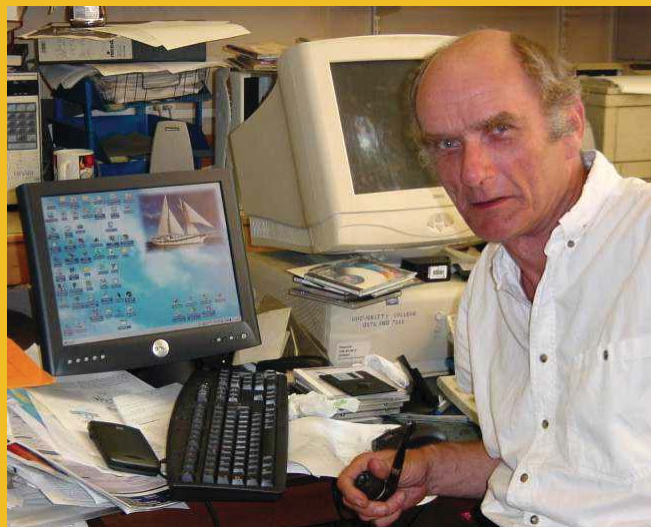# CrossTalk

An Uncommon Scientist with a Lot of Common Sense

Maybe it was jet lag, and maybe it was just a mixture of my own American prejudices and the excitement of visiting London for the first time, but as I walked into David Colquhoun's curiously cluttered office to interview him at University College London (UCL), I couldn't help but feel that I had just stepped into a scene from Mary Poppins. Certainly part of the fascination was Colquhoun's own, unique personality and my first view of him, pecking calmly away at not one but two desktop computers, a laptop and a handheld, with La Traviata playing in the background, and pipe in hand. Having traveled and worked around the globe, including professorial stints at Yale University in the US and as a Humboldt scholar in Germany, he speaks about science and society with a broad worldview. And yet he is wonderfully British, having been for over thirty years of his career at UCL, a place rich in the history of pharmacology, of which Colquhoun speaks with unconscious pride. About his own career and background, he is surprisingly modest, and speaks excitedly of statistics and membrane channels, and refers to his good luck in having stumbled into a career that he loves. Even to me, someone who has anxiously experienced statistics as a requirement rudely foisted on graduate students, Colquhoun can make complex math seem like a matter of common sense, worth pursuing for its own sake. Statistics and matrix algebra are not difficult, he will tell you, because if they were, he would probably not be able to understand them himself. What he makes clear is the power that statistics has for understanding intricate questions of single receptor biology, and for guiding researchers in probing their own research questions and inferences. He also finds it important to apply some common sense to the perceptions and misperceptions of science as part of the wider societal discourse. If you visit his Improbable Science Web Page (http://www.ucl.ac.uk/Pharmacology/quack.html), you will find appraisals of and links to a variety of health-care claims that Colquhoun follows on behalf of lay society.

Professor Colquhoun will also be at the World Congress of Pharmacology in San Francisco to deliver the Second IUPHAR Lecture in Analytical Pharmacology. Whether you really want to learn something about receptor biology, or just want to enjoy the personality of a speaker who is not only scientifically distinguished but also fun, you'll certainly be able to do so at Colquhoun's lecture. — HBS

MI: How did you get into pharmacology?

DC: Well, I did really terribly at school. The only academic record I created at school, I think, was to fail geography three consecutive times, getting lower marks at each attempt. This had never been achieved before. Perhaps it is why I now love maps and charts.

Luckily, my father was a teacher—a disappointed one at that stage, but he knew the right things to do. He could see that I had no talent at languages, which all the rest of my family was good at. He taught French and German all his life. He thought something scientific would be good for me. And the only thing I could get into with my appalling qualifications was pharmacy.

So I became an apprentice pharmacist. I was paid two pounds a week, I remember, which was slave labor even in the fifties. It was actually rather good for me, because I soon realized that the last thing I wanted to do was spend the rest of my life selling condoms. In the shop there was a book called *Martindale's Extra Pharmacopeia*, a big thick book that I spent much of my time reading. I used to take it home and read it on the bus. It had a black cover and the edges of the pages were red so it looked rather like a Bible. So I used to get some funny looks.

MI: They thought you were a zealot?

DC: Perhaps I am, but certainly not that sort. UCL was founded to allow people to get an education regardless of their beliefs, or lack of them. It was founded when the only other universities in England (Scotland was more advanced), Oxford and Cambridge, required you to be a member of the Church of England (and, of course, male). Anyway my father got me into a course at University of Leeds, which specialized in pharmacology. It turned out, like many university courses, to be a bit of a teach-yourself job in the later stages, but it got me started. It also led to a strong belief that teaching and research should not be divorced –otherwise you get teachers who do not themselves understand the subject very well.

MI: And so did you finally feel in your element once you got into pharmacology?

DC: Yes, but it was not the only element I enjoyed. I quite liked the first-year physical chemistry course, which most people didn't. And we had some ancillary lectures on statistics, and the statistician (Welch) who was teaching would stand, back to the class, and write everything out in chalk until the blackboard was full, rub it out, and begin again at the top left-hand corner <laughs>. But the result of this procedure is that he went very slowly and I really found myself fascinated by it. He would have scored zero on the sort of rubbishy teaching audit we are plagued with now, but he had a big effect on me.

MI: Why did you find statistics so fascinating?

DC: I went through a phase of catching up on my education. I started reading books about inference—stuff written by philosophers. But it dawned on me that this was all verbiage; the people who had really thought about the basis of inference were statisticians, not philosophers. Read Fisher, Bayes, and so on, not Popper. That is where you find the whole basis of experimental science—how to get knowledge (and the limits of knowledge) about the natural world from observations. Of course most scientists don't give a damn about it (and most of the time that does no great harm), but I liked it enough to write a book on it later (*Lectures on Biostatistics: An Introduction to Statistics With Applications in Biology and Medicine* [Oxford University, 1971]). Russell had a great influence too, though not because of his views on inference. I still carry round on my PDA a lovely quotation from his work:

"I wish to propose for the reader's favourable consideration a doctrine which may, I fear, appear wildly paradoxical and subversive. The doctrine in question is this: that it is undesirable to believe a proposition when there is no ground whatever for supposing it true. I must, of course, admit that if such an opinion became common it would completely transform our social life and our political system: since both are at present faultless, this must weigh against it. I am also aware (what is more serious) that it would tend to diminish the incomes of clairvoyants, bookmakers, bishops and others who live on the irrational hopes of those who have done nothing to deserve good fortune here or hereafter." *On the value of Scepticism (1935)*

MI: And what was your actual work as a PhD student?

DC: Unfortunately, Walter Perry (then Head in Edinburgh) put me onto passive sensitization. I was trying to measure the binding of immunoglobulins to lung tissue. But there was too much non-specific binding for it to succeed. This was at the same time that Humphrey Rang, whom I later came to know and to work with, was working on the binding of radiolabeled atropine to smooth muscle of the gut for his PhD in Oxford. His work was really the first of the modern era of ligand-binding experiments. Everyone in America seems to think that ligand binding was invented by Sol Snyder. It was actually invented by Paton and Rang, whose paper (1965) is

better than many that followed it.

MI: And at the time you arrived in the 60s, what were your primary interests?

DC: I was helped at this point by Humphrey Rang. I liked him before I even met him because I first discovered about his atropine binding work when a talk was given at the Pharmacological Society. But it was given not by Humphrey Rang, who as the PhD student would normally have given it. Instead it was given by his boss, Bill Paton, who apologized that he had to give the talk, because Humphrey was bobbing around the North Sea in a small sailing boat and he thought that more important! So, I thought, this must be an interesting guy. Subsequently I shared a 30-foot sloop with him for many years. Humphrey Rang had already done a postdoc with J. Murdoch Ritchie and I think he could see that I was floundering a bit. So he said, "Why don't you go to Yale?" I went, and I loved it. I stayed with Ritchie for two years (and learned to fly), and then on to Southampton, where Humphrey had become Chair, for four years. They have an Institute of Sound and Vibration Research, which was quite eminent. Those guys knew all about noise analysis—they had programs that would work out spectral densities. And then Humphrey went to St. George's (London) and I followed him. We were right into noise analysis and voltage jumps then. We got a grant to buy a PDP11 for an unbelievable £76 000.

MI: What is a PDP11?

DC: <Laughs, rummages behind chair.> The PDP8 and 11 were the minicomputers that preceded the PCs. That <holding up a disk, roughly two feet in diameter> is a PDP disk cartridge; it holds 2.2Mb, almost twice a floppy.

MI: But the fact that you were interested in statistics and random processes was really perfectly timed for the advent of studies on single receptors. What were you learning through noise analysis?

DC: Noise analysis will give you an estimate on the current that passes through a single ion channel when it's open. So we were learning what a single molecule was doing from noise analyses. Once you start thinking about single molecules some curious paradoxes arise: Imagine an antagonist bound to receptors and then you suddenly wash out all the free antagonist. The bound stuff will dissociate slowly and it will give you a simple exponential curve, an exponential decay, and the time constants of that decay ought to be one over the dissociation rate constant for that binding reaction (that was shown by A.V. Hill later at UCL, in 1909, ten years before Langmuir). Well I had read somewhere that one over the dissociation rate constant was the mean lifetime of the receptor–antagonist complex; this is the interpretation of the rate constant at the one-molecule level. So say the mean lifetime of the atropine–receptor complex is ten minutes. It is easy to imagine that the time

constant for loss of bound atropine gives you an average length of time from the moment of washout until the dissociation of the bound molecule. But there's a snag in this argument, because it's ten minutes from the moment of wash-off, on average, before the atropine comes off, but the complex had been at equilibrium, before you started the experimental wash-off. So all of those complexes that were present at zero-time when you wash out the antagonist have already been in existence for some time before wash-off. So I thought, in that case, the average time from zero for it to come off should only be a portion (intuitively, half) of the channel lifetime. I could not understand this at all. Donald Jenkinson, who had done his PhD with Bernard Katz, and I used to argue about it endlessly. Then I met Alan Hawkes in the senior Common Room here at UCL, and I said, "Look, I cannot understand why this time constant for wash-off should be the mean lifetime of the complex. It looks to me as if it should be shorter than the mean half-life of the complex." He pointed out to me that this "waiting time problem" is well-known in statistics. You wait longer for a bus if they come randomly than if they come at regular intervals.

MI: The waiting for atropine to dissociate …is like waiting for a bus?

DC: Well, if buses come along every ten minutes on the dot and you turn up randomly at the bus stop, it's fairly common sense that the average time you'll wait to catch the bus is five minutes. But the interesting thing is, if the buses arrive randomly, the average interval, over a long period of time, between buses is ten minutes—assuming you have as many buses in all as in the first example. The fact that you have to wait in the random case ten minutes and not five means that on average you arrive in a twenty-minute gap. And the reason for that is when the buses arrive at random, the intervals between them are all different, and in fact there will be more shorter-than-average intervals than there will be longer-than-average intervals, because of the shape of the exponential distribution. The important thing, though, is that intervals that are longer than average, though they are fewer in number, actually occupy a larger proportion of the time. And it's the proportion of the time they occupy that matters. Because long intervals occupy more time than short intervals, if you show up at random, you tend to turn up in a long interval—actually twice as long as average. And that's why you have to wait longer for the bus that comes at random. And that's why—this is incredible at first sight—if you equilibrate with atropine and say NOW I'm washing out, by saying NOW, you have selected for receptor complexes that are twice as long as average in duration. And true enough, after zero you only see half their life, but since the lifetime of those particular ones is twice the average, it all cancels out. And so it's the most beautiful thing.

At about this time, Bernard Katz published his papers about noise analysis. He supposed (correctly, as usual) that the noise he saw arose from random moment-to-moment fluctuations in the number of ion channels that were open. I had problems with the theory at first and while in Yale I wrote to Alan Hawkes. He wrote

out the theory in terms of matrices, so it was quite general and could be applied to any receptor mechanism at all. We began to write a paper about it, which started off being entirely about noise analysis. Anderson and Stevens had said that the time constant you get from noise analysis is the mean open time. But we found that in many of the examples we calculated, the time constants we got were longer, and at first we couldn't see why. We submitted a paper to *Proceedings of the Royal Society* and at that time, it was necessary to submit it through a Fellow, so we sent it to Bernard Katz, and he helped us see in physical terms why the time constant you get from noise analysis is not generally the mean channel open time. It turns out that the mechanism for channel opening was predicted to occur in little bursts, so you wouldn't get just one opening, you'd get two or more (random, geometrically distributed number) in quick succession. So, what you were seeing in noise analysis was the lifetime of this whole burst. Thanks to Katz's suggestion, this went in before the paper was published in 1977. Meanwhile, in 1976, Neher and Sakmann showed how to record single-channel currents, and we were dancing in the streets because here was sort of a synthesis of an interest in ion channels with one in statistics. Because when we're talking about single molecules, their nature is to behave randomly. The information comes in the form of probability distribution, which is the very nature of the data when you're dealing with single channels. This was a real application of statistics to nature, not just boring experimental errors. I first met Sakmann in 1979 at a conference. And to my surprise, he said he was very interested in my paper with Hawkes – we predicted that openings would come in bursts, and Sakmann thought that they could see them. So I immediately went to work with him to sort it out. If we had got the interpretation right, and it hasn't been proved wrong yet, by measuring this tendency of channel openings to occur in bursts, one is able to measure separately the ability of the agonist to bind to the resting receptor, and the ability of the receptor, once bound, to activate the receptor. In other words we had separated the affinity and the efficacy for the agonist.

MI: Do you find that mathematical, theoretical approaches tend to be overlooked because they are somewhat more demanding to follow?

DC: Not really; after all there is no other way to treat the interpretation of single channel data. The thirteen or so papers that I've written with Alan Hawkes get cited quite a lot, but nevertheless I suspect that most people haven't gone so far as to actually read them right through. It's not that difficult—it's all self-taught as far as I'm concerned. And there are young people in the lab now who are able to do it perfectly well. There's nothing impossible about it, but you need an incentive. To the extent that I can do it, it is because I spent a lot of my first five years in academia thinking about such problems, not writing papers. These days I would probably have been fired, because now you are not allowed time to think, you must just write. I fear this approach will do great harm to science unless we can get over the phase of mindless administrators (and academics) who place

emphasis on totally naïve numerical indices (actually the statistics of impact factors is rather interesting; they are essentially uncorrelated with citations, but one can't expect ones political masters to know enough statistics to appreciate that).

MI: And you're still doing the lab work that tests what you're writing out mathematically.

DC: Oh heavens yes. Mathematics is worth nothing if it does not represent reality. Well, I don't do the wet work myself these days, but I've got four, occasionally five folks in the lab. That is quite as many as I can handle, because I'm heavily involved in analyzing the data, and if they produce too much I can't keep up. I'm doing theory (with Hawkes of course who does the hard bits), and I'm writing the programs that are needed to analyze the data. It is hopeless to rely on commercial programs, which never do exactly what you want (and all too often don't tell you exactly what they *are* doing). At the moment I'm writing a paper that tests our new fitting methods by doing sets of 1000 fits to simulated data so we can see what the distributions of the estimates are, and so get a realistic idea of what we can and can't infer from analysis of experiments. I'm enjoying that a lot because its something I'm doing myself, rather than just keeping a distant eye on postdocs and tagging my name on their papers.

MI: Your Web site suggests that your interests spread beyond single ion channels?

DC: I do get worried about the poor public perception of science at the moment. I fear that much of that results not from their ignorance of science (as scientists often suggest) but from the tendency of scientists to exaggerate the importance of their own work (aided and abetted by journals like *Nature* and *Science*, which do much harm in my view). If the public does not believe us, it is largely our own fault. I suspect this has become much worse since the pressure has grown for universities to have commercial links. The first casualty of money is usually truth. Whenever I begin to wonder if I'm getting paranoid about this, the reality turns out to be worse, not better, than I thought (think of Enron).

MI: So your work continues on both fronts, theoretical and experimental. Are you still having fun?

DC: Oh yes. I'm just happy to have found something that I enjoy doing. Early on, I had this sort of great record of academic failure, and then I got into science. At that stage it was totally unthinkable that I would one day hold Schild's chair or get into the Royal Society (actually I still can't quite believe my luck). It's always seemed to me that there's a considerable virtue in failing young. I've known very bright young people for whom every slight setback was a disaster, and that makes them unhappy (and sometimes leave science altogether). With my background of failure, every slight success is a delightful surprise. That makes one much happier. ♥