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VIDEO INTERVIEW TRANSCRIPT

Marsden, Charles: transcript of a video interview (19-Apr-2016)

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Marsden, Charles: transcript of a video interview (19-Apr-2016)*

Biography: Professor Charles Marsden PhD DSc HonFBPhS (b. 1943) read zoology at the University of London before going to Southampton University where he obtained an MSc in biochemical pharmacology (1967), a PhD in invertebrate neuropharmacology (1969) and a DSc in 1986. Following his PhD, he went to the University of Bergen (Norway) for three years (1969-1972) before going to the Institute of Neurology, London, to work with Professor Gerald Curzon. In 1978 he moved to the Department of Physiology and Pharmacology at the University of Nottingham, where in 1981 he obtained a Wellcome Trust Senior Lectureship, and subsequently a Professorship in Neuropharmacology (1986). From 2002 to 2008 he was Co-Director of the Institute of Neuroscience at Nottingham. During this period he was President of the British Association of Psychopharmacology (BAP; 2000-2002) and of the Serotonin Club (2008). He was awarded the J. R. Vane Medal by the British Pharmacological Society (BPS; 2002) for his contribution to neuropharmacology. In 2012 he was made an Honorary Member of the Serotonin Club, and in 2013 was given a Life Time Achievement Award by the BAP. In 2014 he was made an Honorary Fellow of the BPS (HonFBPhS).

[1]. A CAMBRIDGE CHILDHOOD

Well another sort of interesting aspect to my childhood was the fact that my mother was a psychiatric social worker and we lived, well I was born in Cambridge, and, we lived in Cambridge because the place where she started her psychiatric social work was the London School of Economics and that was, that moved from London to Cambridge during the War, and I was born in 1943. And having got her qualification she worked at Fulbourn Mental Hospital, which was a place that I visited quite often and there were two things that struck me: one was the strange behaviour of the people that were there and who, the patients, and my mother used to try and explain that they weren't well. And quite often she used to bring some home and they would help us plant potatoes and things like that, and stay the night and have extraordinary tales to tell at breakfast time about whom they'd met in the night and so forth, the Queen and such like, total fantasies of course. And then it occurred to me that there was some link I suppose, in later years I realised there was a link with what I'd experienced as a child and these people and the problems that seemed to be increasing around the world, particularly in relation to depression and mental health.

Yes, I mean in later life I became more interested in mental health and in those, at that time, I began to make the contact, the sort of contact between what I had experienced as a child and also the, my interest in mental health. But one of the most striking things that I experienced as a young boy was when my mother took me to Fulbourn Mental Hospital in the late '40s, there was a big, big sort of lion's cage in the garden where the patients were allowed to be. They were enclosed, the seriously ill patients. And then of course in the early '50s the drugs arrived and that completely disappeared in a matter of, I don't know, two or three years, that had gone, and there was a new director called David Clark, who had a much more open approach to treatment. And that, I suppose, was one of the most striking things that I observed: that extraordinary relationship between the introduction of successful drugs and the change in the life of the patients.

* Interview conducted by Professor Tilli Tansey, for the History of Modern Biomedicine Research Group, 19 April 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]. BIOLOGY AT SCHOOL AND BECOMING A SCIENTIST

Yes, why did I become interested in science? Well, one reason I think was I'd always been interested in biology from quite a young age, and even in school I pursued biological interests, like we were able to get support to have an apiary purchased so we actually went and bought a hive, two hives, got the bees, and then we used to sell the honey to the other students. So that was a sort of a long-term interest in biology, biology and animals and how they behave and so on. And then I went to university and I read zoology after doing my A levels at the Cambridge Tech, which was an excellent place to do them at that time because a lot of the staff were extremely able. Most of them had links with Cambridge University and the quality of the teaching was outstanding. So that enhanced my interest in science, being well-taught. And I think being well-taught is very important, and being enthused by being well-taught. And then I went to read zoology in London and I enjoyed that. I also, I enjoyed, I began to become interested in the brain, because that was obviously part of the course. There wasn't a lot on the brain, very, very little in fact. I mean the great interest at that time was the work of Crick and co. in terms of the double helix, for which they'd only recently got the Nobel Prize.

And after doing my degree in zoology, my plan was to become an ecologist. I wanted to study animals in their own habitats and one of my great wishes, from quite an early age actually, even before this, was I used to be, there used to be wonderful photographs in the newspapers of plagues of locusts scavenging the environment. And I thought a great thing to do would be to control those. So that was sort of another aspect. But I got a place in Durham to do the sort of work that I wanted to do at Durham University, but then I was going home, my parents at this time they lived in Saffron Walden in Essex, and I was going home and I was reading an article on the train which was all about fluorescence histochemistry and the amine[rgic] neurons in the brain. And for some reason that really inspired me, so I decided to change tack. I didn't go to Durham, I went to Southampton. I did a master's degree in biochemical pharmacology and then stayed on to do a PhD. And, gradually, I progressed from being a potential zoologist into becoming, basically, a neuropharmacologist/neuroscientist.

[3]. ELECTROCHEMICAL DETECTION OF NEUROTRANSMITTERS

I think probably the major step was the ability, my ability to be able to bring back from the States, the electrochemical detection techniques, which ultimately led to the whole development of successful microdialysis and the ability to measure transmitter release in the brain of, not just anaesthetised animals, but also freely moving animals, so you could link transmitter function to behaviour. And of course that same technique has been applied to human work as well and has been used in human brain. So I think that is, in a way, was a major step that I made in terms of not just developing the techniques, but in the later application.

How did I get to get my hands on these techniques? Well, that's quite an interesting story because it began by Ralph Adams publishing a short letter in *Nature*, which I read, describing his idea that it would be possible to use very small probes in the brain to measure transmitter release by being able to monitor their electrochemical behaviour. And I was intrigued by this, so I wrote to him and he happened to be in Europe at the time, because he was on sabbatical. He said he would like to come and meet up with me and we met in a wine bar just off Queen Square when it was just at the time when wine bars began to exist. And I was going to a meeting in America later that year, in Wisconsin, and we arranged that I would go to Kansas, where he was based, and we would try and see if we could use such probes. And I went first, I went to Wisconsin to the meeting and then went to Chicago, where I met up with a friend, because I was giving a talk at Loyola University. He said he would drive me down to Kansas because he too wanted to meet Ralph Adams, who was a really eminent electrochemist with broad ideas and views.

And, so, we drove down and we were about half way there and it's the only time in my life when I've been stopped and told by the police to get out of the car and put my hands on the roof and not to move. And the reason for all this was that we'd been going at 58 mph rather than 55 mph. So we went on to Kansas and we got there and we did an initial experiment, which to our real excitement when we gave para-

chloramphetamine, which is a drug that releases 5-HT [5-hydroxytryptamine; serotonin], the signal that we were recording increased, indicating that we might be measuring an increased release of 5-HT. So I brought that data back with me to the UK and was able to persuade the MRC [Medical Research Council] to give me funding to go back to the States and see if we could establish this method. We had eight weeks to do it in, and we achieved that.

[4]. DOPAMINERGIC SNAIL NEURONS

Yes, so, of course, you see if you're a research scientist you have so many satisfying events in your life in terms of your work, and I had a very early one. It was while I was doing my PhD. One of the problems with trying to identify dopamine cells in the mollusc and also in other invertebrates, nobody had ever really found a big dopamine nerve cell, a big cell that contained dopamine that they could use to stick an electrode in and measure responses from. It was easy to find big cells that contained serotonin (or 5-HT), but not dopamine. So I always thought this was, I'd really like to find a big dopamine cell, and by chance it did happen for me because there was another student who was interested in haemoglobin in snail brains and she had got or bought on funding 500 *Planorbis corneus* snails, pond snails. And I agreed, together with somebody else, to help her dissect them or collect the fluid that contained the haemoglobin. And in exchange I had a few of these snails. And I immediately took the snails and did the fluorescence histochemistry to see whether I could identify dopamine in any of the large nerve cells, and there was one clear as anything and quite large enough to stick an electrode in. And this has been widely used for such work since then.

[5]. ANIMAL MODELS OF BRAIN FUNCTION

My sort of interest evolved during the course of my career, and I became more and more interested in behaviour, particularly how early development might alter behaviour. And it was with a really, a very productive collaboration with Trevor Robbins at Cambridge that we began to work on the isolation-reared rat, and that is a very simple model that involves either rearing rats in groups of five from when they're weaned, and they are socially reared rats, and rats are social animals. Or you have them individually housed and those are the isolation-reared rats. There's nothing else, nothing is different. They are all in the same room together. What they cannot, what the isolates cannot do, is touch other rats. And that simple procedure within a period of four to six weeks produces long-lasting, well actually, irrevocable changes to the structure and organisation of the brain to their behaviour, their transmitter function, and it gives a sort of insight into how social factors and environmental factors can have profound influence on the development of the brain that, in the long-term, may lead to adult mental health issues.

The majority of my work has been on experimental animals and, in particular, the rat. In later years the mouse became more important because of the development of transgenic models of various receptor systems that I was interested in. And these models have been very important in improving our understanding of how the brain works. I think there is a real problem when you talk about animal research and trying to model a specific disease, so I think it is rather difficult to talk about a rat model of depression. And that is why I have really concentrated on models such as the isolation-reared rat where what we're trying to do is not specifically model a disease, but to try and understand the events that may occur within the brain when the brain is subjected to environmental challenges. And you only have to think of the terrible damage done to the Romanian orphans in the studies from the Institute of Psychiatry in London, to see that there is a parallel between what we see in the isolation-reared rat and what is seen in the brains of those orphans. So I think that you can validly say that there is real information obtained from the experimental animal, but I think you have to be careful in your interpretation and certainly do not try and overemphasize the translational value of the information in terms of specific diseases.

[6]. TEACHING; THE UNIVERSITY OF NOTTINGHAM; THE VALUE OF A SCIENTIFIC TRAINING

While research has been very much my driving sort of force in my career, I also would not have enjoyed it

as much if I hadn't had contact with students, and both teaching and research training. And I think it's very important that we do put the effort into training young researchers. I know that some people think that it's, you know, if you're really interested in research it is not the most appropriate way to spend your time, because you've got to teach them and train them and so forth. But I've really enjoyed the time that I have spent with the students, both undergraduate and postgraduate. At Nottingham we actually have a scheme whereby all our undergraduate medical students have to do a three month research project. And it's surprising how much highly motived students can get done in a short time and how effective they can be. So I think training is very, a very important role for the scientist. Training others to take on the ideas that hopefully you develop during your research. I don't think you can expect all your PhD students to become world famous scientists. There are many other jobs available for people who have PhDs who, jobs that will benefit from their training and research expertise and their ability to be analytical and think through issues carefully and constructively.

[7]. SCIENTIFIC SOCIETIES: BRITISH ASSOCIATION FOR PSYCHOPHARMACOLOGY

Another important sort of feature of my career has been my involvement with various organisations. I've been involved with the British Pharmacological Society; the 'International Club for Serotonin Research' I think it's called today; and also I was involved in the establishment in the Monitoring of Molecules in Neuroscience grouping, which is now an international group. But probably my most important involvement was with the BAP, the British Association for Psychopharmacology, of which I had almost all, I think, the Council jobs that were in existence in my time when I ended up as the President. And after coming off Council, I was involved with the Governance Panel as well. I was the Chairman of that for a couple or three years, the role of which is to make sure that the Association is responding to the needs of its Members as well as observing the Laws of the Association. I think such groupings of scientists are very important because they do allow crosstalk between different types of individuals. So with the British Association of Psychopharmacology there are both clinical psychiatrists and basic scientists, and their meetings give a great opportunity for a good exchange of views and ideas which can improve the translational value of the research done by both sides. And I think that's one of the great roles of any organisation, I think, to allow good crosstalk. That can lead to new research ideas, new research projects.

[8]. BRAIN, BEHAVIOUR AND THE PITFALLS OF MOLECULAR BIOLOGY

I think in any research scientist's career there are probably periods when life can be rather difficult, or a little difficult at least, and during the '80s when I was, my real concern was with function of transmitter systems in the brain and their link with behaviour. The emphasis within the UK and around the research world was with the rise of molecular biology. And it was seen to be, it was thought to be the answer. You could do anything with molecular biology. My view was that you could do anything with molecular biology except show what these molecules or structures did in terms of function. That didn't seem to be of interest to people at that time, but I was very lucky, I was really prevented from having a real problem during this time because I had the funding from the Wellcome Trust. I was a Wellcome Trust Senior Lecturer and I'd got a Chair at Nottingham as well already, and I had secured funding throughout that time. Then, things very quickly changed because after the sort of molecular explosion and the idea and the emergence of receptors, and the multitude of serotonergic receptors, it became very clear that if you are talking about mental disease, just trying to target one receptor was not going to be the solution. You are not going to cure depression by targeting one serotonin receptor. Likewise with schizophrenia. And, so, the ideas that we needed to understand the function of the systems returned, and life improved.

[9]. FORTY YEARS OF RESEARCH IN TRANSMITTER SYSTEMS

What has happened over the 40 or so years that I've been involved in this research? One thing is very striking, one thing has not changed, and it is I think a very important point to understand. When I began in 1966 doing research, at that time the drugs used for the treatment of mental disease, depression, schizophrenia, anxiety, consisted of drugs that acted on dopaminergic systems, serotonergic systems and GABAergic [GABA: gamma-aminobutyric acid] systems, the benzodiazepines. Here we are now, in 2016,

and what are the mechanisms involved with the drugs today? Dopaminergic, serotonergic and GABAergic plus a little bit of glutamate. So in terms of the actual mechanisms, the basic transmitter systems that we are interested in in terms of drug development, they have not radically changed, because all the information that has been produced has yet to produce a really important new drug, a real improvement in the treatment, particularly of depression and schizophrenia. There are ideas, there have been lots of ideas, but, as yet, we still rely on those old systems.

Why are we still using these old systems, 'old' in terms of we've known about for a long time? Probably because the transmitters that are involved in the actions of the drugs that are used in psychiatry today act in a slow modulatory fashion rather than rapid on-off mechanism, so they are more adaptable to drug development. But we do need, we are in real need of improved treatments for the major psychiatric disorders. We need faster-acting anti-depressants; we need anti-psychotic drugs that improve the cognitive functioning of the patients because more days are lost to not being able to work, because of impaired cognitive function than any other aspect. We need drugs that treat the negative symptoms of schizophrenia. And I'm confident that with the work that is in progress at the present time, that in the future we will see those achievements made.

[10]. THE FUTURE? BRAIN AND THE ENVIRONMENT

I think one of the main things that we must do in the future is gain greater understanding of the ways in which the brain is influenced by environment. What are the causes of the mental disorders that we have today? Is it mainly due to early development or are there also factors that occur in later life that may be important? I think that requires a lot of basic research on the functioning of neural pathways within the brain, and in particular understanding how the different neural pathways interact to produce different forms of behaviour, sort of neuronal mapping of behaviour and how the final outcome is determined. And it's of interest that the brain, when I was beginning my career, it was always thought that by the time you were six your brain was fully formed, or even younger than that, that nothing much happened after that and by the time you got to 18 you began to lose your neurons. Those concepts have changed radically now. We know that the brain continues to develop throughout childhood, throughout adolescence, and it actually matures at a much later date that we considered before. And, so, a lot of events can happen between your birth and becoming mature, and we need to understand how those events may influence the development of the brain and how we can develop ways in which we can improve the neural connectivity of the brain, and that may be the approach we need to adopt for the treatment of mental disease in the future.

[END OF TRANSCRIPT]

Further related resources:

1. Overy C, Tansey E M (eds) (2013) *Drugs Affecting 5-HT Systems*. Wellcome Witnesses to Contemporary Medicine, vol. 47. London: Queen Mary, University of London.
2. Tansey E M (intvr); Tansey E M, Zarros A (eds) (2016) *Marsden, Charles: transcript of an audio interview (19-Apr-2016)*. History of Modern Biomedicine Interviews (Digital Collection), item e2016082. London: Queen Mary University of London.
3. Wightman R M, Strope E, Plotsky P M, Adams R N (1976) Monitoring of transmitter metabolites by voltammetry in cerebrospinal fluid following neural pathway stimulation. *Nature* **262:** 145-146.