouldn't really be giving this talk, the work was actually done by a chap called Humphrey Rang, but he's busy sailing the North Sea in a small boat, so I'm giving the talk.' I subsequently shared a boat with Humphrey. But that was the first ligand binding experiment, done far better than many of the subsequent ones. The real classic paper, not terribly widely known, and it was wonderful stuff, I thought. So he'd succeeded with atropine where I'd failed with gamma globulins.

JA: But in Leeds you weren't using radioactive binding…?

DC: No, this was in Edinburgh; the PhD was in Edinburgh. I was using the proteins labelled with radioiodine, doing Ouchterlony plates, and immunoelectro-phoresis and things.

JA: So your PhD more or less ran its course…?

DC: Yes, well Walter Perry was wonderful because he made me an honorary lecturer, and he got me a Scottish Hospitals Endowment Research Trust Fellowship which paid twice as much as the regular PhD thing, about £1,400 compared with about £700 I think, at the time, which was very good. Best of all it allowed me to join the staff club in Edinburgh, which at that time was a wonderful institution; it's since been abolished in one of these managerial putsches to stop people talking to each other too much. And there I used to have a wonderful time. I was in the New Left Club and I met a chap called Peter

Higgs who seemed very vague but very nice. It was exactly at the time of course he was writing his famous 1964 papers, so no wonder he seemed a bit distracted.

JA: What about the other people, the artificial intelligence people? Did you come across them?

DC: Yes, I met Donald Michie [1923–2007] and some of the other people involved.

JA: Richard Gregory [1920–2010] and Christopher Longet-Higgins [1923–2004] and people like that?

DC: I didn't actually know them, no but I met John Maynard Smith [1920–2004] when I was there. That was also interesting. By joining the staff club I met a lot of people who otherwise would have been names to me; that's why I feel so strongly about having good facilities for people to talk to each other.

JA: So when you'd finished with Edinburgh was the choice then clear what you wanted to do beyond that?

DC: Well, I knew I wanted to stay in research and I gathered from reading, perhaps it was a hangover from reading Bernard Katz in the fourth year undergraduate, that UCL was a good place. Heinz Schild [1906–1984] was head of [the pharmacology] department. At that time many of the senior people in physiology and pharmacology had strong German accents. They had been refugees before the war. And he [Schild] had written, while interred during the war, a paper on the statistics of biological assay, which I had read and was impressed by. I thought UCL sounded like a good place to go and so I went to a meeting, I guess it was a Pharm Soc meeting, or possibly The Physiological Society, and said, 'Can someone point out Schild to me?' So they did and I marched up to him and said, 'You know, I'd really like a job in your department. Is that possible?' [laughs] And he said, 'Probably, yes.' He must have checked with somebody and the next thing I knew I had an assistant lectureship. So I came here in 1964 in September; in another couple of months it will be 50 years since I first walked in the door. Whatever happened to all that time, I wonder? [laughter] And it was a wonderful time. I picked a completely silly project, unfortunately. I thought I would try to test functionally the antagonism of one immunoglobulin with another one and made the mistake of carrying on with what I'd done in my PhD. I wanted to apply the Schild equation for competitive antagonism to immunoglobulins. I struggled with this for four years; the equilibration was so slow it was essentially impossible to do, I think.

JA: Did you get any guidance from Schild?

DC: Um… he was pretty hands off. I can't recall, I must have talked to him about it and he thought that was a good thing to do but there was no advice. He wasn't actually that into the mathematics. The Schild equation was a brilliant thing, by far his biggest contribution I think, but no, I was left to struggle pretty much. What I did in that time when I wasn't doing experiments was to write a text book on statistics because I got so interested in it … and it turned out to be

enormously valuable to me once the single channels came along to have got that background. It was just luck really, the sort of thing that couldn't happen now because you'd be under such pressure to publish you would never have time to sit down and think about statistics for a few years and write a book.

JA: Did you have to teach that, or tutor statistics in any way to enhance the way in which the book was written?

DC: Well, I taught it to pharmacology students; Schild insisted that they all know how to analyse a 2 plus 2 dose biological assay. That's quite likely why I got the job in fact in the first place. But I also of course liked to talk to the statisticians here. At that time the statisticians were in the building in front of the college, the Pearson building, and that's close to the Common Room, the Housman room, so they were in there every day and I would often talk to them. Dennis Lindley [1923–2013] the famous Bayesian was head of department [he succeeded George Barnard (1915–2002) in 1967]. I don't think he really noticed me of course because he didn't really approve of my views anyway [laughs] but it was enormously valuable. Oddly enough we had started to think about single molecules in the late 60s here. I had spotted what seemed to me a paradox about competitive antagonists. I won't go into it in detail now but I had read in a book on colloid chemistry … that if you look at the exponential dissociation of a ligand from a receptor when you remove the molecule from free solution, you expect the stuff which is bound to decline exponentially. That was actually shown by A. V. Hill [Archibald Vivian Hill, 1886–1977] in 1909, another UCL hero of mine. It was shown by Langmuir [Irving Langmuir, 1881–1957] nine years later but it was first shown by A. V. Hill [laughs]. I had read in this book that the time constant for this decay is the same as the mean lifetime of the drug receptor complex and that was the first time I had come across thinking in terms of single molecules. But it occurred to me that this was an odd result because if you look at the decay from the time you wash the free ligand out of solution, I could see that's a measure of the time that the molecule stays on after zero time. But of course it's also been on before zero time. So I thought this ought not to measure of the mean lifetime, it ought to measure something less than the mean lifetime. Donald Jenkinson, one of Katz's PhD students who was in the department for most of the time I was here, I can recall arguing about this on the corridor with him, standing on the steps outside this office, arguing what the hell was going on and he couldn't understand it either. So I asked the statisticians in the Housman Room and they said, 'Oh, that's the chap you need' and pointed me to a chap whose name was Alan Hawkes who had done a PhD on the stochastic nature of traffic flow. And he told me, 'Ah, yes, that's the waiting time problem; you'll find it in Vol. 2 of Feller's book on Applied Probability.' And there it all was. [I thought it was beautiful and gave a talk about it in 1969 – I got so excited that I broke the long wooden pointer.]

JA: Is that when you met Hawkes for the first time?

DC: That's when I met Hawkes for the first time, yes, in the late 60s. This was all entirely theoretical at the time. But then in 1970 Bernard Katz introduced

noise analysis, which really, of course, intrigued me. That was the first thing that allowed you to estimate the conductance of a single channel. You couldn't see the single channel, it was too noisy, but from the fluctuation and the frequency characteristics of the fluctuations you could estimate the conductance of a single channel. And that's the first time that that had ever been done.

JA: It had been done in squid photo receptors by Bill Hagins in the mid-1960s. Is that where Katz got the idea from?

DC: That I don't know. There had also been single channels recorded in gramicidin in bilayers, the first exponential distribution I ever saw. Oh actually the first one was in one of [the] Fatt [Paul Fatt, 1924–2014] and Katz papers, on time intervals between miniature synaptic currents. The first one from a single molecule was the gramicidin one. But it was Bernard Katz who introduced it for ligand gated receptors; exploited it very effectively.

Early career as a lecturer

JA: So we are here now in 1968, 1970 and you have a job as an assistant lecturer?

DC: Well, after a year I was made a lecturer. In the 1960s there was a huge expansion of universities following the Robbins report.

JA: Including University College.

DC: Including University College, and all sorts of people got jobs then – you didn't have to do a post-doc – including some that probably shouldn't have done [laughs]. It was very easy then as it is exceedingly difficult now.

JA: So in principle you could have stayed on perpetually at University College on the same position and just gradually moved up the academic ladder?

DC: I suppose so, yes. But Humphrey Rang had just completed a post-doc in the States with Murdoch Ritchie [Joseph Murdoch Ritchie, 1925–2008] and he saw that I was stuck in a rut, experimentally at least, and suggested that I should do the same. So I went off to Yale for a couple of years which … made a huge difference actually because Murdoch Ritchie was a chap who got stuff done.

JA: Did Ritchie give you a job?

DC: No, no, it was probably what we would call a post-doc now; hardly existed in those days.

JA: But it was supported by the UK or it was supported by the States, or who was paying it?

DC: No, it was supported by the States but I was on sabbatical from here. And at the end of a year of course we hadn't finished what we were trying to do and Heinz Schild very kindly agreed to extend my sabbatical to a second year. That wouldn't happen now either. To make matters worse I didn't actually come

back straight away because Humphrey Rang offered me a job in Southampton. He'd accepted a job to be head of pharmacology in Southampton, at a very young age.

JA: What were you doing at Yale?

DC: Well, we were looking at non-myelinated nerve and we were trying to measure the binding of saxitoxin. Using it to count the number of sodium channels. So I was back into the binding business, yeah.

JA: The project worked well?

DC: Not terribly because the radio chemical of the saxitoxin, tritium labelled, ion exchange process but it turned out later that the radiochemical purity was not what we'd been told by our eminent chemist who was actually Richard Henderson [laughs], later of great MRC fame in crystallography. He was supervising the radio labelling. So we were out by a factor of two or three.

JA: But it was clear that there were channels to be bound to and the toxin was actually binding to the channel at that stage, is that correct?

DC: Yes, I think it was pretty clear, yes, from measuring the number of sodium channels functionally; something proportional to the number, directly proportional to the number, the current was flowing through them. You could see that saxitoxin blocked them in a simple Langmurian fashion so it seemed a fair bet there was a single binding site there.

JA: The idea of a channel goes back not all that much, if you don't mind me saying so, before that time?

DC: No, it doesn't. The word itself was not in very wide use at that time but it came in around then, I suppose. Bernard Katz didn't use it much himself for a long time; he'd talk about an aqueous pore. […] It comes to the same thing, I guess. I think we certainly assumed they were proteins much like enzymes or something.

JA: So when you then returned in 1971–2…

DC: About 1972. I went back to Southampton. […] I was a senior lecturer. That was part of the attraction, that Humphrey offered me a senior lectureship there. It was a terrible mistake for him and for me [laughs].

JA: Why do you say that?

DC: Well, the department was run in a very curious way by a chap called Kenneth Munday and Gerald Kerkut [Gerald Allan Kerkut, 1927–2004]. I did have a copy of Humphrey's review copy of Kerkut's book on sodium channels and transporters. The comments in the margins were quite priceless [laughs] and he was very unhappy. We were part of a combined physiology and pharmacology department there but Humphrey had sort of declared UDI, it was all so painful. Then shortly afterwards he left for a job at St George's [London].

JA: Leaving you there…?

DC: Leaving me there for the final year, so I was head of a department which consisted of me and one other [laughs] who was Charles George, actually, a clinical pharmacologist who was subsequently president of the BMA and is now Sir Charles. But we got on fine, we did the teaching and the one good thing about Southampton is its Institute of Sound and Vibration Research, which is a very good group indeed. And it was at that time I started to do some noise analysis myself on a false transmitter. We had done some work on acetylmonoethylcholine, an analogue of acetylcholine. With monoethylcholine in the medium it will get synthesized in the nerve terminal and released. And I thought it would be fun to do noise analysis on this, which I did 100% on my own; no assistance there. I recorded the noise on a Racal tape recorder and lugged it down the road to the Institute of Sound and Vibration Research where they had a programme for working out the power spectra. And that gave rise to a paper done all with my own hands, which is quite uncommon these days.

JA: Excellent. So did you get an estimate, you were trying to calculate the single channel conductors?

DC: Yes, and also what we would have called then the mean open lifetime (though subsequently turned out to be a sort of burst length) to correlate with the time course of the synaptic current you got when miniature synaptic currents containing acetylmonoethylcholine were released, and it correlated quite well.

JA: Were you looking at voltage noise or current noise?

DC: I was looking at current noise. Oddly enough Katz on the whole seemed to prefer voltage noise, but the two electrode voltage clamp for end plates was fairly well established then and seemed more satisfactory to me.

JA: One of the points that's always made is that Katz for some reason thought that the single channel event was an exponential decaying blip, in other words it looked like the mean channel opening rather than a square event which…

DC: Well if he was looking at voltage it would have been.

JA: But did he even harbour ideas that it was a square underlying current event?

DC: I think he must have done, yes. I mean the exponential you're just seeing the charging of the membranes, the amplitude you got would depend on the time constant. And, yeah, but it's odd that he didn't go more for the two electrode clamp I always thought?

JA: Were you interacting with Katz at all during this period?

DC: I can't even remember if we wrote. I don't think I was, actually, though I got to know him quite well when I came back to UCL, which was in 1976, after another three years away from UCL at St George's. At St George's we got our own PDP-11 to do the noise analysis on. We had a special equipment grant from the Wellcome Trust for £76,000 [to buy it]. A lot of money. […] So this

room size PDP-11 sat next door and we did voltage jumps and noise analysis online with it.

JA: When did you move from Southampton to St George's?

DC: That must be after three years so that would be 1975.

JA: By which stage you'd published your noise analysis paper? […] And there was the whole… Anderson and Steven's paper, and the Katz paper, and so on.

DC: Yes. And in 1977 when I was still in St George's, I published the first paper with Alan Hawkes because we had done this noise analysis and I was interested to know what sort of spectrum, noise spectrum, would be predicted for some realistic reaction mechanisms.

Working on single channels

JA: All the while you'd been in Southampton and St George's you'd kept up a correspondence with Alan Hawkes?

DC: Yes, yes, we'd written periodically, yes. And Alan worked out the matrix notation which made it fairly easy to write down the general expression for the noise spectrum, for any particular reaction mechanism assuming that the rate constants for the transitions between states were constant, and that the agonist concentration was constant so they were all pseudo first order reactions. And this seemed very nice. But to our surprise what we found was that the time constant you predict for a relaxation like a synaptic current was longer than the mean open lifetime of the channel. And at first this was written up just as a sort of curious finding and we wanted to publish it in *Proceedings of the Royal Society B* partly because *The Journal of Physiology* wouldn't take non-experimental stuff like that [laughter]. I'd have rather had it in *The Journal of Physiology* but they were a bit po-faced about theory at the time [laughs]. At that time to publish [in *Proc Roy Soc*] you had to submit it via a Fellow so we sent it to Bernard Katz, and that's the first time we had real correspondence with him probably. And he was very interested in it. He said, 'But why, why is the time constant for the relaxation longer than for the mean open lifetime?' because Anderson and Stevens in 1973 had published a nice close agreement between the time constant you get from noise and the time constant you get from miniature synaptic currents and they referred to that as the mean open lifetime. And [laughs] I can't remember now to what extent it was me, to what extent it was Alan, and to what extent it was BK, but we realised what was happening was the channel was opening several times in quick succession, very quick succession, and that was predicted behaviour even for the simplest mechanism for an agonist action, and that what you were seeing with noise analysis was the total length of this little burst of openings. The interruptions in it were very short; for physiological purposes they were irrelevant. But for mechanistic purposes they were very interesting. We drew a picture of this which looked actually like single channels and turned out to be in practice. In fact by the time it came out it was 1977 and by then

the first single channel recording [Neher & Sakmann, 1976] had already just been published, though the resolution in that paper was very low.

JA: So the mathematical prediction of burst structures preceded the experimental data, is that correct?

DC: It did, yes. And we reckoned it had to be that way because the Anderson and Stevens paper had assumed that binding was much faster than opening and shutting (the gating as we would now say). They were completely explicit that there was no reason to assume this, it was arbitrary. Under those conditions openings would occur one at a time and the open lifetime would indeed be the same as the time constant from noise. The trouble is that there's a limit on the association rate constant of acetylcholine; it's limited to 10^8 m^{-1} s^{-1} maybe, at a pinch 10^9, by diffusion and it can't be faster than that. We found that putting in what seemed like realistic numbers, and actually it turned out that there was no physically possible value for the association rate of acetylcholine which would make binding much faster than gating. There was no value that didn't give this burst behaviour, which was just caused by oscillation between the open state and the liganded but shut state. Once [the receptor] is in that intermediate bound but shut state it can either go one of two ways. It can either dissociate and that's the end of the channel activation or it can reopen. And the numbers are such that it seemed it was very likely to be open several times before closing. And so we published that as an entirely theoretical exercise. But shortly afterwards there was a meeting in France to which I got invited and, well, I can't remember if I was invited or I invited myself, because Sakmann was going to be there and I really wanted to meet this guy who had recorded from a single molecule. And he had read our paper and said, 'That's very interesting because we can see these little interruptions and so we must get together.' And that led to quite a long period where we investigated this phenomenon, between 1979 and 1985. It turned out that they hadn't actually seen it, because in 1979 it was before the gigaohm seal was invented and [what they had seen were] rarer, longer, sort of half a millisecond shuttings that sometimes occur during openings but rarely. When you had the gigaohm seal method, which arrived just in time for us to do the experiments, we saw that there were more frequent but shorter shuttings that hadn't been resolved previously but were just what we predicted.

JA: So was Bert imagining that he'd seen single channels?

DC: No, he was seeing these rarer but longer interruptions during the channel opening, which was all that was within the resolution. There is a small component of them which we saw as well, but they are very rare compared with all the short [interruptions], which were only revealed when we uses the gigaohm seal recordings.

JA: What was the nature of your interaction with the Göttingen group? Were you actually there physically to discuss your theoretical work as well as the experimental data that they were getting?

DC: Well, we just went to do experiments. I was over there for sort of three month periods on and off; I went for several years.

JA: So you were one of the early patch clampers?

DC: But I think Bert later repeated a couple of the experiments just to make sure it wasn't to do with the pipe smoke [laughs]. It wasn't.

JA: You were there at the experimental set-up doing, getting seals and looking at the acetylcholine?

DC: Yes, absolutely. Bert would do the dissections at which he's very good and I'm a bit ham-fisted at. He had lots of practice in dissecting of frog cutaneous pectoris and this is before there were recombinant channels of course. And I would either be poking the muscle while he was dissecting, or supplying him with micropipettes. He was very adamant that he couldn't use a pipette that had been polished the day before but in experimental tradition I handed him pipettes some of which were today's and some of which were yesterday's in a random order… [laughter]

JA: No difference?

DC: There was no difference. We had a very frustrating time because in the very first six weeks I went for, we hardly got anything: no seals. And that turned out to be, in some sense Bernard Katz's fault actually because Bernard Katz would use phosphate buffered saline. Which is not so often used now, but it turned out that they were forming tiny crystals of presumably calcium phosphate or something at the end of the pipette.

JA: Yes, yes, the calcium level was too high?

DC: Yes, and that was preventing us getting seals. But once that was solved it went a bit faster. And it was enormous fun; he [Sakmann] was a complete workaholic. And he wanted to do everything himself. And that continued even after he got the Nobel Prize. He wanted to do things himself. The most noticeable characteristic. I know three Nobel Prize winners reasonably well, Andrew Huxley, Bernard Katz, and Bert Sakmann [also Erwin Neher], and they have all done their own experiments. This is the absolute characteristic. And modern science has made that almost impossible.

JA: It's very worrying.

DC: The PI spends his time writing grants, travelling the world, hawking the products and that, I think, is not good.

JA: Was Erwin Neher interacting closely with you as well?

DC: Oh yes, he was in the Göttingen Lab at the time of course along with Fred Sigworth, the electronic whizz, degree in electronic engineering I think in the first place. He [Sigworth] was also a born-again evangelist, I was amazed to discover [laughs] when I got there, so we didn't often talk about that side of things. He was learning Arabic so he could go and convert the infidels but I think he later decided it might be safer to stay in Göttingen [laughter]. Thank

Heavens. But he and I wrote the chapter in the 1985 and 1995 edition [of the Single Channel Recording book] on methods for analysing single channels, which is my most highly cited work. It's got well over a thousand citations. Well, that's according to Google Scholar, according to Web of Science and Scopus it's nothing: they don't even count books, which I think is daft…

JA: Okay, so we're moving forward a little bit now to the Erice conference which brought all those single channel results together and I suppose produced the bible, the book, the Sakmann and Neher book, on single channel recording. Whose idea was that?

DC: I think it was probably largely Erwin's; he seemed to be the driving force behind it. They assembled all sorts of equipment, I think it was probably Fred Sigworth drove it all the way down, through…

JA: Oh, it was experimental?

DC: There was experimental stuff in the first one. And they had got some binocular microscopes in and… I can see Erwin Neher bent over this saying, 'I can't see anything through this' and somebody saying, 'Try taking the lens caps off, Erwin' [laughter]. Of course Erwin was a perfect experimentalist as well; they both were. But the idea for the patch clamp clearly was Erwin Neher's; largely he'd got the idea of recording from small areas when working in Dieter Lux's lab [Hans-Dieter Lux, 1924–1994] where they isolated small areas of membrane in Vaseline and he realised that the secret to lowering the noise was to record from a small area, and that was clearly his crucial input into this whole thing. Because the secret of recording a single channel was simply to reduce the noise by a 1000-fold, or 10,000-fold with the gigaohm seal, which is a hell of a risk but they did it.

JA: So I mean obviously the technology was brought to a state of perfection by the Göttingen group but there have always been these little groups dotted around like there were people at NIH who claimed that they had almost invented patch clamping. Do you give any credence to that?

DC: Yes, it's one, it's unpleasant when these priority rows break out. Harold Lecar [1935–2014] in particular was a bit peeved but, and it's true they had recorded single gramicidin channels before Neher & Sakmann (1976). It didn't impinge much. One was aware that he was a bit fed up. These things are largely luck. I mean my career has been entirely luck. I might not have met Alan Hawkes, single channels might have been invented in the wrong generation for me; it's entirely luck, no credit to me whatsoever except that I was interested in the things and grasped the chances when they appeared, I suppose. That's the only bit I can claim any credit for.

Göttingen and UCL

JA: Following the period that you were working closely with Sakmann at Göttingen, how did your interest in mechanisms of single channel and pharmacology proceed?

DC: Well, I kept on doing the same thing effectively. [Alan Hawkes and I published in 1982 a 59 page paper that gave the theoretical foundation for bursts of openings, and that was probably what got me into the Royal Society – Bernard Ginsborg told me it had taken months to referee it.] The time in Göttingen gave rise to a *Nature* paper but they didn't get as many citations as *The Journal of Physiology* which we wrote in 1985, the only thing I've ever written that got cited as a classic, though the analysis in it was fairly crude actually. It was only much later we discovered how to analyse these things properly. The great outcome for me was that it enabled you to separate the binding and the gating or so we thought. And this was very interesting because that is just another version of the classical, pharmacological problem, the affinity efficacy problem, which had arisen in the 1950s. Bernard Katz in fact had pointed out in 1957, his paper with del Castillo [José del Castillo, 1920–2002] that the simplest possible mechanism for an agonist must have at least three states. There must be a vacant state, an occupied but shut state, and an opening reaction. And these have two separate equilibrium constants and furthermore no binding experiment that you could do, or no equilibrium experiment of any sort that you could do, could separate these two rate constants. That was not really emphasised by Katz so people went on for ages thinking there were ways of separating these two things. That was in 1957.

In 1956 there was a famous paper by a chap called Stevenson, Robert Stevenson, and he was actually in the department at Edinburgh when I was there. He had said that if we want to understand how an agonist works you must consider two separate aspects of it; one is its ability to bind and the other of which is the ability, once bound, to produce a response. And he called those two things affinity and efficacy and they are very much the same thing as the two equilibrium constants in Katz's formulation. Stevenson proposed a way of measuring these things, which is more than Katz did, but it turned out the method he gave was simply wrong. It took me till 1987 to notice the mistake in it. I cannot imagine how I was that slow, given my interest in these things, but it had a complete mistake in it and his methods didn't work. Single channels did appear to work, that was the fascination for me. So we thought we'd revolutionise structure–activity relationships. That hasn't actually really happened [laughs]. I think the interactions which govern the activation of a channel by a ligand are just so subtle and so complicated; it'll probably take another generation before you can design a ligand for a protein. People talk about it a lot but they can't do it; it's all hype.

JA: What do you think is required? Not only is it structural biology but it's also some link between [a] static picture which crystallography gives you and the nature of binding. Is that what you're alluding to?

DC: Yes. When we had the amino acid sequences of the protein and shortly thereafter we had some structures (though not very complete structures for transmembrane ion channels, they don't crystallise very well). We thought all the problems would be solved but as so often, they weren't [laughs]. And I read a review by a chap called Shortle, never heard of him before or since, who was an enzyme person, and he pointed out that since a lot of the forces

between the chains vary with the separation to the power of six, changes in separation which are too small to observe in the highest quality x-ray structure can have huge energetic consequences. Maybe that's one reason why we haven't been enormously successful in improving the predictive ability of any of these things for designing ligands. Or, even understanding exactly what happens during the binding process is still very much a work in progress now.

JA: Do you think it's a quantum mechanical problem or do you think it's a computational problem, or do you think it's just straight chemistry?

DC: Well, people are trying molecular dynamic simulations, but molecular dynamics is interesting, you get an answer but there's nothing to check the answer against [laughs] so you can write a paper but there's absolutely no means of saying whether it's realistic because of course molecular dynamics makes assumptions about the nature of intermolecular forces which may or may not be precise enough to give you the answer you want. And also they're incredibly computationally intensive so it's difficult to get beyond 10 microseconds, which is too short on the scale of the channel opening. So there are huge problems still in attempting to relate the function to the structure. We thought we made a big advance in 2004 when we proposed that there is actually an intermediate shut state between the fully liganded shut state and the open one, a sort of pre-open state. And that seems to be becoming accepted. It depends on fitting a fairly small aspect of the single channel record but it's remarkably consistent with the observations and with one's intuition about what should happen. The history of how that came about is fairly interesting. Again there's some lucky coincidences. By that time I was about to 'retire' in 2004, and the single channel group was taken over by Lucia Sivilotti and she'd been interested in glycine channels. She had been my post-doc but then she became my boss. And I wasn't too keen on glycine to begin with because, well largely because the native channels often seem to get a lot of sub-conductance levels and they cause enormous theoretical complications without casting much light on the real problem. But it turned out that recombinant glycine channels don't have many sublevels; I don't know quite why that is. And furthermore there are probably three binding sites rather than two on a nicotinic receptor. But the concentration dependence is good. [The glycine receptor] will open with one or two bound as well as with three bound, and the concentration dependence is much more pronounced than it is for a nicotinic receptor. We had shown with Sakmann in 1981, our very first paper together, that at very low concentrations you get very short openings which we put down to mono liganded openings, but I think that's probably not quite right.

JA: This is mono-liganded on a multimeric structure?

DC: Yeah. In fact that very first [1981] paper rather concentrated on that because we were so surprised to see these short openings as well as the longer ones. And they did reduce in number at high concentration, although the concentration dependence wasn't exactly as predicted and that's possibly because of these intermediate states which we came across much later,

though there was no hint of that at the time. The concentration dependence of the glycine receptor made it almost ideal for analysis because there was a lot of information in the concentration dependence. You could only see that over a very low concentration range in the nicotinic, but [in the glycine receptor] it had a much wider concentration range. Furthermore, the glycine receptor desensitised at about the right rate; you actually need desensitisation to do these experiments. The desensitization itself is of zero interest to me but it enables you to get, at high concentrations, long sections of record that come from one channel only. One of the huge unsolved problems of patch clamping is you can't tell how many channels you're recording from at low concentrations. At high concentrations you can and that enables you to get a piece of the P_{open} curve, the probability of being open as a function of concentration on an absolute scale, which is wonderful. It doesn't go from nought to one, it goes from nought to, in the case of a nicotinic receptor, nought to 96 or 97%. But you know the 97%, you don't have to normalise it and that's wonderfully informative because that tells you about the efficacy step, the gating step. So glycine receptor, just by chance, happens to have just the right numbers or the heteromeric α1–β1 receptor does. The α2 is not so favourable. And with that we were able to fit various mechanisms and come up with the idea that the receptor has an intermediate state between the resting one and the open state. That seemed to be a good description of the data. By that time we had good fitting methods. [Fitting mechanisms to data] had to be done *ad hoc* in the 1980s. But in 1990 Alan Hawkes came to the rescue again because in order to do a maximum likelihood fit of the mechanism to the results you have to have an equation for the length of an opening. The trouble is the shuttings that interrupt openings are so short that you miss a lot of them, so you get an open time which is longer than the real one. In the 80s both Alan and Frank Ball had written down the Laplace transform of this distribution but everybody said, 'This Laplace transform can't be inverted; it's impossible.' And Alan Hawkes in 1990 came up with a way of inverting it, which strangely enough he'd got through his original interest in traffic studies. Someone in 1940s had published a paper which gave him the hint. It was about two intersecting flows of traffic; when can one cross the other? Well only if there's a gap between the two cars crossing it that's long enough. And so shorter shut times, shorter gaps than that, would be effectively not there. And this was actually sufficiently related to the problem of finding the distribution of apparent open times that enabled him to solve it.

JA: What have you done computationally? Many of these things are invertible by brute force.

DC: We looked at numerical algorithms for inverting Laplace transforms but basically they're not […] terribly reliable. But in any case it turned out to be unnecessary. And the solution is quite weird, as anything I've ever come across. This is way beyond my competence in mathematics, but the solution turned out to be piecewise. I'd never come across a piecewise solution. So if you had a minimum observable shut time of 25 microseconds, say, there was one solution between 25 and 50 microseconds, of course nothing below 25 by

definition, a different solution between 50 and 75, another one between 75 and 100.

And they weren't even sums of exponentials, like the ideal distributions always are, which was sort of weird. They depended on the whole transition matrix multiplied by a polynomial. And the bad thing about the solution was the polynomial got bigger and bigger as you went out from time zero, so you'd end up, if you tried to write down the distribution for a one second shut time, you'd end up with a thousandth order polynomial and it becomes numerically unstable. But then two years later they strike again, Alan Hawkes and a very bright chap in Swansea where he was then working, called Assad Jalali, came up with an asymptotic approximation to this, in other words an approximation that holds for a long time durations of the shut or open time, which is absolutely marvellously precise and elegant. Because an infinite time turned out to be about 100 microseconds. After three times the [minimum detectable] interval…

JA: You're in the asymptotic range.

DC: You're in the asymptotic range and it's essentially the same as the exact solution. Furthermore, this asymptotic solution consisted of a mixture of exponential distributions, and the right number [of exponentials]. In the ideal case an open time distribution will have a mixture of exponentials and the number of components will be the same as the number of open states. And that was true of the asymptotic solution too. The lengths were quite different in case of missed shuttings but the number of components was the same. So it shows that you are fairly safe in using the number of components as a minimum for the number of open states even when you're missing a lot of short events. Anyway with these two things known we could then write a program which calculated the likelihood of an [observed] sequence of open and shut times and it took into account correctly the correlations between the open and shut times which occurs with some mechanisms. It's an extra bit of information you can't get from any macroscopic measurement, this correlation time between one open time and the next one. That was all taken into account correctly by this gigantic matrix multiplication that allowed you to calculate the likelihood and so then we could maximise that likelihood and get estimates of all the rate constants in a [postulated] mechanism in a proper way with an exact allowance for the fact that you couldn't see short openings or short shuttings. And that made a big difference. We did some simulations in 2003 to test the method and with simulated data of course, which is cleaner than real date, but we found we could estimate things up to 250,000 per second. We could successfully recover it from the data where you're missing 90% of the shuttings.

JA: So this becomes what the CJH method?

DC: The HJC method. The Hawkes, Jalali and Colquhoun, which are the two papers about the distributions you get when events are missed, short events are missed. They don't have particularly high number of citations because they're

very mathematical but they're actually critical to everything that's happened since 1990.

Other lives

JA: … I'm continuing the discussion with David Colquhoun in his office and we've got up to David's, as it were, first life as an ion channel biophysicist. But of course now David has a much more distinguished career… no, not more distinguished, an equal career as a defender of academic freedoms, evidence-based medicine and evidence-based pharmacology. And I think what would be really interesting is to know really when and how you got into that area?

DC: Well, I think we have Richard Sykes at Imperial College to thank for that because Richard Sykes got together with Derek Roberts who was at that time a sort of caretaker Provost after Llewellyn-Smith had left. And to everyone's astonishment he tried to give the College away to Imperial. The joke of the time was that Imperial had said, 'Yes, of course we'll have a combined university, we'll combine our two titles. We'll take Imperial from Imperial College and College from University College' [laughs]. So it would be called Imperial College. And it took me about three days to realise that they were actually serious about this. It seemed completely barmy. Two very, very large institutions on their own, quite a long way apart, and what the hell was the point of merging them?

JA: This was 2001?

DC: 2002, I think, yeah. It just seemed crazy. But of course Richard Sykes was well known to be a takeover maniac. When he merged GlaxoWellcome with SmithKlineBeecham he was reviled in the financial press, which gave us some quite juicy quotes to use. So I thought, 'What the hell do you do about this?' So I started a web page, very crude it was, awful; I was terrible at it. But it sufficed and we started collecting signatures. But more to the point we started collecting the raw minutes of meetings between departments at UCL and departments at Imperial. We were told it would all be a very transparent process, these people would meet, the departments would meet and that would go to a committee and that would go to another committee, then they'd publish all the results. Well everyone knows what happens when something has been through three official committees; it's unrecognisable. But fortunately people started sending me the raw minutes and we'd put them up on the web. And it came to a real head after about five weeks when Richard Sykes had a meeting of Senate at Imperial which is quite small compared with our academic board, about 40 people I think, and he told them, 'Well yes, I know I said there would be no redundancies, well of course there will. But don't worry they won't be from Imperial.' And within minutes two people had sent me an account of this meeting [laughs]; 10 minutes later it was public knowledge. The next day the whole thing folded. I think they were sufficiently old that they had not realised the power of the web that makes it really quite difficult to keep secrets. So I take the George Orwell attitude really. He said, 'Journalism is publishing things other people don't want to be published. Everything else is PR' [laughs].

JA: When did you become aware of the web, the internet, as a powerful medium for academic communication like this? Pretty early on, I would imagine.

DC: Yes, when I was in Heidelberg for a year in 1991, we started using email then with 2,400 baud telephone modem; it was very unreliable. But there [were] a few bulletin boards that I used. This is really before the web as we know it now. But there were bulletin boards which were quite useful, so yes I'd been using it quite a long time but it didn't really come to fruition till around 2000 when, and even then I just had a sort of crude web page, it wasn't a proper blog, I don't think WordPress existed then.

JA: So your blog and 'DC Improbable Science' really started after that period, after the Imperial takeover attempt?

DC: Yes, well I got quite hooked at that stage, though I was still working. In 2004 we published this, our new mechanism with the intermediate shut state, which is probably the most interesting thing I've done actually apart from perhaps the very first things. So that was going on at the same time. But it was also the time of course of the invasion of Iraq and I got quite exercised about that and I had a politics page which was largely chronicling the Bush–Blair thing; most of the things we predicted are of course sadly coming true now. And I had another one about education, particularly religious education in schools, which has also come to the boil again just recently. I ended up with three different pages which I was updating and the old pages are still available from my blog. And of course I had one which was predominantly about quackery in those days because I was outraged to discover that five different universities were running Bachelor of Science degrees in homeopathy and so I got onto the Freedom of Information Act which Tony Blair had passed in 2000. He afterwards said he regretted it but it's actually the best thing he ever did in my view. We got hold of some of the things that were taught to these hapless students down the road in Westminster University and other places and so I was also posting on that one. That went okay; the page got bigger and bigger, it was completely unwieldy and crude and other people were much better at this stuff than I was. It improved only when the then Provost, Malcolm Grant, threw me off the UCL server in 2007, which was enormously beneficial to me because I started a proper blog, got a lot of publicity. Ben Goldacre wrote a thing in his column in the *Guardian* saying, 'Why doesn't Malcolm Grant care about academic freedom?' with various exaggerated claims of what I was up to. And the readership went up by fourfold overnight.

JA: So there's a convergence between these three streams but behind, as it were, your moniker as Professor Quackbuster, if I may say… was your history as working in the pharmaceutical industry and particularly in a pharmacy before you went to university. Did that fuel it in any way?

DC: Well, yes, I suppose I'd already been aware from a very young age that homeopathy in particular was bunk and much of the other stuff that was sold was bunk but of course you didn't really have time to do much about it when you were running a group. And the means didn't exist before the blog. You know I wrote the odd article when asked to but they didn't make much impact.

We recently had a proper paper, not just a blog, about acupuncture but that's had over 33,000 views on my blog alone, apart from people who go to the journal and stuff. And that's enormous. You know my statistics textbook sold 5,000 copies; now I can get 5,000 views in a couple of days.

JA: So how do you view a situation with the merging dissemination of information where you essentially have a much greater fame, or almost notoriety, through your internet presence than through your scientific presence?

DC: Yes, I slightly regret it. I mean I must say I give more talks now than I ever have but very few of them want to hear about ion channels, they want to hear about university politics and quackery and things, which is okay. I got invited to go to a Science Foo meeting, this is held in GooglePlex, so I thought it was worth the considerable effort of flying to California for a weekend just to see Googleplex. It was quite an experience because you never know whether the guy in jeans and a T-shirt you were sitting next to was a billionaire or a humble blogger [laughs]. But on the way, I gave a talk in Stanford because I had a post-doc from there and she invited me, and I gave two, it happens most infrequently, one on single ion channels which had about, I don't know, nine enthusiastic people? [laughs] and one on quackery which filled a big lecture theatre. It is slightly galling but there we are.

JA: So do you think, to come back for a second into the physiology, do you think that your interest in ion channels can be disseminated better through the internet? Have you actually recruited aficionados for the physiology because people want to know, 'what does this man do for his real job?'

DC: I guess I get some. Quite a few physiologists I think do read the blog but I rarely write about ion channels on it, actually never come to think of it. It does write on some statistical topics that are related to it. I once did one on Markov queuing in hospitals for [hospital] beds, which was really quite an interesting topic. I did it because my operation had been postponed when I had to have a kidney removed and there was no room in ICU and no bed in National Health Service. But the statistics are quite interesting. I mean that is absolutely bound to happen unless you have the ward barely more than half full which is pretty uneconomical. [And I recently wrote on the blog about the false discovery rate and the misinterpretion of *P* values. That's proved to be popular despite being not really original. It all goes to show that metrics can be a very misleading way to (mis)measure originality and quality.]

JA: You've been very honest about yourself on your blog. Do you regard this as a duty? Or do you in any way resent it? Or do you feel one's forced into it because of the internet?

DC: Honest about myself? How do you mean?

JA: Well, probably people know quite a lot about you.

DC: [laughs] Through the diary section, yes. Yes, I do put you know odd holiday photographs in there as well. There's more substantial things. It doesn't really matter. It's a pity that quite a bit of [blogging] has to be anonymous. The same

is true for the new sites that are springing up for post publication peer review, things like PubPeer which actually publish very good reviews and they allow them to be anonymous. One of the things I'm interested in is the future of publishing which is in a huge state of flux at the moment. I signed Tim Gower's Elsevier boycott at an early stage ... Well, they have become accustomed to earning large profits from universities and now things are changing they're a bit desperate. I had an email from them the other day inviting me to contribute to one of their open access journals. What they didn't mention is what it would cost, a great deal. But there are other things now where you can publish much more cheaply. *PLOS One* was an early one but that's actually quite expensive still. But things like *eLife* [and *Royal Society Open Science*] are great.

JA: So the elephant in the room, it always seems to me, is the review process. How does one do the quality control on publishing? Do you have views about that?

DC: I think post-publication review has to be the future. The trouble is, you know, PubMed, the National Institutes of Health's library site, indexes 30 journals which are pure quackery. And those papers are reviewed by other quacks and they're quite awful. And the same is true of the whole sort of lower end of the publishing business, the standards of peer review are pretty dreadful. Sometimes they're pretty dreadful in *Nature* and *Science* too. I've got some quite recent examples of hyped up papers from those journals so I'm very sympathetic with people like Randy Scheckman when he said he wasn't going to submit things to *Nature* any more. It's true that he made his career by submitting a lot of things to *Nature*.

JA: He's in a good position not to.

DC: He's in a good position not to, yes. Well, I feel this because I can afford to be non-anonymous simply because nobody can really fire me now. But younger people are petrified to speak their mind and they would be in peer review as well. Who is going to write something critical about an important and influential person in a peer review if their name is known? I'm not surprised that they're petrified but I feel a certain amount of duty to speak up for the people because they can't really fire me.

JA: So how do you feel [about] the future? Is the peer review increasing[ly] still going to depend on the small, inner cadre of people who are not afraid to speak up?

DC: No, I think it's going to depend on anybody who understands the subject. And I don't think it matters if it's anonymous. You do need a bit of moderation to keep madmen and trolls out but on PubPeer some of the anonymous reviews have been superb, detailed, calculations. There was one on an Eliza method that purported to work on ridiculously low concentrations and it was dissected beautifully on PubPeer. Of course it really ought to be in the journal itself. I think every journal, every paper should be open on the web and it should have an open comments section afterwards. It would be very much cheaper; I reckon the paper should cost maybe £100 or £200 to publish maximum.

JA: So what does one do about, as you say, the 30 quack journals which are reviewed by people with rather dubious credentials.

DC: They oughtn't to be on PubMed really. I mean it's okay as long as you realise they're quack journals but what you have to realise is the papers, the refereeing process is worthless. And you know there aren't enough people who understand things well to review the huge, vast number of papers now published. And the vast number is the result of the perverse incentives that are put on academics.

Blogs and future plans

JA: So where do you see yourself going over the next few years? As a blogger? As an identifier of false assumptions? As a channel biophysicist? All these are options open to you.

DC: Yes. My contribution in ion channels is now minimal. The single channel group at UCL has been run by Lucia Sivilotti for 10 years now, and very effectively, and my contributions really stopped with our 2008 *Nature* article. I read papers and comment on them sometimes. But I don't usually put in enough that I even deserve to be in the acknowledgements. So that phase is pretty much finished. But the statistics I learnt is enormously useful. My very first paper as a fourth year undergraduate was about statistical inference and I just submitted one again on the same topic because I recently discovered what I should have known a long time ago which is about the idea of false discovery rate. It comes up first in screening tests, you know you can have a screening test which has a specificity of 95% and a sensitivity of 80% and it turns out to be useless for a rare condition: 86% of the people who come out positive are perfectly free of the disease or even more. And you can apply the same reasoning to *P* values. It's slightly more contentious. The reason I hadn't thought of it much before was because it's often labelled Bayesian and I never felt sympathetic to the Bayesian approach to statistics [laughter] if only because you, because of the subjective element in it. But Bayes' theorem is only the rule of conditional probability, it only becomes contentious when the hypothesis you're testing is something you can't imagine being repeated. If you say, 'What's the probability that the earth goes round the sun, you can't imagine a population of universes in which, 95% in which it goes around the sun and 5% it doesn't. In those cases I can't see, I can't like, I can't love, I can't put the prior probability on it and I can't interpret the result. But it's quite different in other cases. For screening it's quite different. The prior probability is just the prevalence of the condition in the population, and that's in principle knowable. And for many a significance test does the same thing. If you test a whole series of drugs, a certain number of them will be active and a certain number won't. And in principle, with enough work, you could determine that. It's just an ordinary probability and that's the prior probability in Bayes terms that you have to put in, and when you do that the results are alarming. I mean you find that if you use a conventional significance test and you see $P = 0.045$ and say that's a discovery you're going to be wrong at least 30% of the time

and quite possibly 80% of the time. And people simply don't realise that. And so that's what my latest paper's about [laughs].

JA: Do you regard your site as a way of disseminating that view as well?

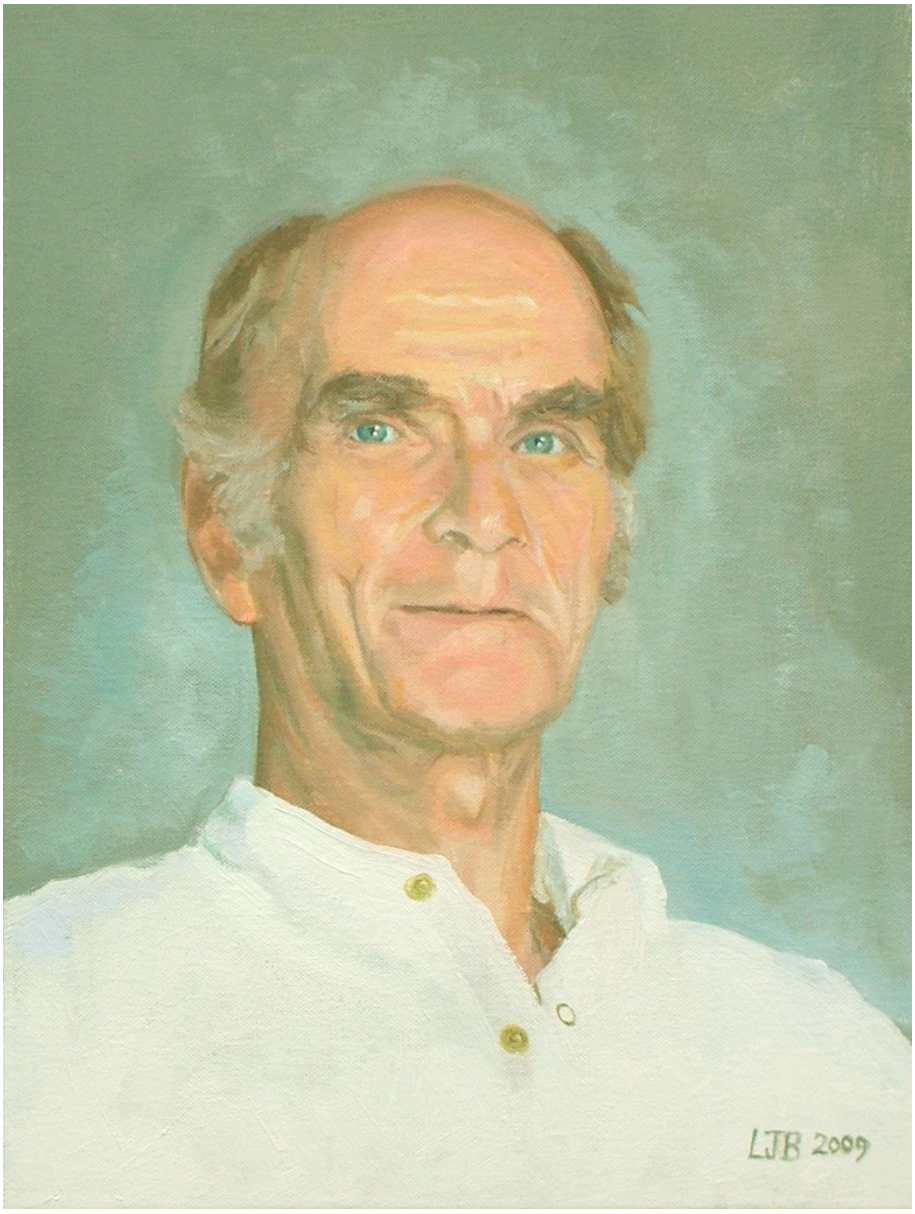
DC: Oh yes, yes. I've already got a post up which has some of the paper in and they don't quibble about that; it's in the hands of *PLOS One* at the moment. We'll see. And, but you know, at my age you don't buy green bananas so I put up a brief version of it on the web and if *PLOS One* don't take it I'll probably put the whole thing on the web [in arXiv] and just see. [It was rejected by *PLOS One*, *eLife* and *PeerJ*; now it has appeared in *Royal Society Open Science*. Now it's appeared in *Royal Society Open Science* and in a bit over 2 months it's had about 27,000 full text views and 3,300 PDF downloads. That's a lot more than the far more original ion channel stuff. At my age you don't buy green bananas, but blogs and preprint servers like arXiv mean that anything can be public in 24 hours. That's the future of publishing, I think.]

JA: Very good: a great way of disseminating the information.

David Colquhoun, thank you very much for a really interesting discussion. I hope you approve of what happens when this eventually does appear on the web in its own right.

DC: Oh, you're welcome.

JA: Thank you.



Portrait of David Colquhoun by his former UCL colleague, Lynn Bindman. Those who know David will be struck by the absence from the image of his otherwise ubiquitous pipe.

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