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Psychopharmacology: clinical and social

Looking at the interviews you've done so far, I think there are some things you have missed.

Such as?

Let me start with how science is organized here and I think probably it's the same in other countries. There is a small echelon of very influential people, who usually have the letters 'SIR' in front of their names and often 'FRS' after it. They take a strategic view of British science and they'll be invited both formally and informally to give advice to politicians. Now there is no psychopharmacologist in this country at that level.

Below that is a second echelon of people who are involved in the tactics of research. They sit on grantogiving bodies and are influential because research needs money. And the money is controlled by relatively few people. To see who has been influential you look at CVs as to whether the person has been on the MRC Neurosciences Board, the Wellcome Mental Health Board, the Mental Health Foundation or one or two others. These people have a view on the tactics of research, so that if somebody comes up with a particular project it will be referred to one of them. But they won't be able to influence whether there will be a shift of psychiatric research from social to biological, etc. Then there's the third group of people below that who are used occasionally as referees and so on. Now many of the people that are highly regarded within psychopharmacology are not so regarded outside because they have not been on these grant-giving bodies. Appointments to grant-giving bodies are essentially by consensus of a whole group of people, mostly from outside the field.

People outside the field often determine the status of those within it?

Yes, psychiatry and psychopharmacology have not been regarded as cutting edge subjects until quite recently. I think there's a change now with neuroscience coming in but that's only been in the last 10 years. Before that it was regarded as very much an 'also' ran. I have been asked by my pharmacology friends, why did you go into psychopharmacology, why

didn't you come into cardiology or gastrointestinal pharmacology like the rest of us? But in my case I did a PhD with a classical pharmacologist and that made all the difference. There was no way I was ever going to look at pharmacology or psychiatry again in the same way.

Who did you did your PhD with?

Well, I did the usual intercalated BSc in Physiology with a gastrointestinal physiologist, Professor Gregory in Liverpool, who was probably one of the leading people in that area and a first-rate scientist. There were only two of us doing this BSc so we had a lot of individual tuition. I developed an interest in doing research in that year. The other thing which happened, which also cast a fairly long shadow forwards, was that I came across a book edited by S.S. Stevens, called *The Handbook of Experimental Psychology.* When I read that, I realized that psychology could be a scientific subject and that psychologists were often better scientists than doctors were. It showed me that you could quantify psychological phenomena and I suppose I spent my career taking that forward.

Anyway, I finished my medical degree. In Liverpool, then, there was no psychiatry and I didn't like the medical setup. I got a good qualification and I decided to go to London. Looking around for a job, I was taken on by Professor Schild who was a classical pharmacologist, famous for all he had done on the quantification of antagonism techniques. He had a grant with Michael Shepherd and Hannah Steinberg from the NIH and they took on three of us – myself, Lorna Wing and J.D. Montagu.

After a golden period with healthy human volunteer work, Hannah Steinberg must have been moving over to animal work at this point.

Yes. Her early nitrous oxide work was superb but she had moved over to animal work and she wasn't all that interested in the work that I was doing. Michael Shepherd oversaw the clinical side of it. Heinz Schild said to me just go off, you know, and measure things in man and look at the effects of different drugs. I said 'well, measure what?' and he said 'measure conditioning effects'. So I read the literature and I found that although there was a vast literature on conditioning effects, there was very little on what happened to unconditioned effects. They had gone straight into conditioning as a sort of paradigm of 'neurotic illness', which I suppose in a way it is for some neurotic states like post-traumatic stress disorder.

Anyway, I thought I'd better try and work out something about unconditioned responses and I did habituation work using some physiological measures, such as skin conductance. Now if I'd have taken advice on this I would have been told you don't have enough precision. I just assumed that we knew what we were doing. Professor Schild was a gutobath man in his own research. But it worked. It wasn't clear until our first study that skin conductance was measuring sweat gland activity. Using this

we did formal bioassays which were the first bioassays ever done in psychopharmacology.

This involved doing what?

Measuring skin conductance responses to a series of unconditioned stimuli and measuring habituation. It followed a logarithmic course, so I just used a logarithmic transformation and got a regression line on it and then you could use this as a measure of alertness, arousal or whatever you wanted to call it.

But all along we wanted to use these techniques in patients and in about 1961, I started to take these techniques to the Maudsley. Lorna Wing was already there doing some other research. I brought these techniques down and we worked together I think for the next two years. We produced a lot of material and got a Maudsley monograph out of it. She was delightful to work with, very patient and a very astute clinician. The third member of the team, was actually probably the most senior and that was J.D. Montagu, who was very good on technical work and I learnt a lot from him. I also learnt when to stop developing techniques because you can go on and on. He had the most magnificent technical knowledge but sometimes he lost sight of the fact he was actually going to apply this technique. The three of us together I think were a good team.

Then I had to decide what I was going to do in the longer term. I'd been speaking to Michael Shepherd about this and he said 'I think you need to do proper psychiatric training' and I agreed. So I applied for and obtained one of the training registrarships at the Maudsley. There wasn't any question of going anywhere else. I had seen the place and it seemed such a critical mass of research, mostly social research – which was Aubrey Lewis' interest. Between John Wing, George Brown, Michael Rutter and Jim Birley, a whole group were working on the social side. I was taken on for the clinical course and I thoroughly enjoyed it. It was an experience in those days with people like Gene Paykel and Bob Kendall and lots of others. I went on the rotation in the usual way.

Was there much pharmacology research?

There was very little pharmacology. Some was being done by Ted Marley but it was very basic psychopharmacology. Dick Rodnight was a biochemist and he was interested in psychopharmacology but the Biochemistry Department had tended to move onto metabolism and phosphorylation.

One of the things you did which is fairly unusual from a training point of view was to get involved in writing the first book on clinical psychopharmacology.

What happened was Michael Shepherd had been asked to write the textbook and he invited myself and eventually Dick Rodnight to collaborate with him. I think it's fair to say I wrote much of it but it was an excellent training because it meant that I laid a foundation for a width of

knowledge in psychopharmacology. Up till then I had been very focused and narrow which is what you have to do if you want to establish a reputation in research. I was looking back recently at what I said about benzodiazepines and I was suspicious of them even then. I regarded them as safer barbiturates but not without dependence potential.

There was also the influence of Aubrey Lewis who is terribly maligned by his inferiors. If you were a junior to him he was very considerate in almost all ways except that he worked on a different level. I'll give you an example – when I coming up to the DPM he was asking what was I revising. I said I was reading Jaspers and I didn't think much of it, 'it's all very philosophical' and he said 'what edition are you reading' and I said 'well, it's the translation, the English'. 'Oh no' he said 'you must go back to the first edition because that was when he was just out of the mental hospitals and in fact it's much more psychiatric'. The problem is that there was no translation of the first edition and my German isn't good enough to sustain a heavy textbook of that sort. But it didn't occur to him that anybody wasn't fluent in German, French, Spanish and so on.

But he was a very kindly man. What he did was to make psychiatry respectable. Up till then, there were only a couple of Chairs in the country. Most medical schools shied off setting up departments because they didn't think it was respectable and there was no academic basis to it. What Aubrey Lewis had to do was to cut through all the undergrowth, take away all the speculation, all of the poor science and start to put it on to a proper basis. He's been criticized because he didn't do a great deal of original research, and there's some basis in that, but nobody could have done much in the way of original research until the ground was cleared and he did that. He clarified our concepts of what is mental health, what is mental illness and what we mean by diagnosis. What he would have thought of DSM-IIIR, I can only shudder because he was a great iconoclast.

So I did the three years, got the DPM, actually with distinction and then I knew I wanted to do research. Schild and Shepherd had gone to the MRC and suggested a Psychopharmacology Unit. The MRC had turned that down, on the grounds that neither of them was a recognized psychopharmacologist. Schild was certainly a distinguished pharmacologist but not a psychopharmacologist. Michael Shepherd was a most able and distinguished psychiatrist, but again I can see how he would not be regarded as having the right background for a Unit of that sort.

Anyway, I was in this package that went into the MRC. Harold Himsworth, the secretary of the MRC, was a great one for picking people out and pushing them forward. He phoned Aubrey Lewis, who had been my PhD examiner, and said is there anything worth salvaging from this and I presume Aubrey Lewis said 'yes, salvage Lader'. The next thing I was being interviewed by Harold Himsworth – this was in 1966, just as I was finishing the DPM course. I sat in a very low easy chair with

Harold, who was about 6'6', towering up above me, asking me questions about this and that and what I wanted to do.

They took me onto the external staff which was a very odd thing to do. The external staff of the MRC is really a place where you put people who had left other Units that had closed down – it was a temporary parking place while they sorted something out, but they put me onto it. They would never upgrade it to a Unit and I've stayed on the external staff ever since, with a core support, a couple of technicians, a secretary, statistician, a couple of senior lecturers and clinical people and it's been a sort of a mini-Unit, but not actually called a Unit. It's very unusual. I only have an honorary status with the University and honorary status with the Institute of Psychiatry. And I have to put in the usual programme of research every five years and they ask me for a report on the previous five years and so on.

One of the curious things is that Aubrey Lewis, Michael Shepherd and Linford Rees who was at the Maudsley still in the late 1950s were founder members of the CINP.

Yes, that was right. You have to remember that there were relatively few real psychopharmacologists. What we had were clinicians with an understanding and a very great interest in psychopharmacology because it was the topic of the time. You have to remember all of the psychotropic drugs practically were discovered in the 1950s – lithium, chlorpromazine, both groups of antidepressants, LSD, and so on. It was very vigorous from that point of view. The problem was there was no basic science to support it. It was an empirical subject. We knew nothing then about 5-HT – it had only been found in the brain a few years before. So there was a great distance between what was happening empirically and clinically on the one hand and what was underpinned by basic sciences on the other. That's why psychopharmacology tended to be either clinical or empirical animal psychopharmacology, the sort of stuff that Hannah Steinberg was doing but again without the link to the neurosciences. The CINP was essentially set up by clinicians who wanted an international forum in which to develop the subject and who also wanted a way of promulgating the use of drugs in psychiatry. They had their own agenda.

You also have to remember that the United States was not interested in drugs. I was lucky, we had almost a 30-year clear run in the 1960s and 1970s, when the Americans were not doing much psychopharmacology. It was only then that they finally gave up their flirtation with psychoanalysis and moved into psychopharmacology, and of course with their resources they've swamped the subject. I'll give you an good example from addiction, which is an area I'm interested in. The MRC spend about \'a32 million a year; I suppose Wellcome spend the same again but NIDA and NIAAA together have a budget of $800 million a year. Even allowing for population differences and for the fact that some of their research

programmes have a service element, which we don't have, we can't compete with funding on that basis. We have to be very selective as to what we do.

About 10 years after the foundation of the CINP, Aubrey Lewis said that if you asked him what had been more important for psychiatry, the advances from social research or from psychopharmacological developments, he would have to say the social developments – a point that has been echoed by Michael Shepherd even quite recently. It seems curious that a lot of the early clinical trial work was done at the Maudsley by people like Linford Rees, Brian Davies and Michael Shepherd but then somewhere in the early 1960s, the Maudsley seems to have turned away from psychopharmacology to the extent that Michael Shepherd and Edward Hare became notable sceptics about drug treatment.

Yes, but you can argue that in fact they were being rather realistic about a lot of things. Look at the problems we have with people with schizophrenia in the community, how difficult it is. We are having to reinvent the wheel – how do we give community care, do we have compulsory treatment orders? The long-term outcome of schizophrenia may be somewhat less severe because you space out the relapses but the deterioration is still there. The patients don't function as well as they might. With antidepressants you get a 30% placebo response and a 70% drug response. There's only a narrow value between them and then we see the problems with the benzo's and so on. And of course with lithium – I mean have we really stopped people coming into hospital with their hypomanic attacks?

So we have to be careful that we don't overvalue the psychotropic drugs that we've got. After all, for the first 30 years we were just producing more haloperidols, more chlorpromazines, more amitriptylines, more diazepams. It's only recently, with the development of receptorology and molecular biology, that you can tailor drugs much more. It's only now that we are in a position where we can develop say 5-HT-1 full antagonists and predict what sort of things they would do. That is where other branches of pharmacology were in the 1950s and 1960s.

You say there were no proper psychopharmacologists. What about proper clinical psychopharmacologists – I see you as being one of these.

There weren't any. There are quite a few now who take a training in psychopharmacology but there were very few in my time. There are a lot of people who you think of as psychopharmacologists who have no formal training in pharmacology. You see this when it comes to matters to do with pharmacokinetics and other strictly pharmacological aspects of the subject.

You also said that during its golden period in the 1960s and 1970s, clinical pharmacology looked down on psychopharmacology.

Yes, clinical pharmacology developed rapidly. A lot of very able people went into it partly because general medicine has always been crowded and this was a way of getting publications quickly and also taking part in the development of whole groups of new compounds. The pharmaceutical industry exploded in the 1950s, 60s and 70s, starting with the antibiotics but there were lots of other areas – beta-blockers and later the alpha-blockers. Because of this there were able people who decided positively to go into clinical pharmacology and do a PhD. They were then able to leapofrog up and their abilities were such that they ended up sometimes as clinical pharmacologists or sometimes back in the mainstream of general medicine in important and influential positions.

That didn't happen with psychiatry. Although we had the drugs, we didn't have the rationale in the same way. We had no idea how anti-depressants worked. Now there were of course surprises in the other parts of pharmacology, nooone predicted that propranolol would be an antihypertensive but they did predict it would have antioangina effects and that was a powerful prediction. There was a feeling that psychopharmacology reflected psychiatry and psychiatry has always had a low reputation with general physicians and neurologists. It hadn't developed that much and that of course I think really was inevitable owing to the complexity of the science at the moment.

Have these problems anything to do with our difficulties in making up our minds whether we should take a categorical or dimensional approach to mental illness? The dimensional point of view was much more common back in the 1960s. Your work on skin responses, naturally led into dimensional viewpoint. What happened? Gordon Claridge suggested that the fuss around R.D. Laing made people very wary of that kind of approach.

I think Laing had no real influence on UK psychiatry. His influence was in parapsychiatry, or metapsychiatry. People who were not in the profession but wanted to have some influence on it – the antipsychiatry brigade.

No, the reason that the categorical view of psychiatry took off was nothing to do with the subject itself. It was entirely to do with the American health care reimbursement system. If you want to get paid for seeing a patient you had to attach a categorical label. You can't attach a dimension. You can't say I've treated someone who has the following dimensional problems – although that's actually what you do. I think if you are dealing with a patient, the best shorthand way of doing it is to have a dimensional formulation. But of course I accept that in this day and age that people get paid by insurance companies and that accordingly treatment is going to be dictated by what label you hand that particular

patient. That's what happened in the United States and that's why DSM-III has taken over. Having produced that, the next stage was that the pharmaceutical companies, in order to get licenses, had to have a definable indication and that was obviously going to be DSM-III or DSM-IIIR. This has reinforced the categorization of psychiatric syndromes – I think prematurely. But there are things where science is overoridden by business interests.

One of the things that was big in the 1960s was psychophysiology and the general area of psychosomatics.

I was working in psychophysiology, essentially because I wanted measures that I could use to increase the precision of the clinical ratings. In fact, in that Maudsley monograph I increased the assessment of sedative actions by an order of magnitude over even very careful clinical ratings. This was a way of getting additional precision to do the sort of things which a classical pharmacologist wants to do, which is doseoeffect curves, interactions, isobols and things of that sort.

I used psychophysiology because you couldn't use the EEG, which was potentially much better but it's more complicated and you couldn't quantify it in the 1960s. It was difficult enough to quantify heart rate and skin conductance. You would spend hours with a ruler analysing paper traces but by simplifying the experimental paradigm, and just using unconditional stimuli, I could quantify responses. Now these happened to be autonomic measures and that inevitably meant that psychosomatic conditions were going to be relevant, although I was never myself overly interested in psychosomatic aspects of it. I was certainly interested in the idea that some of these psychophysiological measures could give you an insight into psychosomatic conditions. For instance, there was the idea that if you get a hypertensive reaction as part of a sudden response to a stress then maybe eventually that hypertension will fix. That's probably what does happen. But the problem was that psychosomatic medicine was one of these rather fringe topics. There were a lot of respectable people in it but the meetings that you went to were quite odd. There wasn't a lot of science and I used to try and keep my distance. I was never a member of the Psychosomatic Society although I spoke at a few of their meetings.

On that score, one of the things that hits me is the power of business and politics to redefine psychosomatic syndromes. I'm thinking at the moment of hyperventilation which has become panic disorder.

Well, not totally. We always used to say if you go back far enough and look at German literature at the turn of the century, you're sure to find that someone described panic disorder and everything else. After all we are not the first people to observe phenomena. That's why, for example, it's very interesting why schizophrenia isn't well described before the 19th

century but apart from that we are very often reinventing the wheel. What we are also doing is moving the wheels round and putting them on different corners of the old tramcar.

But there's a large group of people who have fluctuating types of symptoms and what you label them is neither here nor there. They respond to stress with physical symptoms and they are inconvenienced by them. Some of those physical symptoms will set up a vicious circle like hyperventilation or the perceptions of palpitations and you get the catastrophic interpretations and so on.

Can I switch to the foundation of the BAP? Whatever the reason, whether the Maudsley was pro- or anti-drug, when it came to the founding of the BAP, it was very much founded by non-Maudsley, non-Oxford/Cambridge people, why do you suppose that was?

I started off by saying how British science is organized, where the influence is and how the money goes. Societies like the BAP and the other one that I was involved with, the Society for Studying Addiction, which is much much older, don't have much direct influence on that. What they can provide is a forum where people realize there may be a hiatus and they start to do something about it. But it has to be the senior people who realize that. So I've been a member of the BAP from the start and I've been President and so on but I've no illusions about it being a very influential body.

One thing which I don't think anybody's mentioned to you about the original founding of the BAP is that amongst all the other issues such as calling it an Academy, advertising it in the *Lancet*, the meeting at the RSM, keeping it very much clinical, there was a suggestion that it would have a closed membership. That was anathema to me because when you work in an academic setting you have youngsters doing PhDs who want to go to these meetings and want to become a member. The one thing I was not going to join was a closed membership society. A quite small number of members were being talked about originally. To me that would have been a great disincentive to the youngsters. What happens with a closed society is that you pack it in with clinicians who've got an interest in psychopharmacology for 10 years and then they move on to something other and block the places. So that was why I was against it.

Has this happened to the American College?

Well, yes. I know some very good younger psychopharmacologists who can't get into ACNP because it has a closed membership. It doesn't allow the subject to develop. Coming back to the lack of Maudsley involvement, it just happened that way. Firstly there wasn't a lot of psychopharmacology there. There were Ted Marley on the basic side and John Stephenson at that time. Barry Blackwell had moved on to the United States and then

there was myself. So it wasn't that the Maudsley was against it; there weren't many people in the Maudsley interested.

The most senior person in the 'opposition' was Philip Bradley. We had meetings up in Birmingham with Ian Stolerman who was working with him, Channi Kumar, who was much more involved in psychopharmacology in those days, and we actually got more people outside the academy to oppose it than were inside the academy to support it. It was almost a 2:1 ratio. A lot of people in industry thought they were going to be taken for a ride – that the Academy was going to say that all clinical studies had to be done by members of the Academy on an accreditation basis and the industry of course didn't want that. They could see a rip-off coming.

I think Max Hamilton hadn't originally realized what was going on. But he then realized he had perhaps been given too optimistic a picture and he back-pedalled on it. At one stage he was almost ready to resign as President unless there was a resolution of the conflicts. And then we did have some compromise. If you look back at the Constitution there was an associate membership, which I insisted on. There was no limit to the number of members. We changed it to Association which was much more UK term, than Academy.

We thought it had all settled down until of course everything cracked open again at the Guernsey meeting, which I boycotted. It seemed to me again that this was the old guard coming in, the clinicians, and saying we should have a nice prestigious, expensive meeting in Guernsey. That's why the meetings ever since have been in slightly seedy university settings but they've been very successful meetings. I don't think you'd get that kind of attendance at hotels in Guernsey or whatever.

The division between the higher paid clinicians with an interest in psychopharmacology and people who regard themselves as professional psychopharmacologists still lies below the surface. You also have to remember that half of pharmacologists work in industry. That was something else that was forgotten by clinicians who were interested in psychopharmacology. Psychopharmacology is unusual in that half of cardocarrying pharmacologists work in industry so you have to have good representation of that constituency.

Another strain emerged almost from the start in that quite a few people saw the BAP as the biological psychiatry section of the Royal College, in exile as it were and there has been something of a tendency ever since if things aren't going right for some people to say well let's up sticks and move back into the College.

The major influences on the Royal College, of course, were social and more recently psychodynamic; drugs were never very influential. I think it would have been a mistake to have set up a psychopharmacology society as a biological psychiatry section manqué. There is obviously a close relationship between them but there are large areas of biological psychiatry that have nothing to do with drugs.

But the BAP has been a biological psychiatry society almost rather than a psychopharmacology association. At BAP meetings we get sessions, for instance on neuroimaging, that are not directly to do with drugs.

That's true but also we have a lot of straightforward psychopharmacology as well. You have to have a balance because the drugs are going to be used in a biological psychiatry context. Beyond that they are used at two other levels, one is by general jobbing psychiatrists who obviously have to know about therapeutics although they don't have to know that much about psychopharmacology. You can give an antidepressant perfectly adequately and competently without knowing what it's doing to the amines in the brain. And of course increasingly a lot of psychopharmacology is done in primary care but there are relatively few general practitioners who have any interest in how the drugs actually work. GPs have never been members of the BAP.

You mentioned the benzodiazepines and you also said that way back in the 1968 textbook, you hedged your bets then as to what the role of these drugs would be; do you want to give me an overview of how the benzodiazepine saga evolved and why has it been such an issue in Britain – perhaps more than anywhere else?

There are several reasons. First, if you look at the literature in the 1960s, I wasn't out of line in saying that they weren't the major step that the drug companies were trying to make them out to be. It was in the 1970s that I parted company with the mainstream people who were then saying these were safe and effective drugs. In the UK, the usage was amongst the highest and my original worry about the benzo's was that this amount of usage cannot be justified and therefore maybe this was coming about because the drugs were producing dependence even in normal doses.

Peter Tyrer and I started questioning what was happening about 1975 to 1978. The issue caught on the United Kingdom because a group of us were quite vociferous about it, and because GPs were beginning to notice themselves that there were problems. The UK had a strong antipsychiatry movement and probably an even wider antiscience movement, and the media were looking for a whipping boy. People were saying that 'my life's been destroyed since I went onto Valium or whatever'. Professionals were prepared to give quotes and saying these were dangerous drugs. No professionals of the same status were prepared to say that this was all nonsense. John Marks had a try but he was regarded as tainted because he had just retired as managing director of Roche.

After television picked up the story, the press took it up and then of course eventually the lawyers took it up and although we think of the United States as the country where the lawyers chase the ambulances and so on, in this country, we've had two or three big firms of lawyers who specialized in negligence and they took up the issues. They saw that there was possibly some mileage in it. Whether or not they had compassion on

their client or not was immaterial. It was part of their job to push their clients' claims as much as possible.

The net effect is still patchy because although we've made an impression on the precribing of anxiolytics, prescribing hypnotics has hardly altered and yet the problem is a very similar one. A lot of elderly people are particularly affected.

But why a particular thing suddenly takes off in one country and not another is fairly difficult to predict. France should have had much more problems because they've got twice the usage that we have. The United States are much more consumer conscious but there's a big lobby there which says they're not actually using enough benzo's. What they gloss over is the fact that because you get anxious doesn't automatically mean you have to have a benzo. But there's a different perception of the issues over there as well and I think the pharmaceutical industry have become much more subtle in the way that they get people to espouse their cause.

Do you want to comment on that further? There's been a recent book, Toxic Psychiatry *(see Glossary) which has made fairly sweeping claims in that regard.*

I haven't read the book but I know the sort of things that were said. The pharmaceutical industry, of course, is a very big and very successful industry. It works on wide profit margins. But it's high risk. It takes $200 million to develop a new drug. A company is often developing a drug at the same time as its other competitors are and often a company is not first in the field. So in the past they worked hard to get the support of the opinion formers in order to get some penetration of their compounds – people like you and I and all the senior members of the BAP.

Now what's happening of course is that things are changing. The days when consultants would write a prescription and the GP would say well that's interesting and start using it himself have gone. The GP wants to know what the cost of it is. The drug companies have the problem of how to penetrate the GP market without being able to use the specialist as their spearhead. Obviously drug companies are not charitable organizations; they have a legitimate right to promote their products within ethical limits. But companies vary. We talk about the pharmaceutical industry but that's an overosimplification. You've got big companies, which are very energetic and they will hold meetings and they will try and dictate who they have on a particular meeting agenda. You have others who are 'nootouch' companies. They will give the money without strings; all they want is an educational spinooff. Then there are others in between. In the development of drugs, they may or may not take advice.

When it comes to marketing, there are rules and regulations about this but there are subtle ways to influence you. If you're giving a lecture and you've been flown half-way round the world by a company, not many people will stand up and say that the company's products are inferior to another company's product. They are, at least, going to say that amongst

the products worth prescribing are A, B and C even if they are perhaps a little less likely to use the compound of the company who is supporting them. It's human nature. So the thing to do is if you don't believe in the company's product, not to accept the invitation . . .

Chasing the benzodiazepine issue somewhat further, what appears to have happened is the media seem to have got their teeth into this story and perhaps through it into the idea of the medical story generally. What impact do you think the media are having on the practice of medicine more generally now.

I think the influence of the law is even greater. Patients are much more ready to sue. I do some medicoolegal work and one is asked to comment as to whether it is worth going to legal aid. I find increasingly that some of these claims are totally unsustainable. Even if some damage was sustained as a result of the drug treatment, the drug treatment was perfectly routine.

What happens, then, is that the hazard of legal action makes you become more defensive in what you are doing. I will give a lecture this evening on benzodiazepine withdrawal and someone will ask 'well what do I have to do to stop my patient suing me'. I think what you have to remember is the sheer nuisance of being sued – it's so time consuming. People who have had this problem say they'd do almost anything to avoid going through that again. There's no substance in many of the complaints but you have to get the notes out and prepare a defence, speak to the solicitor for the Medical Defence Union and so I think that people do try and avoid that as much as possible.

The latest concerns in this regard have centred around temazapem, with apocryphal stories about little old ladies sending their husbands down to the pub to sell their supply. Is there any truth to this – and just how dangerous is temazepam?

The evidence we have seen on the Technical Committee on the Advisory Council on the Misuse of Drugs at the Home Office would suggest that benzodiazepines in general, but in the UK temazepam in particular, pose major problems in the addiction field. Temazepam was originally formulated as liquid-filled capsules, the contents of which could be easily injected. Addicts used it as an adjunct to opioids such as heroin, to smooth out the effects of cocaine and amphetamines, to give them courage to commit the offences needed to sustain their other habits, but increasingly as a primary drug of addiction. A substantial proportion of temazepam addicts inject, with all the subsequent dangers of transmission of HIV and hepatitis. These arguments led us to recommend stricter scheduling of temazepam but this recommendation is still under consideration by the appropriate government departments. Needless to say, cost consideration has raised its ugly head. Meanwhile, temazepam is freely available and indeed there are stories in the literature of little old ladies selling on their temmies in the pub. However, world-wide the problem is flunitrazepam, Rohypnol, which is taken either by mouth or quite often by snorting.

Some countries have already banned this compound. I find the whole addiction field quite fascinating but my research forays into it have been focused on a few aspects.

One could argue that neuroleptics cause more severe and more substantial problems than the benzodiazepines

Yes, but schizophrenic patients are not likely to have a voice or to have access to MPs in the same way and the benzo's are very widely used. A lot of people know about them. Something like one in three women and maybe one in five men have taken a benzo. People know someone who's taking them and they can identify with somebody who's having problems. So you're dealing with something that is very widely used and that gives the newspapers and the media a head start.

Then there are, of course, the 'villains of the piece', the drug companies, who are busy promoting these drugs. There's also the idea that they are promoting these drugs for the worries of everyday life, whereas the neuroleptics are used mainly for serious mental illness. So there's the idea of the medicalization and the trivialization of psychological responses. Then there's the political dimension – that it's all due to social and political problems! There are other reasons which I can reel off. Women, for example, take them twice as frequently as men, so there's the idea maybe that we are dealing here with something that male doctors give women to keep them quiet! The media interest has all died down in this country now but it's coming up in other countries I'm told.

You've been prepared to be quoted in the media; do you not think that in handling things through the media you cannot expect to get what you want across?

That depends. The media varies. I always make myself available. If I give a lecture, and somebody from the newspaper phones up and my secretary takes the number, when I phone back I can often sense the surprise in the reply 'oh, you phoned back'. They don't expect that. Once you do that and you're prepared to talk sensibly about it at a fair length and let them go through all their questions they will often, and this happens to me quite frequently, they will say, can I fax you what I am going to write. Now you can't ask for any right of veto or any influence on what they say but you can correct matters of fact and they want that. They don't want to be get a reputation of someone who is loose with the facts. Like barristers, journalists are instant experts for 10 minutes or 10 days or whatever. But you have to take the risk that they may misquote you.

If you get quoted right three times for every time you are misquoted that's fair. But you've got to know how a journalist works and the constraints they're under. You can't go away and say 'oh, I'll think about that for three days'. It's dead in three days. When a piece of news comes up, you've got to either comment on it or you say I'm not the person

that you want for this and try and give them somebody who is. They've got a job to do. When you get them on your side, they are very helpful.

Are you saying that the stock response that journalists are only in a story to sensationalize it is too paranoid?

No, it depends on the media or the newspaper. You don't expect *The Sun* with its readership to use the same sort of headlines as *The Times*. If you get a medical or science correspondent, it doesn't mean they'll have a technical background. I often ask how much technical background they've got and if they say 'I've got a PhD in pharmacology', obviously I can put it into such and such terms and leave it to them to de-jargonize it. If they say 'well I don't know anything at all', I say 'well bear with me and I'll try and explain it as simply as possible' and you talk about chemicals in the brain. But that's part of my job. I've never lost sight of the fact that I'm paid by the public to do research. The least I can do is to commit myself to telling them what I am doing, or what is going on in my particular area of expertise.

One of your more recent interests has been in sudden death in psychiatric hospitals, which seems to have something to do with the dose of neuroleptics being pushed up. This seems to have an awful lot to do with clinical practitioners acting empirically and not on the basis of any training in psychopharmacology, which leaves them open to the idea that if a small dose of the drug is useful, a larger dose will be more useful – it's very much ad-hocery.

But it's for us to do the research and educate them. This is what has happened with the benzo's. Doctors don't give indefinite prescriptions anymore. We need to educate our junior staff and those of our colleagues who are using high doses of neuroleptics; and we need to point out that there some dangers. Chlorpromazine should not be used. In cases that I have seen, its pharmacokinetics tend to become unpredicable at high dose – especially when other drugs are mixed in.

This is part of a wider problem of polypharmacy involved in treating disturbed patients. You've a responsibility to the nursing staff and carers not to have a severely psychotic patient who becomes aggressive. Our practice is to use benzo's for sedation which is more logical.

It's for us to identify a problem, to do the research into it and then to give appropriate advice. That's why I wrote a paper in the *British Journal of Psychiatry*, although it was all anecdotal. If somebody does die unexpectedly on a neuroleptic, the first thing you do after trying to resuscitate is to take a blood sample and see what the blood levels were. It is a legitimate role for a clinical psychopharmacologist to look into these problems. Our colleagues who have got the day-to-day problems of dealing with these patients may only see one case in their professional lives, they're not going to be able to work it out.

Between benzodiazepine guidelines and neuroleptic dose guidelines, what about the issue of guidelines? These are obviously needed but are we at risk of choking off progress with all these rules?

I've been 'guilty' of introducing guidelines. Guidelines are only as good as the people you can persuade to give up a day or two to sit and develop them. And even then they are only guidelines, they are not rules and regulations. We know that diazepam is only licensed for four weeks' use but if you go on for five weeks you justify that. It's only when you're doing something for which there's no body of opinion to support you that you're on your own. Guidelines are just a consensus – what most people would do but there can be quite a substantial minority that does it differently.

Has the development of biological psychiatry and its codification in DSM-IIIR led to something of an Anglo-American cultural imperialism in psychiatry?

With the amount of money that the Americans have to do research they are always going to dominate – once they get interested. As I've said before, we had a good run for our money in the 1960s and 1970s, until they woke up to psychopharmacology. The decade of the brain came along, then, and they could just throw money at projects. They have budgets which outrank ours severalfold so we've got to be very specific. Not quite niche research because we are still doing better than that – but I think we ought to be coordinating things a lot more in this country if we are to continue to compete with the Americans.

They waste a lot of money but some of it sticks and some of the things they do are extremely competent. Some of it's very imaginative and some of it isn't. But even the unimaginative work is done with such controls and so on that it's very important. The clinical trials they do influence the field because they do them so well.

You've also been very heavily involved in the Society for Addiction. Can you tell me about your involvement in that?

Yes. I've always been interested in addiction. You can't work in psychopharmacology and not realize that a whole group of compounds of various types are addictive. You can't compartmentalize these things. The problem is that, clinically, working with addictions is a very difficult thing to do. I greatly admire the people who manage to do it.

When I got more involved with benzodiazepines, it became quite clear that there was a whole area of addiction that I had to work into. Hannes Petursson and I did some systematic research into addiction – tolerance to compounds, withdrawal, challenge tests. That was all in the second Maudsley monograph that I wrote, which is widely quoted. Then my friends in addiction said why don't you come and help us out. There aren't many pharmacologists in the addiction field. I was put up for the

Presidency of the Society for the Study of Addiction and I was gratified by that and I had 10 years which I really enjoyed.

In a way, my strength was that as I wasn't really fully in the field, I could stand back from all the tensions of this group and that. I could balance alcohol against drugs of dependence and nicotine and so on and still pursue my own interest in benzo's. The Society, I think, quadrupled its membership under my Presidency. Its financial situation is now 10 times better. But it was an example of a Society that was ripe for development. Now you've got psychologists and sociologists and all sorts of people who go along and it's no longer dominated by the medics. That's to its advantage.

The problems you deal with are sort of an unwritten chapter in psychopharmacology in this country. All the focus is on the antidepressants, neuroleptics and minor tranquillizers but the down side is not covered

A lot of people who are first-rate pharmacologists, working in the addiction field, are in the United States. They do not regard themselves as psychopharmacologists, which is unfortunate but it reflects the organization of the topic. For example, in the United States, the NIMH is separate from NIDA which is separate from NIAAA, although I think these two will be pushed back into the melting pot soon.

Over here the addictions have been separated out and of course the Royal College of Psychiatrists has had an addiction section for a long time now. There is a lot of addiction work which throws light on the aspects of psychopharmacology. For example, dopamine is a common thread. Nevertheless, psychotropics like the antidepressants, which are not addictive, lead us to believe that they can be studied separately, so that many in psychopharmacology have nothing to do with the addictions and this is unfortunate.

What about the LSD story? There was a certain apocalyptic quality to that. It came, it created psychopharmacology, and then it vanished.

I'm not so sure about that. LSD was an interesting area. There were groups of people who were particularly interested in it. There was some speculation, some hypotheses which developed from LSD, but you also have to remember that we didn't have much idea what LSD did and a substantial body of opinion developed among academic psychiatrists that the LSD phenomena did not resemble schizophrenia. Some elements are the same but so what, there are other drugs which produce hallucinations – you can give anticholinergics and get hallucinations. There was a feeling that this was not an appropriate model for schizophrenia. So it was sideotracked and the people who went on pursuing it were regarded as not being justified.

The second thing was the therapeutic aspect of it for which there was enthusiasm. Patients given LSD were always the poor prognosis, difficult

to define patients; patients with personality disorders, patients with alcohol problems of various kinds. When it was given to anxious patients and schizophrenic patients it was a disaster and it became marginalized as a result. And then we started to get reports of abuse on LSD. A few people jumped out of windows and the whole thing had very worrying implications. A few people continued with it in a desultory sort of way.

I was in a meeting last year 'Fifty Years of LSD' to honour Hoffman. There was a small group of people there of his age, in their 70s and 80s, who had used LSD extensively and spoke of it with a certain nostalgia – how they'd found it useful. When you asked them what did it actually do, there were no controlled studies and they had no great specificity of what it was doing. It was quite obvious that whatever the scientific aspects of LSD, which were very important – the 5-HT story and so on – the therapeutic aspects had really been exaggerated, the side effects had been ignored and so on. And interestingly at this meeting, there was nobody who had dealt with the topic of LSD misuse. So there was a very curious sort of flavour to this. I wasn't involved with LSD because it had reached its peak in this country in the 1950s and by the 1960s it was already discredited. But it was interesting. I could get an insight into what had been very important. My only regret was that the man who could probably have thrown more light on it than anybody had died earlier that year. That of course was one of the greatest of the real psychopharmacologists, Danny Freedman. He had worked with LSD, as well as most other things. A first-class mind.

Finally, following on Valium and LSD, fluoxetine has become the latest media drug. How do you read that?

The Prozac story is a very interesting exercise illustrating all the influences which impinge on the pharmaceutical industry, the prescribers of drugs and their patients. The United States is the biggest drug market and if a drug is successful there, views about it tend to be very US-orientated. Fluoxetine has been very successful despite increasing numbers of competitors and despite a temporary setback with the exaggerated concerns about suicidality and aggression. More recently, the claims that fluoxetine can change personality remind one of the old controversies about amphetamines and LSD in the 1950s. My view is that there is a significant prevalence of minor and moderate chronic depression in the community and these are people who are being helped by what is an effective antidepressant. The media hype reflects the wide use of fluoxetine and also the search by Americans for perfection in mental health.

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