VIDEO INTERVIEW TRANSCRIPT

Bakhle, Mick: transcript of a video interview (10-Aug-2016)

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Bakhle, Mick: transcript of a video interview (10-Aug-2016)*

Biography: Dr Yeshwant Shriharsh (Mick) Bakhle DPhil DSc (b. 1936) read chemistry, took chemical pharmacology as a supplementary subject, and went on to do his DPhil in the Department of Pharmacology at Oxford; in 1993 he received a DSc. After two post-doctoral years as a Fulbright Fellow at Yale, he joined the Department of Pharmacology at the Royal College of Surgeons in London in 1965, working with John Vane and was appointed Reader in Biochemical Pharmacology in 1980. After nearly 30 years at the Royal College of Surgeons, he moved to the National Heart and Lung Institute at Imperial College, where he is a Senior Research Fellow. For five years (2001-2006), he was a Senior Editor of the *British Journal of Pharmacology*, and became Press Editor in 2006.

[1]. STUDYING CHEMISTRY, BECOMING A PHARMACOLOGIST

I started to get involved in pharmacology because towards the end of the course I was doing in chemistry at Oxford, I couldn’t really get excited, I couldn’t see a purpose to what I was learning. I could appreciate the slick, new synthesis of this, that or the other. I could see that that chemical sleight of hand was really fun, but I didn’t see what was at the end of it. And in that last year you’re allowed to take a special subject, and there was a special subject in chemical pharmacology, which I knew something about because one of my predecessors at Corpus and, as it happened, in the Department of Pharmacology, was a chemist and had done this course, and so I knew a little bit about it. And it was a bit different from the biochemistry special subject, which most of the other chemists took. So I thought, ‘Well, let’s have a go of this.’ And I did. And it was interesting to me because I could see that this was chemistry, which was pointing at improving drugs that you could design or try to at least design drugs to carry out specific pharmacological actions because you’d had a natural compound, for instance, like atropine. So how can we get something which does the same job as atropine, but you make it in a test tube rather than growing it in a plant? That was really the basis of what it was, as far as I thought, so that was what I did. And I enjoyed it, the course, and rather importantly, it was one of I think two examinations I’ve ever enjoyed doing. I really enjoyed three hours writing about it. I used to hate exams, but that was wonderful, and I had a great time.

And as a result of that I did my Part 2 in the Pharmacology Department with H R Ing, who was the resident chemist in the Pharmacology Department in Oxford. And he had, you know, been involved with the whole idea of structure activity relationships from a very early time; 1930s, something like that, he’d started doing it. So that was my Part 2, and then I did a DPhil in the same Department, doing chemistry, trying to make simple analogues for digitoxin, digitalis. You know, the same idea is that you’ve got something which is essentially a herbal remedy, you have to grow foxglove plants and extract it, and you have to standardise it; quite a lot of fuss. If you can make a chemical which you can purify and produce, and you have the same effect, there was an end to what you were doing. And that was really how I got started and I sort of never went back to chemistry. But it’s always been good for me, I think, because it gives me - certainly in those days - it gave me an almost molecular view of pharmacology, because most of the pharmacologists in those times - that was say very early 1960s - were medically qualified or physiologists, who knew a lot about physiology, but they found it very difficult to grasp what is known as the mole concept, you know. The fact that grams of something doesn’t necessarily tell you the whole story. You want to know how many moles there are, because that’s the real way of finding out potencies.

* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 10 August 2016, in the School of History, Queen Mary University of London. Transcribed by Mrs Debra Gee, and edited by Professor Tilli Tansey and Dr Apostolos Zarros.
[2]. ANGIOTENSIN CONVERTING ENZYME INHIBITORS; SÉRGIO FERREIRA AND BRADYKININ

My major, or my only success, must be the work I did with the angiotensin converting enzyme inhibitors, because they have come all the way from experiments done in the lab to an effective and important therapeutic agent. There’s no doubt that cardiovascular medicine has benefitted enormously; people have [been] benefitting enormously from angiotensin converting enzyme inhibitors, because of their effect on hypertension. What these inhibitors do is they block angiotensin converting enzyme. Angiotensin converting enzyme is important because it is the essential step that converts an inactive product, which is angiotensin I, circulating in the body to the active product, which is angiotensin II, which raises your blood pressure and does other things. So if you block that enzyme, no matter how much angiotensin I is formed, it doesn’t have any effect because it’s an inactive product. And that essentially is what the inhibitors do. What’s interesting is that all the experts, and even most of the drug companies, did not believe that [an] angiotensin converting enzyme inhibitor would be effective in what we call “essential hypertension”. We don’t really know what causes the hypertension. But somebody actually did the experiment, and they showed that this stuff actually worked in a model of essential hypertension. That was it. They were off and running. And now of course you use angiotensin converting enzyme inhibitors for more than hypertension: congestive heart failure, protect kidneys if you are diabetic, and so forth. And I think it was the success of the converting enzyme inhibitors that allowed the companies - because they did most of the work - to go back to looking for an angiotensin receptor antagonist, which is now almost as popular as converting enzyme inhibitors as a treatment for hypertension.

So, I mean, I think the way in which the work went from the initial extract, I mean, Sérgio Ferreira brought this brown goo, which was a particular extract of a Brazilian snake venom. That same venom has an enzyme which makes bradykinin. When the snake bites you, it injects the venom in and half of the venom makes bradykinin in your blood, because it has kallikrein types of enzyme. And the sort of other half of the venom contains something which Sérgio called “bradykinin potentiating factor”. It was something which made bradykinin, which - generally speaking - doesn't last for long in blood, last longer. It potentiates the action of bradykinin. And that was what he brought over, and that is what we were going to have a look at, and eventually - because, you know, brown goos are not very nice to work with - we did have a look at it, and much to certainly my surprise, it inhibited angiotensin conversion as well as affecting bradykinin clearance inactivation. And this new activity was completely uncalled for, unpredicted, and so you know it was clear that Sérgio would have to do something, and in fact he went back and collaborated with a guy from Brookhaven in New Jersey - no, Long Island - and to isolate from this goo several specific peptides.

Sérgio had been working on this venom because of his bradykinin connections. His supervisor was a very famous Brazilian pharmacologist called Rocha e Silva, and Rocha e Silva had essentially discovered bradykinin. He was the first person to show that this happened, that you had bradykinin generation, that it was a peptide, a nonapeptide, I think they knew that. I don’t think he showed, I don’t know, he didn’t show the formula; he wasn’t able to sequence it, but he characterised bradykinin as one of the peptides that could be generated, and it could be generated in everybody by kallikrein which again was an everyday enzyme in blood which had itself had to be activated by usually an inflammatory cascade, inflammatory stimulus. So bradykinin, it’s interesting, bradykinin lowers your blood pressure, and it turns out that it’s the same enzyme angiotensin converting enzyme, and it happens to be the same enzyme that destroys bradykinin.

[3]. ANGIOTENSIN CONVERTING ENZYME; EFFECTIVE THERAPY FOR ESSENTIAL HYPERTENSION

Now I think it’s interesting that it’s the same enzyme, angiotensin converting enzyme, that inactivates bradykinin and that activates angiotensin. So the physiological significance of that is that bradykinin lowers your blood pressure, and angiotensin II raises your blood pressure. So this one enzyme inactivates a vasodepressor and activates a vasopressor. So this enzyme is giving you two strokes with the same action and they are pressor outcomes. But what we didn’t know until we did, if you like, the experiments in essential
hypertensives, was that the blood pressure in an essential hypertensive is actually sensitive to the level of angiotensin in the body, because up until now we had been controlling high blood pressure really by playing around with noradrenaline and the sympathetic nervous system. And nobody imagined that this would happen in essential hypertensives. And when it did, well I mean it really was so effective, it blew a great big hole, and there’s been so many people I think now, had a major, major, major change in their therapy and effective. It was great. So I suppose that is, seeing it go all the way from a brown goo into a really very successful treatment, is clearly something which I really wanted to achieve and, I didn’t achieve that myself obviously, but I think we started, we started the process so that it was more or less impossible not to do the rest of the experiments. But there was a lot of disbelief amongst the clinicians and amongst the drug companies, my goodness me, that it would ever be worthwhile, you know? And you could see the strength of their argument.

[4]. SIR JOHN VANE: ANGIOTENSIN CONVERTING ENZYME AND ASPIRIN

It’s, I think, interesting that certainly for John Vane the two areas in which he’s made the greatest contribution, the angiotensin converting enzyme inhibitors, which was really done under his influence, and his continuous encouragement. I mean the fact that he didn’t actually do very many of the experiments himself is irrelevant. The point is he was up there telling us to do it, ‘Go on, do it, do it, do it!’ And in fact he fought for the compound in Squibb when he was consulting there. And he kept on saying, ‘You must commercialise this, you must commercialise it, you must commercialise it,’ and they were very reluctant. Anyway, both in the angiotensin converting enzyme and in fact the prostaglandin business and aspirin, at the time he made his, if you like, his critical discoveries, his critical experiments, he was an incomer. He’d had no background, he’d absolutely no background in the renin angiotensin system. There were people in the Cleveland Clinic who had been working with the renin angiotensin system for years and years and years, and this guy from England with you know a Brazilian and venom goo comes in and says, ‘Hey guys, I’ve got this wonderful new idea and it’s going…’ I’m not surprised people didn’t believe him, because he had no background. You would have the same reaction now if somebody comes in off the street, ‘I’ve got this great idea!’ ‘What have you been doing the last five years?’ ‘Oh, I’ve been doing something else.’ And the same thing with aspirin. I mean he got involved with the whole of the aspirin story, not because he was interested in it really, in prostaglandins, or had done any previous work on prostaglandins, but because Priscilla Piper came from Harry Collier’s lab to do a PhD on a project, which Harry Collier had essentially invented. And John said, ‘Oh yes, I think we can have a look at that problem using my cascade, bioassay technique.’ So Priscilla came over and she did the experiments.

Priscilla was doing those experiments looking at anaphylaxis and the effects of aspirin on anaphylaxis because, if you look at Harry Collier’s work, he was pretty convinced that the effect of aspirin on a guinea pig in anaphylaxis - which was known then to be beneficial - was connected with bradykinin. He really, I think, believed that it was either bradykinin antagonist [that] was aspirin, or aspirin somehow blocked the inhibition - blocked the formation - of bradykinin. And it was, if you like, typical of the way science works out that the very first figure in the classic Piper and Vane paper, which dealt with products of guinea pig anaphylaxis, showed quite clearly that although there was all sorts of stuff coming out of lung during anaphylaxis, none of it was bradykinin. So, sadly the very first result blew a hole in Harry Collier’s theory.

And at the back of that there was a set of results which showed that aspirin and/or indomethacin prevented the release of all these things from an anaphylactic lung. But at that stage, at that paper, nobody knew how it happened. They knew it happened but they didn’t have any idea how it happened. And so the point is John Vane had absolutely no idea about prostaglandin; he knew something about bradykinin, and he, what he was I think, attracted him was this new material, which appeared to come out of the guinea pig lung which he called “RCS” [rabbit aorta contracting substance], which didn’t behave like anything we’d seen before, and that had been apparently switched off if you treated the lung with aspirin or with indomethacin. It took him two years to actually do the experiment, the critical experiment.

John Vane came in and saw me one day and said, to see me one day in the lab, and he said, ‘Mick, is there any reason why aspirin should interfere with the metabolism of arachidonic acid?’ We knew arachidonic
acid was the precursor to the prostaglandins. He said, ‘Is there any reason why it should interfere with that metabolism?’ And I said, ‘No, there’s no reason.’ I mean, and that’s right, there is no reason. You’d expect the best way of interfering with the metabolism of arachidonic acid is to have an analogue of arachidonic acid, another fatty acid with a slightly the wrong stereochemistry, which would block up everything. Not something like aspirin, which is a short, stubby compound, acetylsalicylic acid; very small compound. Nothing like the long, wobbly thing which arachidonic acid is like. And you know there was no reason. But you see he went ahead and did the unreasonable experiment because he had a feeling, and bingo! That’s it. Do the unreasonable experiment sometimes, and it works.

[5]. **PERFUSED LUNGS**

I got involved with a perfused lung as a model system to study, really, the metabolism of endogenous compound within the pulmonary circulation. And in fact it went out all sorts of different ways, and I think that demonstration of the pulmonary endothelium as an active metabolic organ and not just a lining, an anti-platelet aggregatory lining to the vasculature. That was the beginning, I think, of people’s interest in the endothelium as a very active physiologically significant control organ.

I was involved in the perfused lung and one of the ways that it developed was to look at the perfused lung from different species, which is fairly, in a sense, boring; should have been fairly boring. I remember my supervisor saying that species differences was the last resort of a desperate man. And I remember that. I really did sympathise and I agreed with him that, you know, if that was the best thing you could say about your results, it’s not very much. But I thought that we had done most of our work with rat and guinea pig lung, because they are common things. But being at the [Royal] College of Surgeons, we had slightly improved access to bits of human lung, and I thought, ‘Nobody’s ever done this, let’s have a go.’ And so we used to use bits of human lung, perfuse it through the pulmonary vessels and see how things came, disappeared, what happened to it, and so on, and so forth. And in fact it turned out to be really quite interesting. One of the things which was very interesting was the fact that the guinea pig lung behaved towards arachidonic acid really quite differently compared with the human and rat lung. And in fact, as it happened, if John Vane had done, and Priscilla Piper had done, their experiments with anaphylactic human or rat lung, they would never have seen this mysterious RCS business, which was the critical thing which really sparked John’s interest in the whole of the prostaglandin business. That mysterious RCS business is probably a mixture of thromboxane and something called “hydroperoxide, PGH.”. Now, I don’t know why, but the human lung and the rat lung hardly make any of it at all, and you can pour all sorts of, amounts of, arachidonic acid through these isolated lungs and you hardly get anything coming out in those terms. Then, when they use a rat lung or a guinea pig lung or a hamster lung or a human lung, the answers are somewhat different. Sometimes the rat is closer to the human and sometimes the guinea pig is closer to the human. And so in one way it is important, but because we are finally - most of us - are finally interested in what happens in man, in humans, and we’re not that much interested in guinea pig and rat health as much as we’re interested in human health.

[6]. **BRITISH PHARMACOLOGICAL SOCIETY**

The BPS [British Pharmacological Society] is something that, in a sense, I’ve grown up with, because it was considered to be absolutely a part of being a pharmacologist in all the Departments I’ve ever been in. And so it was, you know, not a matter of if, but when would you become a Member. When would you give your first, in those days you had to give at least one communication to become a Member, and when would you do that? And in the Department in the [Royal] College of Surgeons it was a big event, because everybody who was up to give a paper would be drilled and they would have to give a rehearsal and people would ask the most unpleasant questions, purposely, and say, ‘Okay, you’ve got to be ready for something way out from nowhere that you’ve never thought about before, and you’ve got to be able to handle it somehow.’

But what you mustn’t do is to pretend it doesn’t matter. If somebody asks you a question you have to treat them seriously, even though you have to say, ‘You know, that’s a nice question. I wish I knew the answer. I just have no idea.’ You can’t say, ‘Oh, it doesn’t matter,’ because it’s rude and it’s not scientific.
So the rehearsals, and the rehearsals were an absolutely important, intrinsic part of the whole business. But training in pharmacology was not just doing the experiment, it was communication. You had to communicate. You had to tell people about your results in an understandable way, and then handle the questions in a sensible way. Too often I felt other people would react almost with hostility to a question. You asked them a question and they seemed to believe it had some ulterior motive, when certainly for me, very often the matter was sheer ignorance of the subject.

In the Department of the [Royal] College of Surgeons we had this very strong tradition of having foreign post-docs, and you know, Sérgio Ferreira, Salvador Moncada, Arnold Herman, oh and Americans also of course. But none of them were familiar with the particular experience of giving a paper to the Pharm Soc. And of course for those whose native tongue was not English, this was a double problem. And so we used to rehearse not just what you said, but how you said it, all that sort of stuff. It was a very serious, it was a very serious undertaking, and a lot of time and effort and preparation went into producing a communication for the BPS. And later on, of course, when you were a little bit better at it, you would start asking questions about other people, you know, about how they were doing their work, what was happening, what would happen if you hadn’t, have you tried this? Have you tried the other? And so it was, I remember Sérgio Ferreira was very much involved in going to meetings, giving papers, participating in the questions, and of course in the bar afterwards, where so much good pharmacology is done and planned and discussed. This was the place that BPS meetings were immensely valuable in talking about problems, getting ideas from people, and everybody would put their tuppencworth in, and you did it. And it was an important part of your science. It was an important part of your science. It wasn’t an add-on, it was an important part of the science that you were doing.

[7]. **SURVEYS OF PHARMACOLOGY**

When I came back from Yale after two years, I did a year, spent a year at Oxford before I went down to the [Royal] College of Surgeons in London. And in that year, Bill Paton came, who was a Professor at Oxford then, came up to me and said, ‘Look, there’s this survey,’ a survey it was called in those days, “A Survey of Pharmacology”. I said, ‘Well, what’s this Survey of Pharmacology?’ And he said, ‘Well, what we’re trying to do is get some numbers, get some data about who is running pharmacology courses, how many students do they have, what Faculty do they have, where do the students go, what courses are there? Any information, because there were people who are saying, ‘Well, do we need a pharmacology degree? A BSc in pharmacology as distinct from anything else? And how many degrees are there, who is offering them?’” There was a time when I think only two universities offered BSc’s in pharmacology. And now I don’t know how many there are. But there was no hard data in those days, and Bill Paton, probably by himself and maybe with some help, anyway somebody had constructed a complete four or five page, pages of boxes to fill in, questions to ask and things like that. Who are the staff? What are their qualifications? How many students do you have? What do you teach them? Do you know where they go? And so on and so forth. And so we circulated, or these had been circulated to all the Pharmacology Departments.

All the Pharmacology Departments, the university Pharmacology Departments, and to the drug company Pharmacology Departments, as far as we could get them, we knew about them. Essentially we would identify a BPS Member say in a drug company Department and send it to him and say, ‘Could you make sure everybody fills this in?’ And it wasn’t commercially sensitive, but trying to find out, because it was important to say, to be able to say that we are preparing people for a real job which actually exists, and that when they get into that job, their employers use them and their skills without having to retrain them completely, and all of that. So it’s a matter of producing something that was capable of use straight away. Now all that had been designed and Bill Paton said, ‘Look, I’ve got all the answers in, but I need somebody to go through them and extract the numbers and try to collate this and that.’ And he said, ‘Would you like to do it?’ And you know, when you’re made an offer like that by Bill Paton, there’s only one answer. So I did it and I, you know, extracted all the numbers and put them together in other sorts of tables, tried to make some sense out of this or make some correlations with A and B, and Bill Paton looked at that and said, ‘[mumble mumble],’ and very sensibly he wrote most of the words, because he knew in a sense what he was trying,
not to prove, but what he really wanted to find out. Since I hadn’t been in at the beginning I couldn’t really know what he was trying to ask.

He wrote the paper because he knew the questions he wanted to ask. Of course we didn’t know at that time what the answers would be. But it was the first collection of data, numbers, about what was happening in pharmacology. And I think it was, I think the Society found it interesting, and of course Departments must have used it to their own benefit, obviously, to argue one or the other cases, whatever they wanted to argue.

The second one, which followed some years later, again was generated, the need for it was generated within the BPS Executive Committee, and Straughan was the lead on this because again he was, I think at that time, a Member of the Committee, and he said, ‘Alright, you go out there and get it organised.’ And he said, ‘Well, you know, Mick, you did it last time, you’d better come on board because then we know we can use your experience with it,’ because Bill Paton then didn’t want to have any more to do with it. I think he might in fact have been, he got quite ill towards the end, and he didn’t want to do it anyway. And so we did that, and then there were, I think, another one later on, and there was a final one, which was done by a commercial firm. Again, with the same purpose, to find out what was happening. And you know the big changes, which were very apparent of course, was the fact that in the very first one many of the people, the Faculty, in Pharmacology Departments were medically-qualified. And even by the time we can to the second one and the third one, that was falling off very, very rapidly, and they were nearly all science graduates. So it was showing that people were coming into pharmacology from science rather than only from medicine, which had previously been a major, major entry point. You could argue that pharmacology was becoming more of a science and less of a clinical speciality. And it was perhaps becoming a bit more divorced from its end product. But you can’t help that with science, because science is something that you deal in clean, carefully designed and defined limits. That’s what the scientific method says: you must do these experiments in a way which is interpretable.

8. THOUGHTS ON PHARMACOLOGY: PURE AND DIRTY SCIENCE

And so you have this bizarre thing, I think particularly perhaps, well certainly in pharmacology, is you have a semi-schizophrenia between the people who are anxious to do the real science, I mean, the molecular structure of the receptor and the mathematics of the interactions, and the genetics and all things, all that sort of stuff. And that’s all high science. But at the end of the day you still have to say either, ‘What disease is this going to help us with?’ or ‘If I give it to somebody, are they going to go blue or are they going to fall over or are they going to be fine?’ And, in a way, if I’m interested in what’s going to happen in the person, I don’t care what happens, almost don’t care what happens, to NFkB [nuclear factor kappa B] or some intracellular kinase. Is it going to make him better? So you have this pull in two different, you have to be a schizophrenic to match both of those things somehow together, and particularly, I think particularly in pharmacology, or much closer, much closer to having always to do the dirty experiment, because the system you are finally interested in is a dirty system, it’s the whole human body. Whereas in physiology it’s a little bit cleaner, because for one thing - generally speaking - physiology is concerned with healthy people. In pharmacology you have the extra layer of dirt, which is pathology. Nobody cares really about it - as they used to say - nobody cares about the car until it goes wrong. And as far as we’re concerned, you need to have the wrong car; if there isn’t a disease, most people aren’t interested. But of course it should be the case that they are, but scientifically, of course, you are because it’s all new knowledge. But finally, finally, at the end of the day, you are always driven to say what difference does it make to a pathology, somewhere or another or not. That’s the problem. It is a dirty science.

9. EDITING THE BRITISH JOURNAL OF PHARMACOLOGY

I think it was 2001 when I got a letter saying, from the Editor-in-Chief from the BJP, saying, ‘Would I become a Senior Editor?’, which rather surprised me, because I had not ever thought of myself as that. And it all turned out that they were rejigging the organisation of the journal, and so the Editor-in-Chief was going to have four or five Senior Editors to help him with the journal. And the Senior Editor’s task really is to act as a sort of filter and to, you know, the real no-hopers we just send back and say, ‘I’m sorry, maybe you
should try somewhere else,’ and then the ones where we say, ‘Okay, let’s try these for refereeing,’ you then allocate them to different, suitable Editors and then the reports come back, and you look at the reports and you make some decision, because it’s a Senior Editor’s decision: go ahead, revision or not. And so that was something that introduced me to the idea that you saw a lot of, we saw a lot of papers. Because we didn’t, Senior Editors didn’t review them, they didn’t referee the papers, we weren’t in that sense really interested in the data, which we expected the referees and the Editors to check. But we were interested, if you like, in how did it look? How did it appear? Did it, could you understand what was going on? It was not the data so much but how it was being communicated that seemed to me to be the Senior Editor’s task: to improve the communication rather than, if you like, improve the data. That, of course, at times did overlap sometimes, you know. You said every so often you would see something and you would say, ‘I’m sorry, you can’t possibly say that.’

Sometimes you had to say, ‘You can’t possibly say that from that set of data, you know? That’s going too far.’ I’m now a Press Editor, and one of the things that I talk about is how to prepare manuscripts, and this really trying to ensure, if you like, clarity, make sure. Some of it is also about what the Americans call ‘presentation’, which is very important, because nowadays all the papers are identified by somebody who is looking in PubMed. And, actually, PubMed is a very democratic process, because the paper that’s in a journal with an impact factor of 1.5 is next door to a Nature paper and so there is no filter on the impact factor, no if you like, scientific snobbery involved. ‘If it’s not in J. Physiol, I don’t want to read it, or I don’t believe it.’ No, no, you see it all there. And the first thing you see in the entries is the title, and I say, ‘You have to make a good title.’ You can’t, if you have an uninteresting title people are going to pass over your paper and go to the next one, because there are going to be, when you put up your key words, there will be a minimum of 200 papers which meet, a minimum of 200, probably more like 20,000. But you know, so you’ve got to catch the attention of the reader, because you want them to read your paper and to see your conclusions about this subject, if you like, at the expense of somebody else. The thing is you have to do that, and that’s the right way, because you want to present it so that people read your results. That’s what publication is about, that’s what communication is about, and that communication is absolutely what happened.

And the same thing I say when I go sometimes to Brazil to talk about this stuff, I say, ‘Look, good science is 50% good results and 50% communication, because if you don’t manage to communicate your results, they are lost.’ The first person, the first thing that happens when you start things is your supervisor says, ‘Go and read this paper. Go and read this paper.’ I say this to them, ‘Look, could you guess from this title what it’s about? What do you think the main message of the paper is?’ And the main message of that paper is something which is nowadays absolutely critical. ‘It says that a therapy that worked in the young rat doesn’t work in the old rat.’ And I go on to rant to them about geriatrics as a subspecialty that people should do, because that’s going to be our problems. I said, ‘For me, it is absolutely the problem.’ [Laughs], I said, ‘So you want to have something in that title that reflects really the main message, and there’s only one message you can go for in the title, so you have to take one message only, put that in the title and make it represent the whole.’ I said, ‘The other thing, of course, is that there is one thing in this title that will make me not actually even read the title.’ And I said, ‘Have a look and tell me.’ And then I say, ‘Okay, you’ve probably guessed it; “minor effects”. Who is going to spend their time reading about minor effects?’ I know what they mean, they mean that in the old rat it doesn’t work. But you can’t say it like that, because it switches people off. I said, ‘This is a suicide thing.’ And I said, ‘You have to be, you don’t have to write a newspaper headline, and it must be true. You can’t say more than you show in the paper. But you have to make it something that’s going to catch somebody’s eye. Catch your eye, catch somebody else’s eye, as they scan down that page of 20 titles. Oh, what’s that? Even if you think, ‘I don’t believe that.’ Never mind. You’ve got them. And, with a bit of luck, they will read your abstract.’ And I talk to them about the abstract, why that’s important. But these two things: the title and the abstract, are almost more important than the data that you put into the paper, because without that nobody’s going to go into the paper, because there are so many other offerings on the same topic. They’re not going to do it, they just don’t have the time.
[10]. PHARMACOLOGY IN THE FUTURE: LEVELS OF COMPLEXITY

I find it very difficult to predict or think of a future and, because in a sense, I have now been convinced that scientific advances are good for science, but they may not be good for pharmacology in terms of what I think is the purpose of pharmacology, i.e. drug discovery. I say this because I have a feeling that a lot of the present-day - not everybody agrees with - lack of new chemical entities, is because drug companies have molecularised their drug discovery programmes, and I accept the fact that it's the only way in which you can screen 5,000 compounds in 55 minutes, is with something like an array, a DNA or RNA array, whatever sort of thing it is.

Unfortunately, it appears right now that good pharmacological science, good science, doesn’t always survive being moved up one layer of complexity, that is to say from an isolated receptor into just say the whole cell. And, of course, when you start going from a cell to a congregation of cells like a lump of tissue, that is something else, and then, of course, you go up into something slightly bigger like maybe an organised organ and then and then and then... But all these layers, all these layers of complexities, comes back to what I call pharmacology being a dirty science. We have finally to do it in a very complicated environment, and the cleanest, best, nicest, science is true sometimes only in that environment. It doesn’t mean it doesn’t happen in a bigger environment. It just means it gets overtaken by all the other stuff that is going on. It’s like you can hear it in the single cell, put it along with the other and it gets drowned out; you can’t hear the message because it gets lost. And so the big advance - no doubt - in recent years has been the whole human genome project and the molecular biology which allows you to do some beautiful science, really good science. But people and companies bought into this, the idea that you give me the gene and I’ll give you the drug. And, in fact, all of our diseases - most of our diseases - we'll be able to find genes which are relevant to them, and therefore you know it'll all be done. Well, it just hasn’t happened.

I mean, this is the difficulty I find myself in is that the science is so good, but the outcome, it’s difficult to see the outcome being as good as the science, and I don’t know why except this problem of complexity, that we haven’t, I mean people now invent stuff called “systems biology”, as far as I know, it is trying to reproduce obviously on a computer, the complexity that we observe in a set of cells, whole organ, tissue, whatever it might be. But I really don’t know how effective that can be. I plain don’t know. It’s not a value judgement, it’s ignorance. It would seem to me that the forward march of science has to be not the way that we have been going, which has been a reductionist, because that’s the way the cleanest science gets done, you know, a single bodied problem. It’s great you can solve that; two or three bodies, you’re lost, even with mathematics quantum mechanics you can’t do it. Even with big computers, it just doesn’t work. So we have to develop science in a way that allows us to reproduce the complexities of the real tissue and the real body. And I don’t know whether those complexities are reasonably approachable even by computing techniques when we can reproduce them to a great extent by, you know, whole organ, whole animal, whatever it is, experiments.

[11]. DRUG SAFETY, PUBLIC EXPECTATIONS AND MODELLING

The way I think science will have to go is to somehow produce models which are complex enough and which, for you to be able to use data that you have generated in your nice, clean scientific experiments in the right way, and with some hopes of success. But finally, finally, it’s going to come down to putting it into people and seeing what happens, and there are going to be inevitably things like Northwick Park, it’s happened again in the French, one of the French trials, there was something like that. It’s not people being incompetent or looking for profit and not caring, because they all know what the price is. They know that the people who did the thalidomide for instance, they went bankrupt, they couldn’t do with it. The fact that thalidomide has now come back in a different form, the famous phrase is “repurposing” I believe, is immaterial. The point is that at the time nobody knew about the effects of thalidomide, because nobody had done the experiment which actually demonstrated, which you can, you could, there are animal experiments, if you do them, which will show you the totality. But they weren’t on the schedule, nobody had thought about them, they weren’t done, and we got thalidomide. Same thing with Northwick Park, nobody had thought this would happen, because they thought they’d done all the right, they had all the roles
which were asked of them, they did. If you do it in a slightly different way, because you know it’s going to happen, now you keep changing the variables in the model, until you reproduce what happens in man, then you can show there is a model system to check that. And now of course everybody who is in that field, all the companies in that field, are using one that NIBSC [National Institute for Biological Standards and Control] developed, that assay system is now being used by them.

So I don’t know how science is going to be able to, in a sense, de-reduce itself, no longer do the reductionist, which was necessary, but now complex, make it more complex in a modelling system, so it gets something. I’m sure that there will be computer models for this or that, but finally it will come down to putting it into a whole animal, and putting it into whole people, and seeing what happens.

[END OF TRANSCRIPT]

Further related resources:


