THE PLACE OF EXPERIMENTAL PSYCHOLOGY IN PSYCHOPHARMACOLOGY
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By the time of first CINP meeting you had been in psychopharmacology for some time. Can you tell me how you came into it, what you were doing and who you were working with?

My being at the Rome meeting was somewhat to my surprise. I had been in touch with various people who knew of our work, including several Americans, such as Joel Elkes at Johns Hopkins and Jonathan Cole, at the Psychopharmacology Service Centre in Bethesda. I also knew British and European pharmacologists, psychologists and psychiatrists. And so I received an invitation.

Like many people in those days, I came to psychopharmacology in a fairly haphazard way. I had a BA degree in psychology and wanted more science training. I consulted the professor of Pharmacology at University College London, whom I knew through music, Frank Winton. He was a former Cambridge physiologist and unusually, an early member of the Institute of Psychoanalysis, and so had an interest in things psychological. He suggested that I should join his department. I said "oh I don't know anything about drugs", but he laughed and said that I could teach them English in return. I had won a University of London postgraduate studentship in psychology with which I could do a PhD in almost any London Department that would have me. After a lot of heart-searching I did what he suggested.

To begin with it was very lonely because hardly anybody else was working in the field. Frank suggested that I should work on nitrous oxide - laughing gas. So I began by working with humans. In retrospect this seems to have been a brave thing to do. I gave student volunteers and colleagues concentrations of nitrous oxide between 20 - 40% in oxygen. These doses were relatively small and I tried to establish whether N_2O impaired the performance of cognitive and motor tasks according to their relative complexity -it did (1). And also whether N_2O behaved like sleep and could be used to improve memory and to test the interference theory of forgetting - it could (2). This is again of scientific interest to-day because of current research on implicit learning. The memory experiments, done in collaboration with Arthur Summerfield had a high media profile because the Daily Express summarised them under the heading "Alcohol is good for the memory" which went the rounds as far as the New York Times and the radio in South Africa and Canada. One of the London Evening Standard's leader journalists reported finding it easier to memorise her shopping list if she had a quick nip after breakfast. I was mortified by the brash publicity, whereas in to-day's climate it would have been proper to feel gratified. I also collaborated with Roger Russell, professor of Psychology at University College London to show that N_2O could reduce experimentally induced "stress", much like alcohol (by setting subjects a difficult task, an insoluble problem. Again stress reduction has become a big topic to-day.

I had some interesting subjects for my N_2O pilot experiments, for example, the biologist J B S Haldane. He thought that he would fail all the cognitive tests but found the experiments valuable because he compared the effects of N_2O with those of simulated submarine experiments and anoxia in which he had been involved during the war. Nitrous oxide had a vogue during the sixties and seventies, when youngsters were supposed to sit around at parties with little canisters strapped to their backs and taking a sniff whenever they thought they needed cheering up. But some experimental subjects did not like the sensations. Have you had it?

No,

It can make one feel rather abnormal, rhythmical and overwhelmingly "drunk". I obviously had to try it out myself several times and didn't like it at all. But nitrous oxide is of interest again now because it is in the atmosphere and we seem to have small concentrations in our bodies, and so it might well have slight effects on people's behaviour at times. As well as the drunk feeling it also changed the perception of time.

A scientist whose encouragement meant a good deal to me was J. H., later, Sir John Gaddum who was professor of Pharmacology at Edinburgh and then head of the Babraham ARC Research Institute. He asked me to compose a few pages on psychological methods of studying psychoactive drugs for his text-book. I remember once complaining to him that this was such lonely work and that a lot of the time I didn't know what I was doing and he said "No, no you must carry on. Finding out about the brain as you are doing is the most important gap left in biology". Gradually of course, I was able to work with various interesting collaborators.

By the time I got to the CINP in Rome I was on the staff of the Pharmacology department at UCL, which for a psychologist was unusual.

You were one of the first academics to be designated a psychopharmacologist. When did they create the post for you?

I was made a reader in psychopharmacology in the University of London in 1962. It was the first university title in psychopharmacology in Western Europe I think and probably the USA too. There were laboratories of psychopharmacology springing up in the States then, but not academic posts as far as I know. We early psychopharmacologists were busily "networking" and great friends, and I remember trying to explain to my American colleagues what this quaint title of a "Reader" meant. In 1970 I became the first Professor of Psychopharmacology.

In the 1960's our main research work became known as "Purple Hearts". By chance it coincided with a wave of popular interest. I was asked to contribute a chapter to Clarke's Applied Pharmacology, and Andrew Wilson, one of the authors, said "Please do the barbiturates and I wish somebody would find out what these mixtures do". I said "what mixtures?", because I really didn't know much about them and he said "mixtures with amphetamines". The best known of these was a propriatory preparation called 'Drinamyl'; the tablets were mauve and vaguely heartshaped and scored down the middle.

So my collaborator Ruth Rushton and I gave small doses of barbiturates to hooded rats, who seemed to like them. Their locomotor activity was stimulated by them, which in those days was an unusual finding, since barbiturates, like alcohol, were officially regarded only as CNS depressants. One day we added a small dose of amphetamine to the barbiturate. To our astonishment this produced an enormous potentiation of spontaneous motor activity in the rats. At first we didn't believe it but then we had to because it happened again and again (3) and other investigations in a variety of experimental contexts found similar potentiating effects. It also worked in man since amphetamine-barbiturate combinations produced a better mood and also slightly better performance of simple tasks than the separate ingredients in students (4). There was good agreement between dose ratios that worked well in rats and mice and those used in man, especially 1mg/kg dexamphetamine and 6.5mg/kg amylobarbitone by weight - which was in fact the Drinamyl ratio which was fairly widely used to help mildly anxious and/or depressed people, especially, it was said, bored housewives. Just about then it was discovered by teenagers to produce "high moods", especially if mixed with alcohol.

We constructed "isobol" diagrams (from Greek 'isos' 'equal' and 'bolos' 'effect') which enabled one to read off equi-active dose combinations, illustrating the agreement between optimum dose ratios in rat, mouse and human. We extended this to other drugs, including benzodiazepines combinded with amphetamine, which produced even more pronounced motor activity. Recently we were able to use the Cambridge University Computer (all of it for 10 minutes, so that we had to work at midnight) to construct high resolution 3-dimensional isobols in colour.

There were many opportunities to lecture abroad including at SmithKline and French in Philadelphia, where drugs had first been combined to produce Drinamyl. We tried to find out just how they had hit on the particular drugs, doses and dose ratios. Was it just good luck or that there was some special kind of logic. In Philadelphia I met one of the people who had been involved in putting together the two drugs. Apparently what had happened was that the Chairman of the company wanted something relaxing, but not too relaxing, so he put together the smallest marketed tablet of dexamphetamine which was 5 mg and the smallest marketed tablet of amylobarbitone, 0.5 grain or 32.5mg, and that gave this ratio of 1:6.5. So it was really pretty lucky that that turned out to be the best mix. It took us some time to find the best amphetamine chlordiazepoxide combination, and interestingly the ingredient dose of dexamphetamine was about the same as with amylobarbitone. It is a pity that amphetamine is no longer much used medically but these combinations remain of scientific and heuristic interest. It seems that combinations of drugs in all kinds of fields, as far apart as cancer and HIV, can achieve better therapeutic effects than single drugs, and this relatively under-investigated phenomenon probably has a big future.

The problem of drug interactions has really pursued me through my career. Our recent work with benzodiazepine/antidepressant combinations and backward walking in mice was again an example of the surprises one can get when one works with mixtures. Elizabeth Sykes, Christine Davis, Claire Stanford and I combined clenbuterol, which is a beta-adrenoceptor agonist and a potential antidepressant, with chlordiazepoxide - in the hope that the combination would lift locomotor activity to some extent, as we had found with amphetamine and chlordiazepoxide. Instead, we got spectactular and prolonged backward walking. The mice walked backwards energetically, for many minutes at a time (4). This has developed into an effective and simple potential screening test for antidepressants and anxiolytics which we are hoping that an enterprising industry may take up.

Backwards walking mice were reported first in connection with opiates, LSD and mescaline, and some people have suggested that backward walking is really a hallucination of sliding down a hill; if you believe that you are sliding down a hill you would push back with your front paws to stop yourself, and the effect would be to walk backwards. Whether that applies to humans is doubtful, but might be worth investigating.

The only human backward walking we have traced is in connection with Parkinson's disease where it occasionally happens. Apparently patients cannot help walking backwards and when they reach a wall, they press their back into it. The mouse backward walking also happens with combinations of salbutamol and chlordiazepoxide, and it seems possible that some asthmatics who take benzodiazepines get a kick out of their Ventolin inhalers which are very popular. There must however be many people who are co-prescribed antidepressants and benzodiazepines. It might well be worth while studying the combinations deliberately in humans.

Fascinating

In the 1960's our amphetamine - barbiturate work led to a time of great activity. University College provided accommodation, and together with Professor Arthur Summerfield at Birbeck College, we got grants from NIMH, which made a huge difference to our progress. Grant seeking is now the order of the day, but then it was still unusual and we felt both pioneering and slightly apologetic that we had more money than other people. But of course nearly all went on salaries. We tended to use simple equipment, such as Y-mazes, hole boards and activity cages, and so our expenditure on equipment was modest. Most of our results were obtained by scoring methods which depended on visual inspection which with experience became very accurate, with high inter-observer reliability but were labour intensive. For example we developed a simple but accurate method for drug induced "ataxia" using measures of footprints. And of course we had no PC's or photo-copiers in the 1960's.

Who were the principal people who influenced you at this time ?

Well there was Gaddum and Andrew Wilson who became Professor in Liverpool and who was one of the first clinical pharmacologists in the UK . Roger Russell was here from the USA and we published together. He was a great innovation for this country because he was the first animal psychologist who headed of a department. Bill Paton who became Professor of Pharmacology at Oxford and had discovered hexamethonium with Nora Zaimis. Arthur Summerfield at UCL who was a very systematic expert at experimental design and statistics. With him I did most of the N_2O memory experiments. He became Professor of Psychology at Birkbeck College.

Then there was Daphné Joyce, also at Birkbeck who collaborated with us some of the time; her early work on 5HT has become a classic. Dick Joyce who was at the London Hospital Medical School where he did human experiemnts on, for example, drugs vs dummies; he has been working in Switzerland for years now. Michael Chance was an ethologist at Birmingham who worked with drugs, and Paul Silverman wrote an ethologically orientated book on psychopharmcology, Animal Behaviour in the Laboratory, which deserves to be better known.

Channi Kumar from Cambridge and Ian Stolerman from the School of Pharmacy came later as PhD students and worked particularly on drug dependence in rodents, and Roger Porsolt was with Daphné Joyce up the road at Birkbeck and now heads a commercial psychopharmacology laboratory in Paris. David Sanger was a post-graduate student at UCL with us for two years. Michael Besser a rather grand endocrinologist and now Professor of Medicine at Barts worked on drug combinations with us, which was particularly helpful because he had access to medical subjects and of course lots of endocrinological knowhow. Milos Krsiak, now professor of pharmacology at the Charles University, Prague, spent a year with us and started interesting experiments on how the behaviour of drugged rats could "rub off" on that of their undrugged partners. There was a great spread of people and skills. I also learnt a lot from many colleagues in the Medical Sciences Faculty at UCL, especially Sir Andrew Huxley, Bob Simmons and Donald Jenkinson, as well as from many pharmacologists, psychologists, psychiatrists and statisticians in- and outside the College, and of course Americans, all too numerous to mention, except perhaps for special friends like Murray Jarvik, Gerry Klerman, Conan Kornetsky, Len Cook and Peter Dews.

One of the most important people early on was my collaborator Ruth Rushton who had been a GP but who joined us and was an excellent experimenter. The rat experiments were exacting and minutely timed, and usually 3 of us would need to get together to do them. We also had a splendid technician called Marian Dorr who married one of my PhD students, David Katz; David was one of the first to show how the social context could affect reactions to morphine.

Philip Harrison-Read now a successful psychiatrist with a special research interest in lithium was also of that generation.

Much later I collaborated with Elizabeth Sykes who had done classical work with John Smythies in Edinburgh on structure - activity relationships of mescaline in rats in the hope of locating the hallucinagenic fraction of the molecule. She and I had many discussions during the period when people were trying to make experimental sense of the hallucinogens. Nora Zaimis, by then professor of Pharmacology at the Royal Free, gave LSD and mescaline to day-old chicks and demonstrated that they almost immediately behaved oddly.

Philip Bradley who was professor of Pharmacology at Birmingham was influential, as was Michael Shepherd a professor of Psychiatry at the Maudsley. They and I did not actually collaborate, but we discussed many topics and problems over the years. and contributed to symposia and other meetings.

What was the feeling about what all this work might actually reveal? Did you have a feeling that this was a new frontier? Merton Sandler for instance talks about having been in the area for years without having realised that it was a new area but you seem more clearly to have been aware that it was a new area right from the start?

Yes and no. It was certainly new to me. But I did know what German scientists like Kraepelin had done, and I did know that there had been Grace Eggleton at UCL, a physiologist, who had shown before the war in a rudimentary but correct way, that the same blood concentration of alcohol was more potent if the concentration was increasing than decreasing, and if it was increasing quickly rather than slowly, which are useful principles to bear in mind. So I knew that there had been isolated antecedents but I also believed that what my collaborators and I were discovering was new, and I found drugs and their power and of course the discovery of new ones intensely interesting.

Between 62 and 74 when the BAP began what were the main forums for you to talk about your work?

We gave papers or took part in symposia on aspects of our work at many different societies. For example there was the Association for the Study of Animal Behaviour for whom some of the rat exploratory behaviour work was relevant. The British Pharmacological Society was very welcoming throughout. Two symposia under the auspices of the Biological Council and the British Pharmacological Society had me as secretary, and I edited the proceedings, jointly with the Ciba Foundation in one case. Both these books Animal Behaviour and Drug Action in 1964 and The Scientific Basis of Drug Dependence in 1969 became well known. I saw copies of them on students' desks in the States which was a surprise since I had no idea how far anybody in the USA read what we wrote in the UK. The British Psychological Society and the RSM also invited us to take part in Symposia, as did the Biochemical Society, International Congresses of Psychology and the CINP. I even gave a paper to a special meeting of the British Adlerian Society and at various other somewhat unexpected bodies, as well as talks at many pharmaceutical companies, research institutes and universities and colleges in the UK, the USA and Europe. Though hard work, this kept one's mind elastic and one exchanged ideas with a great variety of students and experts. Once you have got your own specialist society, this can confine you a bit and you need to make greater efforts to keep outside contacts.

A point you made earlier is that you think that in the early years because you all knew each other, and got on well it was possible to get things done. What impact do you think the sheer scale of things now has on development..

It seems to me that sometimes quality has not been as good and findings have not been as novel. It is much easier to produce novelty when there is not yet a huge corpus of findings, as there is now. Sometimes now, when I listen to communications I find myself thinking, well it is good for you people to have done this work, but if you had made a few searches and read a few papers you would have found that this particular point has been discovered before. On the other hand, young scientists profit from repeating and checking their elders' work, and this is one of the best ways of learning.

Also nowadays, with such a large psychopharmacology population it is almost inevitable that there are people who are "in" and other people who are "out", and those who are in speak in symposia and get kudos and the rest feel excluded. And so you sometimes hear the same people going over more or less similar ground. Many things do of course need to be said more than once, but I also think that people have become less willing to talk informally about current work and ideas because of our intensely competitive climate. Priority seems to be vital these days. Everybody struggles to fulfil targets and justify themselves. These problems can also arise with industrial collaboration. But there are examples where open exchange of views and information have worked to everyone's advantage.

When the BAP was born you were one of the most prominent non- clinical people, the only non-clinical person on Council?

Yes. That was also a bit of an accident. I saw the foundation announcement in the BMJ and went along, and someone from the floor (I think it was Paul Silverman) proposed my name, and there was a ballot and I got elected. Then I realised that other people felt that it should all have been organised differently. I was surprised at the strength of feeling, but strange things can happen when new societies are formed in a new area; many people want to be involved. In the end it was all sorted out. In a sense I suppose that most societies start with a group of friends.

You mentioned secrecy. What role do you think industry has had on the development of psychopharmacology ?

Mixed. The unique advantage of industry is of course that scientists get exciting new drugs to work with backed by big resources if success is in the offing. Sometimes you can find someone in industry, as we have done more than once, who is interested and the time is right for them - you can do very well then. They support you financially and give you your head. Maybe you won't get very much feedback from them but it does not matter because you can do the work and publish it and they can use what they want of it and they do. For example, we had excellent collaboration over a number of years with the late Maurice Shapero who was research director at Ward Blenkinsop later taken over by a big German company. A drug, a benzodioxane which was being tested as a centrally acting muscle relaxant, had been found by accident to increase mounting behaviour in male rats and we were asked to investigate. We were able to confirm this increase in mounting in otherwise sexually fairly inactive male rats and Professor Ian Russell at the MRC Unit at UCL found that the drug produced erections for several hours in singly housed male monkeys.

It was decided that I should test the drug more extensively in monkeys. I managed to arrange facilities in the primate station of a high prestige American university. So, armed with my white powder and a carefully-phrased technical memorandum, I set off to test pairs of "pigtails" (M.

nemestrina) for sexual activity, precisely defined. Despite the fact that only highly potent male monkeys were available who presumably exhibited a ceiling effect, there was no doubt that it was an interesting and powerful drug. Immediately after being given the drug the male monkeys showed marked muscle relaxation. This wore off after a few minutes and they became active, co-operative and helpful, even allowing the females to help themselves to raisins before they did - which was unheard of in un-drugged males.

This lack of aggression seemed to us even more interesting than the subsequent sexual stimulation, but the German company felt that a sexual stimulant with potential use in man was too risky and the project came to an end. For years afterwards we received enquiries from interested scientists and practitioners about the drug, and I suspect that if work on it were resumed now, it might be a great success. Drugs that reduce aggression are of at least as much interest as drugs that stimulate male sexual behaviour, and this drug apparently does both!

Apart from a few people in the early days psychologists have been very reluctant to go anywhere near drugs at all - as though that would compromise them..

I'm not sure that I entirely agree that psychologists have been reluctant. I seem to remember that in the early days almost anybody who was interested came to meetings and collaborated in research and there were a number of psychologists in this country who worked with drugs. Nowadays there are, quite rightly, ethical guidelines for giving drugs to human volunteers or to animals, including rodents but this has also increased expense and hassle and deterred some institutions and individuals, as of course has the occasional bad press and drug misuse.

In terms of the first CINP meeting or two, what were the issues that come back to you as being important...

One of the main administrative issues I suppose was who was going to be on the committee and run the show and how different nationalities and disciplines could be fairly represented. The main scientific issues centred around drugs and schizophrenia, in the broadest possible sense: neuroleptics, comparisons with other methods of treatment, psychotomimetics and thier role as tools for research, different methodologies and approaches. In the index of the first CINP Proceedings book, the largest number of entries was under 'chlorpromazine' with reserpine, LSD and serotonin not far behind. There was also gowing interest in instituting research collaboration between different countries and disciplines. There were quite considerable communication difficulties, partly language and partly ethos. For example I was by then working with both animals and humans and that was considered by some colleagues very unusual and undoable. And when they had a discussion panel, on the whole people gave mini-papers rather than discussed. I was sitting on the platform waiting to say my piece when I had a note from Joel Elkes, the chairman, saying something like "do please discuss and do not give a paper, we'd be very grateful". So I discussed and was praised by Aubrey Lewis. Aubrey Lewis was another influence. He was rather terrifying.

Why?

He was Mr British Psychiatry and had a formidable reputation. I knew him semi-socially through work and he was always very interesting to talk to. But I gather that, for example, there was a famous Saturday morning journal club at the Maudsley which he ran and which made everybody who had to give a talk very nervous.

You mentioned Joel Elkes. People seem to be split on whether he was important or not. Some say that he was because of the enthusiasm and ideas he brought to things, what's your impression?

He certainly was very skilled and helpful at meetings. I am still in touch with him now. His work with Philip Bradley on LSD quickly became well known. I think he was actually a nice sort of outgoing person who had many ideas and at the CINP meetings we had in Washington and elsewhere, he was very much a presence.

What did you make of Max Hamilton? He seems to have influenced the field at 2 or 3 distinct points. He came in with the rating scale in the 60s and came back as the BAP President.

I don't quite know why he was president of so many organisations because basically he was not an institutional type at all. But he was willing to give quite firm opinions on subjects such as how constitutions should be worded or how high subscriptions should be. Of course the Hamilton Depression Scale became very well known. Maybe people were grateful to have someone definite even if they disagreed with him. When organizations are being set up it needs someone who says loudly and clearly how things ought to be. Max was also involved in the foundation of the European College of Psychopharmacology.

Looking back at some of your early work on nitrous oxide, one of the striking things for me about this is that you were aware of Kraepelin's earlier psychopharmacology work. It shows an interest in history that is unusual.

Well, we had to find decent references for our own work and he was one of the first psychopharmacologists. I went to the Wellcome library and looked out what I could of the early work. I remember that he described a test of manual dexterity which involved threading needles under the influence of caffeine. The interest in history was partly due to the training of Sir Cyril Burt. We realised that Germany was a strong source in the early beginnings because Burt was very scholarly. That's really how I came across Kraepelin; I don't know why so few people know about him. Then there were hallucinogens.

As in mescaline?

Yes there's a long history of mescaline that goes back to about the 17th or the 18th century. I had a big bibliography on this. That was probably one of the earliest psychoactive drugs apart from alcohol and opiates. Opiates are particularly interesting at the moment because of the link with endorphins. To begin with I kept well away from the huge, complex and largely biochemical literature on endorphins but they have turned out tremendously appealing. Some people think it rather miraculous that we should make our own opiates but to me it seems quite natural. After all, we make our own adrenaline and 5HT, and so why was it such a sensation?

Any thoughts?

I don't know. At the time, 1975, we went off and bought Nature and there was the first article. When I looked at it later in the College library most of the page had been worn away by numerous thumbs. To us it was particularly interesting because we knew Kosterlitz and Hughes, although not well. Kosterlitz had been host at a symposium on opiates in which I took part a few years before. It's not so amazing though that painkillers should be made in the brain. Would you be surprised if LSD were found in the brain?

After the discovery of endogenous opiates, no but that was really the watershed and the question is why did it cause such surprise? It made sense of pharmacology in a way that a compound like LSD - a fairly exotic compound, alien to the brain, didn't.

Well is it?

Perhaps not but until opiates were actually found in the brain you had people like Jaspers and so on talking about drugs like mescaline in terms of them being poisons. After the discovery of the endorphins, drugs were not quite the same poisons - they are actually there in us to begin with so you're not actually corrupting some spiritually pure thing. You are altering the balance.

Altering the balance. I think that's actually the most useful way to look at it - to say that one is altering the balance or improving or restoring the balance. It is a better approach than expecting a particular drug to do one particular thing exclusively.

Now that one knows more about the brain, it makes more sense to look at it as a highly complex and constantly shifting network. It may be unrealistic to expect one single drug, unless, it is a multi-faceted drug, to "cure" something. Whatever you administer you may disturb something else as well. The drug companies on the whole don't like that concept.

But, for example, if there had been more discussion about what used to be called "autopharmacology", something like the endorphins would not have been such a sensation - when you think about it, it becomes fairly obvious that all sorts of substances we call "drugs" are actually variants of naturally occuring endogenous substances.

Autopharmacology is not a term you find around much really.

It is not in every textbook but it was in some (Greek "autos" = "self"). Often it is words that determine what happens. I can give you an example from our own work. We published a paper on drug dependence in rats who were used to drinking solutions from a bottle. The paper was called "Development of morphine dependence in rats: lack of effect of previous ingestion of other drugs" (5). We asked whether rats, given the opportunity to drink amphetamine or benzodiazepine solutions would become dependent on these drugs and would then more easily become morphine addicts. And the answer was no. There was no connection at all. Now in the USA there was something called "the stepping stone theory" which says just that. You graduate from cannabis to heroin. If we had called this paper "The Stepping Stone Theory Rejected" instead of the boring title we gave it..

You'd have had much more citations ..

and more impact.

I'm sure you're right. Some people coin the right phrase. People like Tim Crow with Type One and Type Two Schizophrenia, which is all wrong but the marketing principle works. Merton Sandler had the same point that he and Michael Pare in effect produced the amine theories of depression seven years before Schildkraut but they didn't quite call it something catchy like the catecholamine theory of depression. Now you began working on humans with compounds such as nitrous oxide but later moved onto animal work. Why the change from human to animal? .

I think in those days animal work, especially rodent work, was regarded as much more basic than work with humans. It was "real" science. One felt it was more controllable than experiments with human subjects, and of course much of experimental psychology was based on rodent behaviour and so there was good background information, and one could test many more mice and rats than humans in the same time and devise ingenious animal models. To begin with our animal work was very restricted because we had little equipment and used semi-naturalistic methods of testing, which was actually good. They were very gentle and meaningful situations for the animals.

Could you argue that to some extent that the animal work today is less sensitive because we have these high powered animal houses and people have lost a feel for animal ethology?

I would agree with that. Some current work seems to me too mechanical and routine and probably doesn't tell us much about animals or about drug effects. It may tell us something about underlying processes but even then I'm not sure about that. But there was a lot of pigeon pecking and rat bar-pressing at that earlier time that was in many respects not much more sensitive.

You mentioned Roger Russell as one of the people who helped to develop animal work.

He not only developed animal work; he set up the laboratory and enabled the rest of us to have this facility. Until one actually works there one does not realise how much work it is to get an animal lab going. The work I did with Roger was actually human work. But he had set up a small animal lab at UCL with Ralph Watson as a permanent member of staff and he and I were able to show that male rats stopped growing if you changed their habitat, for example, their home cage, but if one restored the normal environment they started to grow again. This paper was listed by the Royal Society in its recommendations for implementing in the Home Office Act in 1986 (6).

So, you're saying that before possibly the middle 1950's it would have been quite rare for any pharmacology department to have much in the line of an animal house for ...

For behaviour work. There were many animal houses for medical sciences but not for behaviour studies. Roger Russell set up behaviour laboratories, first at the Maudsley and then at University College where it started with just two small rooms in a basement. It was said that the space had been condemned as a book bindery but it was all right for psychologists and rats.

What kind of things did you hope to tease out with the animal work?

We devised "animal models" which mimicked in some simple way what happens to human subjects. For example, we subjected rats to mild and simple forms of "stress", such as changing their environment or diet and gave drugs to see whether they would reduce the effects of stress, measured mostly by loss of body weight. Both chlorpromazine and alcohol reduced the weight loss effect. This was a simple and useful measure. We also measured blood sugar and again the drugs reduced blood sugar rises in response to stress.

In the late 50's there would have been people who were using animals to test what the drugs did in the brain and you also had people working with animals and their behaviour per se, but was there anyone before you interested in the actual impact of drugs on animal behaviour? I can't imagine there were terribly many.

No there weren't many. I suppose Roger Russell, although drugs were not his main theme. There was Malouka Khairy - she was Egyptian. She worked in the UCL animal lab and did work with dieldrin and showed it did impair muscular performance. Ralph Watson who was in charge of the laboratory often collaborated with me at the time. Gradually most of the major psychology departments in this country established animal laboratories and many of them worked with drugs.

If one tries to get a picture of how over the years psychopharmacology has developed, it probably is still as it was at the start, with scientists and practitioners trying mutually to reinforce each others' skills. It is one of the strengths of the BAP that it continues to bring them together. When I started out I had many contacts with psychoanalysts and psychotherapists and used to listen to their papers and try to work out how one could transform their statements into experiments. It was not always easy.

In the early days, looking at the question of drugs and how they may be used to actually investigate behaviour, Eysenck was a big name ...

Yes. He wrote a book called "Experiments with Drugs" in 1963. It was very much linked with his theories of personality, stimulant and depressant drugs causing opposite effects, later expanded to include parallels between the effects of different drugs and personality type, some of which have stood the test of time.

Was this work eclipsed because of the cloud over LSD made it seem like a bad idea to give drugs to healthy volunteers? People like Gordon Claridge for instance pursued Eysenck's work through the early 70's and then it stopped. But you don't really hear of Eysenck's theories being conclusively disproved ?

I do not think that Eysenck's ideas were dependent on LSD . Since that time we have had have had to come to terms with the fact that drugs which act on the CNS mostly have highly complex actions. It has also progressively become more difficult to do experiments with human volunteers for justified ethical and practical reasons. LSD did have an impact partly because its effects could be spectactular and because people used it illegally. It slowly became realised that it was not a safe drug to play around with, and Sandoz stopped making it.

One did hear awful anecdotes such as people throwing themselves out of windows under the impression that they could fly. It works in very small amounts, thousands of a milligram, which is pharmacologically interesting because it suggests a naturally occurring substance, but this makes it extremely poweful and far too risky to use. In addition to the general ethical tightening up on human experiments more and more substances are now available, and experimenters cannot really try them out on themselves as they used to.

Are you saying that during the late 50s and 60s you or anyone else working in the field would try out most of the things themselves.

Yes, if one worked with volunteers such as medical students, or at least be willing to. And that is partly why I never worked with LSD because I would not take it. At one time as you know it was thought that it might give special insights into psychotic behaviour.

So what happened to Eysenck's approach. He was an invited speaker at one or two of the early CINP meetings

He was certainly at a symposium in Bonn where he and I spoke and even argued on the same platform, but I think this was an International Congress of Psychology. How far his way of looking at drugs in terms of a theory of stimulation and depression and personality types and what this meant personality and brain-wise ever fitted into the mainstream of thinking is hard to say, though this does not mean that he was wrong. On the whole receptor and neurotransmitter ways of thinking are very remote from human behaviour ways of thinking. Silvio Garattini mentioned recently that in his opinion there was still a big gap between what drugs did clinically and what they ought to do according to their biochemistry, and that it was still possible to talk about these two aspects quite separately. People sometimes drag in receptors because they feel that it is expected of them and it makes their work respectable, but I don't think that there is necessarily a close connection.

If you think of Eysenck you think of learning theory. One of the interesting things about the early days with neuroleptics were that people were looking at the effects of chlorpromazine on conditioned reflexes and on the rope test... What was the rope test?

It was a conditioning test where a rodent could learn to avoid a shock by climbing up a rope that hung down in the middle of the cage. There were actually two strands of research. There were the psychologists who were using mostly established tests like Skinnerian type responses to map what drugs did for responses to different schedules of signals, and then there were the other kinds of test which were mainly devised or dusted down by pharmacologists who wanted quick returns, a simple method which gave big effects. And there they devised a host of tests from antagonising body temperature falls to rather more behavioural tests, such as food intake, mouse "waxy flexibility" or ataxia, sleep measures etc, but usually fairly gross behaviours. They hoped that these could distinguish between several related but not too similar substances by this means, largely on an empirical basis.

When we did the backward walking experiments, we moved from an interesting interaction between drugs which had not been expected and which could be obtained very reliably to a potential method of screening. This is much more the sort of pharmacological type of behaviour, that is, an empirical test which happens to discriminate, for whatever reasons, between clinically different drugs. We have discussed it with many scientists including ethologists, and I suppose you could say that walking backwards might be a fear response but there isn't much evidence of that, from careful observations of the behaviour, as in the films we have made.

There are problems with animal work these days. The whole question of the animal liberation movement and all that has come to the fore in the last 10 years. Do you want to comment on why these things have happened?

Some of it is justified. I have myself seen, not in this country, unnecessarily strident animal experiments. But it would be a great loss to medicine and to science if all animal work were stopped. At the same time it is right that work should only be carried out on important medical and scientific problems and should be subject to regulation. It should be done with the minimum number of animals, and should be competently done. And scientists and physicians should realise that you can extrapolate from animals to man. If you could not it would be fairly unjustifiable to do these experiments at all. In the past I have often found a good deal of resistance to the idea of extrapolation. People may feel that man is so much more complex, special and interesting than animals. I don't think so. If you do ethological work as I have been involved in you realise that animals actually have an enormous behaviour repertoire. They can be very pleased and stimulated to explore the environment or scared and disappointed. To deny this seems to me unrealistic.

You became very interested in the whole area of substance abuse and the big thing for me reading through your articles is the emphasis that you had on the interaction between the drug and learning or the drug, learning and the environment. Do you want to tell me why you got into that and what do you think the outcomes have been.

This came from work with Ruth Rushton on drug combinations where we found differences between habituated and naive rats. Naive rodents showed the highly stimulant effect of drug combinations but rodents habituated to the test environment didn't. I It seems pretty obvious that there must be interactions. But some people, particularly pharmacologists, wanted to look at the "pure" drug effect irrespective of any other factors such as the internal and external milieu, and basically I do not think that you can do that.

Would you go so far as to say that there's no such thing as a pure drug, or if there is it's an artefact almost?

Almost. Certainly with psychoactive drugs I would have thought so. Because you can only test a drug on manifestations of overt behaviour. The manifest effect is a compound of drug plus personality plus environment plus suggestion and so on. Therefore, I think for example that double-blind clinical trials may often be misleading because there again there is a search for a "pure drug" effect compared with a placebo but in real life drugs aren't given without any suggestions. In real life you say to the patient "this is going to help you" and that is a reinforcement which may work very well with some drugs, for example, those that inter alia increase suggestibilty or which are prescribed by a confident doctor but not so well with others. Therefore it is quite important to vary not just the drug dose but also to vary the environment and vary the personality as far as you can.

Vary the personality?

By that I mean one should that test drugs on different kinds of personality to discover which drug suits which kind of individual. To get the optimum drug effect in a patient you ought to look at their personalities and the environment quite specifically. But why is there such keeness to find this pure drug effect?

I guess that's the way science goes forward, you try and get it as close to a pure effect as you can and in so doing you find out the other influences on what you're looking at .....

But is this really helpful if you're trying to develop drugs for practical use because you're actually taking away the practical use. Now it may be that that this teaches you something else which you can only learn that way.

In the field of dependence on drugs I guess the interactions between the environment and drug are more obvious than in any other area of psychopharmacology. There are people like Jane Stewart working in this area now.

Yes, and others who moved this forward also. There was a USA scientist called Ross I think, who gave drugs such as amphetamines and barbiturates with opposite instructions, for example, that amphetamine would make subjects sleep but that sort of research isn't very strong at the moment is it? Maybe I am wrong.

The curious thing about it is that there's been so much good animal work done in the whole area of interaction between drugs and learning that hasn't translated it seems into the clinical situation. Have you any ideas why that's the case?

Maybe psychiatrists deep down still don't think that animal work is relevant to man. And I suppose another reason could be that it's easier to ignore animal experiments if you are working as a practitioner. It's easier to say "oh drug X does so and so" and not to get too involved in the often equivocal evidence on drug-environment interactions.

I guess politically it's always easier to just give a drug than to try to change the environment?

Absolutely. On the other hand did you see a recent newspaper report that people in hospital got better more quickly if they had a view of trees than if they had nothing much to look at. This really seems to be pathetically obvious but even so it has to be demonstrated.

Malcolm Lader worked with you...

Yes he did, on amphetamine-barbiturate combinations in medical students. He has been very consistent in evaluating different drugs and experimental and clinical situations. I am not sure how far the dependence problems with benzodiazepines are as fierce as the media maintain. I suspect it's like so many drugs. It becomes known that there is interest in a particular somewhat dramatic effect and then it becomes a self- fulfilling prophesy. It's rather like amphetamine becoming completely proscribed and naughty in the 1960's when for many years it had been helpful with not much trouble for middle aged housewives or whatever. On the other hand, the longer a drug is successfully in use, the more over-prescribing is liable to occur.

It's awfully curious isn't it that people can go along quite happily for 20 years with no problems really and then all of a sudden things change and it seems like the end of the world if you have these terribly nasty drugs.

I wonder why? Maybe somebody publishes something which gets taken up or somebody is on an influential committee. I'm not sure that it's always justified. On the whole I feel that drug addiction has been made too prominent in the media and for some reason which I do not fully understand they have made it seem extremely interesting. If you are at a party and say you work on drug addiction you are immediately an object of curiosity.

Addiction of course has repercussions way beyond drugs, in the sense that there are all sorts of dependencies which seem to be quite as strong as drug ones but somewhat different because they don't involve ingesting anything. In our present society there seems to be a high place for activities which become compulsive and very central to people - gambling, collecting, shopping, eating, computer games, physical exercise and whatever.

In the middle 80s, you became very interested in the whole idea of people becoming addicted to exercise. Can you tell me why you got into this area? You must have been one of the earliest people to start talking about exerice addiction in this country.

Yes I suppose so in this country; David Veale was another. Elizabeth Sykes and I wrote a review article which was pretty early in the field (6). Exercise is relevant in psychopharmacology because it seems to release endorphins into the blood stream and endorphins are very interesting substances. We had a post-graduate student who wanted to do a PhD on exercise and depression and she was an aerobics fan. Then came an invitation to chair a symposium

on psychological aspects of endorphins. In order to do this I thought I'd better bone up on endorphins. Exercise was discussed and the favourable mood effects of exercise were stressed, and so I built my introduction to the symposium around exercise. The meeting was held early in the morning, about 8.30, just after summer time had started, so it was really 7.30, and we thought nobody would turn up but in fact it was very well attended. Eventually it led to publication of the review article in an American journal on the possible role of endorphins in the mood effect following exercise - at its extreme the controversial but well known "runners high". We found some literature on this, mostly American. The review we published was apparently very successful - people wrote from all over the world for copies including The Japanese Horse Society. We were pleased since it had been a terribly hard job to get it written because it compressed large quantities of scattered work into a small space, and we had as yet no PC.

Because endorphins are interesting in the same way as drugs are interesting, one went on do more work on exercise and its psychological benefits. Although there is plenty of evidence, it is still not widely known that physical exercise has favourable psychological effects on mood and self worth. I think that for anyone interested in well being it is a very interesting topic. People have also done animal work since you can get animals to exercise spontaneously, for example, by giving rodents activity wheels. Rats will cover several kilometres a night if given the chance. And because the public interest in physical exercise is quite great it does bring with it media attention, which these days is probably very valuable. We were fortunate to get a grant from the Wolfson Foundation for this sort of work and a research assistant, Elizabeth and I were keen to determine how long the mood benefits last and whether benefits differ for different kinds of people and circumstances (7).

Can you give me some outline of what kind of findings seem to be coming out?

Habitual human runners will become anxious, depressed and generally unwell if deprived of their habitual running for even a fortnight. Experienced exercisers have a different mood response before their weekly exercise session, as compared with beginners, the advanced class feel much less well and happy than the beginners. On a scale from positive to negative feelings the advanced ones do rather badly pre-exercise but do pretty well post-exercise. The beginners are much better pre-exercise and about the same as the advanced post-exercise. So the end point is the same but the beginning is different. It does seem to us that the advanced class is much more dependent on exercise and miss it much more.

What about the impact of exercise on mental state, quite apart from it making you feel good, do you think it has any further effects? If you go back 100 years or so, before we had drug treatments or psychotherapy, people like Pierre Janet talked in terms of lengthy hikes in the mountains being therapeutic for people who've got mental problems

There is a good deal of work, some of it carefully controlled, which shows that physical exercise relieves anxiety and depression provided that they are not too severe. If depression is really severe, one probably cannot get people to exercise. But there is now growing a consensus of evidence for mood improvement in patients. And deliberate exercise prescription by GP's is beginning, but its not happening yet, I think, in psychiatric hospitals.

No, it's a thing that I actually feel quite strongly about. We take people in and we immobilise them which cannot be good. Is there anything that could be done.

It has been said that hospitals are not places for sick people. You could build exercise into a structured programme so that patients have the exercise to look forward to. Also I think that you want to be very supportive very early on, so that they get praise and feedback for doing it -

to get them off to a good start. And then with luck exercise will acquire a reward value of its own. To begin with one probably has to make it a group activity and take them out, which in psychiatry may be difficult.

I don't think so really. What kind of exercise programme would you do?

It would depend on what people like. Some like aerobics and some like aerobic dance, which are energetic activities. Some like swimming but that's not very social. And running is not very social either. Brisk walking can produce good results. Anything that people like, probably.

Actually the evidence for patients is somewhat better than for normals. The reason I think is that it's easier to test patients and therefore more controlled work can be done. One problem with all this exercise work is control groups and the comparability of exercise regimes. You will find that often not enough detail is given in publications. When trying to draw conclusions, it would be useful to be told what the exercise was like and the structure of the session but mostly papers just say "subjects did aerobics for an hour".

You also need a very good teacher. We have one at Middlesex University who is very enthusiastic and dedicated and so she can adapt herself to our experimental needs. But there have hardly been any trials in which, for example, antidepressant drugs and exercise, or drugs combined with exercise were compared.

As I said it seems crazy we just sort of immobilise people. They are left to wander up and down this ward and perhaps go along to the day hospital and make some baskets. I'm sure they need something more active.

Quite so. People think when they send somebody to a mental hospital that they will be fixed up but often the treatment seems to be rather haphazard. I also think that exercise might be an effective, cheap and relatively pleasant treatment for drug addicts, since endorphins might substitute for methadone.

For the last 30 or 40 odd years, for the first time in human history we've been able to tease apart elements of human behaviour by using drugs, what in your view has the whole effect of psychopharmacology been on culture - on what we understand of ourselves?

Drugs have become part of society. But even the word drug itself has changed its meaning from meaning medicines, which make you better, to psychoactive compounds, which are used "socially" and this is not so good. As for what psychopharmacology as a whole has found out, as I have said, probably most psychoactive drugs will turn out to be available in the brain naturally and to that extent I think psychopharmacology has been hugely influential because it has suggested new ways into the brain which nowadays with modern scanners can actually be checked and taken further. As a subject, psychopharmacology is rather more socially useful than many others. It is more interesting and challenging but it's also more rewarding because you do have the possibility of dramatic effects which you don't have in many subjects. With, for example, psychotherapy people sometimes have to struggle hard to get an effect but with drugs it is intrinsically easier.

Yes, huge effects which are too big to control.

But that is one of its attractions and I think drug companies could do much more than they do. To give more emphasis to new methods and new drugs and to encourage innovation.

You've commented on a great number of women who have worked in the field - why have they been hidden from view so much?

Certainly, I always understood that I would go to University and that I suppose was even in those days fairly unusual for a woman. At the time, when I started in psychopharmacology, I was probably the only woman who had any sort of established university position, then Daphné Joyce went to Bikbeck. And later Elizabeth Sykes worked in Edinburgh and Bangor. More recently of course there have been several prominent women in this country, Sandra File, Sheila Handley and Susan Iversen.

Nonetheless women are still expected to be assistants and agony aunts rather than independent scientists, let alone heads of departments. I also think that some male research students may find it harder to be supervised by a woman, which is understandable, if not desirable.

Why?

Because women for a long time have not been taken very seriously. So, while I didn't think it was odd for me to do science, other people must have been very aware that here there was a female. Somebody once said to me that women can do quite well in new and unusual subjects and that again I hadn't thought of.

Once it becomes mainstream the men tend to move in and take positions.. . It's always been a puzzle to me since women are obviously much more intelligent than men

Are they?

I hate to admit it but exam results show it clearly

Perhaps women are more adaptable and innovative because they have to be, and there is evidence that they are more verbal. I know that I felt that I must work harder than men to justify myself. To begin with I did everything myself which teaches one a lot, but is very hard work Maybe men are actually better at getting other people to do things for them. If women are more intelligent than men, then why are men so dominant?

Well, women as you say have been tied to the house. They haven't had the opportunities but give them a level playing field and they'll win any day of the week.

In some ways I think yes. I have been involved with academic women's affairs for some years. The number of women professors has recently gone up at UCL to something like 20 from 4 thirteen years ago, this is about 3 times the national average but still only 9 per cent of the total professoriate at the college. In clinical subjects according to a recent report there seem to be hardly any women professors and things are unlikely to improve overnight. There is still a feeling that womens' work is not taken seriously and as a result they don't have the confidence to put forward new ideas, no matter how potentially fruitful, and the current hyper-competitive climate makes it harder for them. So, women on the whole do less well in contributing to a subject. This is a pity and a loss to science, and something that I should very much like to see improved.

People said that my own work was "pioneering", and it is certainly encouraging to know, for example, that some of one's findings and methods were of interest at the time and are, in

some form or another, still so now. But if what I experienced is typical of "pioneering", it was above all extremely concentrated and demanding work, with luck and success outweighing disappointments. And this is how my scientific life seems to be continuing today, and I would not have it otherwise.

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