11 Alec Coppen

Biological psychiatry in Britain

Let's begin with how you came into the area.

I came out of the army in 1946 with no particular idea about what to do with my life and then after I read a book on abnormal psychology (*Outline of Abnormal Psychology*) by William MacDougal, I thought this area would be very interesting. So I thought well this is what I'm going to do, knowing absolutely nothing about the area, and then I found out that if I was going to do psychiatry I'd have to do medicine.

So, I looked around the medical schools and of course in 1946, everyone was trying to get into University – if you'd been in the forces you could get in if you passed the matriculation and then they would select again after the first year's results. I couldn't get into London because that meant waiting an extra year, so I decided to go to Bristol which seemed to be quite an agreeable place.

The first year was probably the most difficult academic year of my life really because you had to take your first MB and they had to weed out up to 60% of our year. But it was a very interesting year because you know everyone had been in the services so you had quite a lot of interesting people there. After that it was a straightforward medical degree – again a very mature year and an interesting time. I think at that time everyone who had been in the army got free tuition and I think something like \'a350 a year to live on. Then we did a house job but only had a very meagre salary.

After that there was only one place to go and that was to the Maudsley. As I was going on holiday I decided to ask the Dean if they would interview me early, which I suppose was a bit of a cheek. Anyway they interviewed me and I obtained a job at the Maudsley. After my general psychiatric training there, I went to the metabolic ward, which was ward 7, which I think is still probably there.

Who was there at that time?

Well, there was James Gibbons, Gerald Russell, John Hinton and others. My particular interest then was in the blood – brain barrier. I was using

sodium[24] as an index of transport and I found an impairment of transport but it subsequently became difficult to do these sort of experiments.

This was on people who were depressed . . .

People who were depressed and after recovery. We found a decrease in sodium[24] entering into the cerebrospinal fluid from the blood. Using blood – plasma sodium ratios, I worked out some sort of transport parameters. It was difficult to do but it fitted my ideal experiment, where you examine a group of normals and then a group of depressives when they are depressed and depressives after they recover. I might say that right from the beginning I was interested in mood.

Why?

Well, clinical research is a matter of practicalities. I thought neurosis was too difficult, too ill—defined. I thought schizophrenia was probably the same but depression and what we now call bipolar illness was interesting because people got ill and then they got well, so I didn't think there was any tremendous irreversible brain damage. I think it was a good choice actually.

Who else was working in this area?

There was James Gibbons, looking at body electrolytes. When I joined the MRC unit we continued using exchangeable sodium but then we could also measure total body sodium and potassium. We got measures of intracellular and extracellular sodium and the results were amazing. To summarize it, David Shaw and I found that, during a period of illness, residual sodium which is exchangeable bone sodium plus intracellular sodium actually increased and when they got better it decreased. In mania we found the same thing but to an even greater extent. We also had measures of total body water using tritiated water, radioactive bromine to measure extracellular water and body potassium using the body counter at the Royal Marsden in Surrey (Coppen and Shaw, 1963).

At the same time in the 1950s, I was also working on stress. In those days I think stress was just going out of fashion. You know these things are cyclical and stress is back now. But certainly in my time at the Maudsley, people were getting a bit fed up with the concept of stress. It could either mean the disturbances you feel or being exposed to disturbances in the environment. Obviously, therefore, there are two quite different things. I did my share in that area, looking at environmental influences on pre—eclamptic toxaemia. I did a study in Croydon at Mayday Hospital and we showed that primiparae with a lot of environmental distress like being chucked out of their lodgings because they got pregnant, were more likely to get pre-eclamptic toxaemia. My conclusion was that environmental factors played a small part in the picture but there were

also constitutional factors. They were more neurotic, had more sexual difficulties and a variation in body build.

That was work Linford Rees had begun.

That's right, I've been a great friend of Linford Rees since 1954. Another person I met then was Valerie Cowie, who has made great contributions to genetics. She became a long-term friend of mine. She's a brilliant lady. Then there was Elliott Slater who I think was one of the great people of British Psychiatry – the number one for my money. I've worked with him and I found him very stimulating. One of the best minds I've ever met.

So I was interested in body build and the androgeny index. Androgeny was based on the non—genital differences between men and women. The most common index used was the shoulder to hip measurement. Before puperty you cannot differentiate between girls and boys on this but during puberty under the influence of the sex hormones this changes, so it is obviously a sort of record of the endocrine development during puberty. What I found was that certain schizophrenics have an abnormal androgeny score. They approximated to a rather neutral build; depressives showed that a little bit but not as much. Homosexual men were perfectly normal. But the schizophrenics certainly had an abnormal body build. We took that as far as we could and looked at other factors like calf X-rays. I don't know if you know but you can sex someone's calf X-ray with 70% accuracy. So we looked at that. The idea was to get some idea of someone's endocrine development during puperty.

Did this fit in much with Eysenck's models of temperament and personality?

Yes, it did but a better dimensional model of personality I think is that of Sjobring, the Swedish psychiatrist in the 1930s and 1940s and his successor Essen-Moller. Sjobring had three dimensions of personality and in fact my wife and I translated his personality questionnaire into English – I had a Swedish wife and therefore I used to go to Sweden regularly. One of Sjobring's dimensions is validity, which translates as energy. Another is stability, which has to do with introversion – extraversion and the third is solidity, which is psychic organization. He called them by these funny names because he didn't want them to have any values attached to them. But the result that came out of our studies is that the unipolar depressives have low validity even when they have recovered – they don't change on recovery.

Validity, the energy dimension, I think is very important. I think it's a vital thing in personality and high validity is very useful. I think I've got high validity. My solidity in organizing things is average and my stability, extroversion – introversion, is average also. I could tell you the profiles of very distinguised people but that's obviously confidential. But the characteristic that everyone has who's achieved anything is energy. If you

haven't got energy, however much intelligence you've got, it doesn't do you any good. This is why some people don't make a very positive contribution – because they are so critical they are paralysed. You know you've got to be naive to do research.

You think so?

Oh, yes. You've got to be critically naive. You've got to put your hypotheses forward and see what happens. I think what I can do is I can ask questions that are answerable. They've got to be interesting questions of course and they've got to fit in with the fashion. As I said stress went out and stress came back.

Stress has only come back in the last five years.

There are a lot of unsubstantiated statements made about stress and illness even from the WHO. For example, look at hypertension in people with severe depression. There's no one who's more disturbed emotionally than someone who has a severe depression but there is no evidence that these patients have hypertension and no evidence that stress reduction would have any impact on the morbidity of hypertension. But these things come back insidiously. Psychotherapy is another example of changing fashion. When I went to the Maudsley, there was always some American coming along to talk about the definitive research as to whether psychotherpay is effective or not and we used to troop along to listen. Robert Cawley was going to do a study of the effectiveness of psychotherapy but at the end of the day I think he felt it couldn't be done. In the end, I don't think anyone has defined the issues in terms of things you can measure. Psychotherapy went out of fashion and then counselling came in – marriage guidance and things like that.

Your early work culminated in the 1967 article which had an immense impact. What kind of feedback did you get for the 1967 article – it was very much the British equivalent of Joe Schildkraut's article.

I got a very good feedback (Coppen, 1967). It became one of the first citations classics in the area of biological psychiatry. You still see it cited by people who want to show a historical perspective. Some people find it very hard to think anything of importance might have happened more than 20 years ago.

One of the differences between here and the US, when Joe Schildkraut was doing his bit, was that they didn't have the tradition of biological work in small little places that there was here. They didn't have the Archie Todrick's working up in places like Dumfries.

I think small groups actually are quite a good thing. The old MRC tradition was that once you were accepted, you were more or less in a tenured position. Once they picked you, they backed you. I think it must

be awful working for five-year grants and so on. I used to put in grant applications for what I had already done and I found that was a quite good idea.

It depends on who you have with you. The people who worked with me in Epsom included Art Prange and Peter Whybrow, who were both interested in thyroid activity. The thing I've learnt from a lot of this is that to have a good response to antidepressant drugs, first of all you've got to have a normally working thyroid and you've got to be well nourished, you've got to have enough folic acid. Ted Reynolds opened my eyes to folic acid. I've done a lot of experiments on it since then. Brookesbanks was our steroid investigator. He was very good. But really we were always a small group, never very big.

Now, in contrast, I think what we lack and what they've got in the States are opportunities. If you have problems in the States you can go off and start again in another State. But what can you do in this country. Everything is done by small groups of people. The MRC is a small group of people with a basic representation from psychiatry and most of those were social psychiatrists so they were very, very conservative. People who did come from biological psychiatry didn't have much influence.

What about endocrine work. In the mid-1950s there were people like Hemphill and Reiss and Harris at the Maudsley.

Yes, Harris was very distinguished and he did a lot of work on the portal circulation of the pituitary but he wasn't a clinical researcher. It's always been hard to be a clinical researcher. People escape to animals or to administration. A lot of people who did the initial work stopped doing any more, you know, once they became editors or heads of department and so on. If you do ten years in clinical research, that's a pretty good average. I've kept doing it till today but that's unusual; most people give it up much sooner. Also, I think, a lot of people have a limited amount of research in them. You do it when you're a young person and that's it.

In a sense the unit with Derek Richter and yourself was one of the few places were the marriage of neurochemistry and clinical research actually happened. Can you tell me about your move to West Park.

Well, we moved first to a hospital around here called St Ebba's but they decided to change it into a hospital for mental subnormality. Then Derek Richter and I went to West Park to see Theo Schlitt, who was the medical superintendent, and said what we wanted to do and that was it. We got an architect from Brighton, who constructed a laboratory adjacent to one of the wards which became our clinical investigation ward. John Bailey was working with me at that time. He was a very important person in the unit actually because he was the chap who could arrange the practicalities of a study. You've got to have a person who can make up for your lack of organizational capacity. John Bailey was that for me. We sat down

and drew up plans for the architect and the whole Unit was up and going in six months.

I always say that the first thing you must do when you start research is to have an idea and be doing it. Everything else is rubbish. If you spend all your life waiting for the right grant you'll do nothing. The only thing you and I haven't got much of is time. So even in St Ebbas' where basically the only thing we had was a corridor, we were doing whole body measurements with a bedrest I pinched from my wife and a radioactive counter – that was 1961 and 1962. It's important to get things working. It doesn't matter about the environment. It doesn't matter if you've got a secretary or not or a nice desk.

My idea in West Park was, as Claude Bernard said, to bring the bedside to the laboratory. We had the laboratories tacked onto the ward. We designed a ward that would hold men and women. I think 16 was the maximum but we very rarely ran it full. My principle was that you should give a very good clinical service to the patient. They shouldn't suffer because they've been investigated and from the beginning that was our philosophy really. So we followed up our patients which led us into lithium. We felt it was good that we should continue to see the patient but we also learnt that seeing patients long term is very educational. Very few academic people do that actually.

You produced some very interesting electrolyte results that have never been refuted in any way and arguably the mode of action of lithium could be seen to fit in to that, why did that kind of idea all of a sudden go dead. Why did it not . . .

Well, lithium and electrolytes didn't fit together very well to be quite honest. Lithium had few effects on electrolytes that we could detect in our whole body measurements. The effects of lithium on 5-HT were much more marked. We found that it normalised 5-HT transport in depression. Work on lithium also led us to the 5-HT hypothesis.

How did that come about?

That came out of one of the crucial experiments of 20th century psychopharmacology! (Coppen, Shaw and Farrell, 1963). You have to remember how incredibly little knowledge we had in 1960. One idea was that amines were important and most people, particularly the Americans, had put their money on noradrenaline. We thought it was worth looking at other compounds and I was impressed by a paper that was published by Kety and associates, who gave monoamine oxidase inhibitors plus tryptophan to schizophrenics. It didn't do anything for schizophrenia but they thought the patients felt better on it and were less depressed. It was a very good example of the importance of careful reporting of clinical responses.

I said well, okay, 5-HT may be important in depression. So what we did was we got a selection of people with severe depression and put all of them on a monoamine oxidase inhibitor and to one lot we added a

placebo-tryptophan and to the other we added the active form. This was done on a random basis and the trial was double—blind. The difference in response was dramatic. If you look at the data, it wasn't a small difference, there was a big difference between the two groups. These results have been replicated several times. This combination of an MAOI and tryptophan was really the first 5-HT treatment. I claim that it was the first observation that suggested that 5-HT was important in depression – an idea that is now the centre of a multi-billion pound drug market. For many years, people said yah-boo sucks – there's nothing in this and, as I said, fashions are everything in medicine and 5-HT was not in fashion.

When we tried to get people from pharmaceutical companies interested, they didn't want to know. In fact, in the 1970s, Eli Lilly had a conference, about a drug they had called fluoxetine which they didn't know what to do with. So they had a conference at their base in Surrey and they asked me to make a contribution. Of course I was enthusiastic about 5HT and the possibilities in mood disorders. I always remember the Vice President of Research saying 'I thank Dr Coppen for his contribution but I can tell you we won't be developing fluoxetine as an antidepressant'.

Really?

Yes. That was a bit like a person saying 'people are fed up with these boys from Liverpool, they'll never go anywhere . . .'. In fact they must have made billions of dollars out of it now.

So, at this time we had three horses. We had the amine horse, the electrolyte horse and we had the endocrine horse. My hypothesis was that maybe one of those things upsets the balance. There could be too much cortisol, which might affect the distribution of electrolytes and 5-HT. This interesting research on electrolytes we couldn't take any further because my philosophy has been if you find an abnormality try and manipulate it and see what happens to the patient . . .

But there was no easy way to manipulate electrolytes.

No there wasn't. We tried diuretics and steroids but that didn't do it. So we left this area because we couldn't really take it any further and as I said lithium didn't seem to be working through anything to do with electrolytes.

Where did your interest in lithium come from?

Well, the world of biological psychiatrists was very small in the 1960s. Everyone knew everyone. You're asking me about people in this country, you can easily ask me about people in the world. I've known Mogen Schou since about 1959 I think. I knew about his work and that's why we got onto lithium because I thought ho, ho, here's an electrolyte – so we looked at this but on the whole it was fairly disappointing.

What was your view on the controversy that blew up between Mogen Schou and Michael Shepherd?

Well, Michael Shepherd himself never took part in any of the debates about it. I remember, at great cost, I got a very nice meeting together at the Royal College and we booked Michael Shepherd to debate with Schou but he never came along. This was about 1967. He would never talk to Schou about it. You know, Schou's first experiment was the mirror image approach looking at patients before and after lithium and, of course, you can criticize that because it implies something about the natural course of the illness that you couldn't properly define. Then he did a random discontinuation study, which was pretty convincing but you could say that the relapses were lithium withdrawal, which it may be with bipolars. Anyway we were meeting in the 1960s in a group called the Denghausen group.

Yes, tell me about that.

That was very interesting. It was promoted by Nate Kline who was a great entrepreneur, a very flamboyant character and he collected people who he thought were good and interesting. He got some good people along there from Europe. We had Arvid Carlsson, Linford Rees, Merton Sandler and Julian Mendlewicz and we had various Americans, who were all people of great standing. The idea was to have a meeting without the impediments of having to read papers. The idea was just to have a meeting of people who could discuss various subjects in depth. We would sit down in the sunshine on some Caribbean island – the only visual aid was the blackboard, which would usually get blown over by the offshore winds – and have three days of discussion. They were very, very good.

Schou was a member of that group. We all used to discuss the various problems he was having with his data and I thought at this stage, it must have been 1967, that we would have to do a prospective study. Our 1971 study, which I think was one of our best studies, was a result of that. In those days, you met in a pub and hammered out a protocol. So we got I think Michael Shepherd and Edward Hare, who was a great sceptic about any treatment, and Ronnie Maggs, who was a most charming man, and Bruce Burns from Belmont and Ramon Noguera (Coppen *et al.*, 1971).

It was a very interesting design – the idea was that we keep a group of patients on lithium or placebo lithium for two years. The psychiatrist looking after them, who was blind to their lithium status, could give them any other treatment they needed. What I wanted to do was to mimic the everyday clinical situation. The results that came out were absolutely staggering. We found that the morbidity in patients on lithum in terms of rated illness was very much lower and the amount of other medication needed was very much decreased. I always remember Ted Hare coming along with his colleague Ramon Gardner and he said that this can't be

right. He and Gardner went throught he results but they couldn't find any fault with them.

We looked at unipolar as well as bipolar and we found a very good result in both. I didn't like that but it showed a number of things. One was that the outcome of treating depressive illness is very bad when you follow people up but that you could change that completely by proper long-term treatment. After that we decided to set up a lithium clinic because this was obviously a service we should offer our patients. Recently, I have followed up these patients, some of whom have been on lithium for twenty years and using the outcome measure of death by suicide, I found that the outcome of long—term treatment with lithium and other drugs is staggeringly good. Instead of having a suicide rate of seven per thousand, which is the norm, we had a suicide rate of less that one per thousand.

People have said that this is just our selection of patients and so on. In fact it's not. We had the same sort of patients as everyone else. The only thing I would say is that we didn't have much co-morbidity with alcoholism because we had an alcoholic unit and alcoholics tended to go there. So we had fewer than most psychiatrists coping with bipolar depression but then we had more patients referred by people, who would say 'oh, you must be interested in Mrs Bloggs, she's terribly interesting' – but which was code for . . .

We haven't been able to treat her . . .

That's right. Anybody who has a research unit is familiar with that. So they were severe cases. There was very little dropout in the first year, partly, I think, because we had this instant feedback of the lithium level which is very good and makes for good compliance. And we have always given it once a day at night. There's no justification whatsoever in giving lithium more than once a day. And, secondly, after our 1983 paper on dosage, we concluded that 0.6 mmol/litre was the optimum dosage – that the higher levels, in fact, were not so good as 0.6 (Coppen *et al.*, 1983). Our hypothesis for that was that the higher levels were cutting into the thyroid and you need a good thyroid activity for the best clinical response. So we actually shifted everyone in the lithium clinic to low doses in 1983. In fact, we have shown in our series that the morbidity actually decreased in subsequent years after we switched them all to low dosage.

So I think lithium is a very good, safe treatment. We now have 16 years of outcome data and our death rates by suicide per thousand patients is less than one. There's a study from Gothenberg due out this summer with rates of 1.5. This was not done in a lithium clinic but there was regularly monitored lithium compliance data. I would say if you don't have monitored lithium levels you don't know what you are talking about. There is also Muller-Oerlinghausen's four-nation study. In contrast, one of the most important recent studies on suicide is the 1988 one from the

Maudsley and I worked out their suicide rate per thousand patients at about six. The WHO trial from Heinz Lehmann worked out at about eight per thousand and Keith Hawton and his colleagues in Oxford last year showed that the suicide rate of patients discharged from a psychiatric hospital in Oxford was something like ten per thousand patient years. Horrendous. People are obviously not getting continuation therapy, not getting treatment which has been well established for twenty years. Our data showed an 80% reduction in suicide rate compared with these figures which is fantastic.

I think suicide is a good proxy measure of morbidity. Most people don't have morbidity data but they have the suicide data. I think this is one of the big findings in medicine actually but in spite of this most psychiatrists don't treat depressions very well, they don't give continuation therapy. My big concern at the moment is trying to get people to take some notice of this. The Department of Health in their recent White Paper want to reduce suicide rates but they don't give any idea of how it can be done. And despite the fact that we have now an established method for doing this – which is treating depression, which is responsible for 70% of suicides in the general population – some members of the psychiatric profession are saying these targets cannot be met. They can. Treating depression properly means treating the episodes and giving continuation therapy.

Why do you think people haven't taken as much notice of this data as they should? If this were tumours, there would be a big fuss – it would be a media issue. Why is it you think?

I don't know. I think the *Zeitgeist*is a bit against this. Psychiatric illnesses are seen as a sort of social illness, or depression and suicide are anyway – a social illness that should be treated by social methods. I think this is out-of-date science dating back to the 1950s or earlier but it persists in psychiatry. A lot of people who are in psychiatry are not really interested in the medical model. They went into psychiatry to get away from it. That's one reason. Another is that lithium is very cheap. There is not much money there commercially. But I think the next big issue is going to be the question of long-term treatment of a depressive illness. I think what will happen, and it has already begun to happen in the United States, is that patients are going to start suing doctors who haven't informed them of the course of the illness. There is a general agreement about the course of the illness now – it's pretty bad – so everyone should be told about it.

In the States, long-term treatment is getting a lot of publicity – much more than in this country but in the recent advice to general practitioners from the Royal Colleges, there was very little about long-term treatment, although it did emphasize the importance of continuation therapy. Now I am happy with any sort of long-term treatment as long as it's been

shown to work. If you think cognitive therapy is useful okay you should offer them cognitive therapy. But not to offer patients long-term treatment I think is very bad medicine. But this view is not fashionable. I'm a very unfashionable person in British psychiatry at the moment.

You feel that.

Oh, yes. I think things are probably changing. I think the Maudsley under Aubrey Lewis was essentially socially minded and it stayed that way under Dennis Hill even though he started in biological psychiatry. I think biological psychiatry hasn't been popular in this country, even thought the big revolution in the management of schizophrenia is tied to psychopharmacology. I can remember just before the chlorpromazine revolution, if you went into a schizophrenic ward, you really were going into quite a terrible place. It was really quite sad really. People have got no idea about that now. Psychiatrists seem to feel that they are going to dirty their hands somehow, if they do follow-up clinics. They get nurses to do it or someone else to do it. But a change will come. It will come from patient groups as well as professionally.

Let me move over to 5-HT, which has become a big issue since the 1967 article.

That stemmed from the 1963 experiments I have already mentioned. Having established the clinical evidence, we decided first to look at tryptophan levels in plasma because that's something you could get at. So we developed a method for looking at free and total tryptophan levels – which is quite difficult really because it changes very rapidly and you have to standardize the time of day and all sorts of things are very important. Anyway, we came up with some findings, which are still a bit controversial, that there was a deficiency of free tryptophan in plasma. This fitted in very well with the 5-HT hypothesis. We then got on to the platelet which is a very nice accessible organelle. The other thing we looked at in the early 1960s when people did cerebrospinal fluid studies, was CSF concentrations and we found a low concentration of 5-HIAA, the 5-HT metabolite, in depressed patients. That was about 1963.

Who else was working in this area?

George Ashcroft was and the other was Herman van Praag. We were the first actually to show an effect on mood. Then there was the probenecid story, which gave us the idea about the rate of synthesis of 5-HT. Herman van Praag was very active in that. He was subject to a lot of abuse in Holland because of it. You know, left-wing politics in those days meant you were antiscience as well. I remember we had a meeting there and the demonstrators were all letting off smoke bombs and things outside which was quite interesting. Nice young men actually. There were these banners up and I asked one of the demonstrators to translate it for me because I

didn't speak Dutch. He was very nice and pleasant although he'd just been threatening to kill Herman van Praag but it was just a sort of phase.

That was when?

It was in the 1960s I suppose. Poor Herman had a bad time. We get these various clusters between left-wing politics and green issues. When we were measuring body potassium, every so often the radioactive count would go up because the big powers were letting off bombs. We could pick up Russian and American bombs this way. The thing about radioactivity is that it's very easy to measure, whereas with lots of other pollution you can't. You don't know what pollutants there are in the atmosphere because there's no way of measuring them.

Who else was with you in the Unit?

Well, Eccleston was, he was a good chap. Karabi Ghose, who was a very bright person, who was interested in the alpha receptors. We've never been a very large unit at any time. Art Prange had gone by then I think. Peter Whybrow had gone to a very distinguished career in the US Stuart Montgomery came to us then and Maryse Metcalfe was our psychologist.

We've always had more ideas than we had people really. But I think you can do multiple investigations at the same time. It's just boring doing one thing. If you're doing clinical research the limitation is the number of suitable patients. Everyone who does clinical research comes across this problem. My idea has always been do as much as one can. I think if any unit produced more than 15 suitable depressives a year they are cooking their books somehow. It can't be done.

Platelet 5-HT uptake had a funny career; it got overtaken by radio-labelled imipramine binding which has been fools' gold as it were.

That's right. We never went into that area ourselves but I knew Sol Langer and he did a very important study and then there were some contradictory reports and since then the controversy has raged on a bit, hasn't it. What would you say the state of play is now?

People would say that there are too many methodological problems with it.

What you find in science is that in the end you never convince anyone. You just get a silence – which means that people have decided to drop the issue. No one stands up and says I was wrong and this was a stupid thing to have done. They just don't carry on with it.

You think it would have been useful if one or two people stood up and said that they were wrong.

Yes. In a way I did that. Although I didn't say it in so many words. Again, digressing to plasma level and clinical response and the therapeutic window and all that. Some Danes said if you get the plasma concentration of

nortriptyline right there will be 100% response. So we had a look at amitriptyline and our initial study which was published in 1972 was confirmatory. We thought oh boy, psychopharmacology is going to be dead simple now. Just give enough to get the right concentration and that's it.

Stuart Montgomery came in on this didn't he? Tell me about how he came to you.

I think he'd been with Linford Rees. He hadn't been in psychopharmacology very long at this stage. He had quite a varied career – he was a poet and a few other things. He was a very interesting chap, very enthusiastic and immediately took to psychopharmacology. This was at the time of the therapeutic window. And we did a study which actually didn't confirm our original findings and then I said well let's set up a WHO study which I think in a way was one of the decisive factors. We showed there was almost no correlation when we had large groups. We published that in the *Lancet*(Coppen *et al.*, 1978).

But, of course, you have the therapeutic window chaps still going on saying that there is a therapeutic window but in fact mainstream interest died a death. So we had one very positive finding which we never explained – there was no collusion; the ratings were independent and the plasma levels we got from Guy's. We just put the two together and we found this fantastic correlation. So you do get correlations purely by chance.

Let me take up your third horse, the endocrine one. Tell me where that came from.

Yes, well, that was terribly in the air in the 1950s and 1960s. Besser at Barts was the first chap to do the dexamethasone suppression test, the DST. But because he used large doses of dexamethasone every patient with depression was suppressed. You had to find the optimum dose and then . . . And then of course there was Barney Carrol.

Now what happened there? One of the ways to read all this is that really an awful lot was happening here in the UK from the 1950s onwards but all of a sudden the US flare for propaganda commandeered the field.

If I may go back to 5-HT. 5-HT never really became respectable until the Americans accepted it more or less in the middle 1970s. Then it seemed as though the 5-HT hypothesis had been invented in America, although they had for years fought with us about it. Joe Schildkraut was one of the great protagonists. I used to be on committees with him. So we knew each other's arguments backwards. But if it hasn't been invented in the States, it doesn't count.

So Barney Carroll invented the Dex Test.

He's a great enthusiast and basically we were all agreed that it was a quite a sensitive way of detecting a depressive illness. Now at this stage it was getting such a big thing so I said we'll have to go into this but we must do other groups. So we tested normals, and schizophrenics, and dementias and neurotics too and the thing that came out was that its sensitive to depression but it was not specific.

You ended up heading up the WHO study on this – how did that come about?

Well, I was invited to join the World Health Mental Illness Centre in the 1960s and I found it very interesting. I used to go to Geneva and meet people in the same field. I always felt we ought to have a practical scheme that we were working on because as I said earlier you must be doing something, not talking about what you would do if you had enough money. The only thing no one has got is time. Having come out of the army and going into medicine I always felt that I hadn't had enough time anyway.

Anyway, it struck me that to test the DST in depression was an investigation the WHO could do. So we constructed a protocol. The cortisol was measured in Epsom and all the different centres had to do was to follow the protocol and send us the blood. It was a very standardized trial. With these international studies, if you do a collaborative study, it's a serious business. Because if one centre does it badly what do you say, you have to include it. There was one centre, if you read the article, which gave us problems. However, the other results were conclusive and I think it really killed the Dex test (Coppen *et al.*, 1987).

I think that's one of our major contributions to that area. When I say killed it, we killed it as a naive diagnostic test – you see it was sensitive but not specific. People are still using it but the truth is that it's no good hanging on to dead ideas once they're dead. I think it had a good run for its money. There used to be psychopharmacology labs who were offering it as a service and charging so many dollars for a Dex test and so on.

Coming back to your idea that these things go round full circle, and the idea that you mentioned which was that cortisol might have an effect on tryptophan and thereby on 5-HT, this was around in the 1960s but I've recently heard it put forward as though it's just being proposed for the first time. Gerald Curzon is another name to mention in this connection I suppose.

Oh, yes. Gerald Curzon did a lot of first-rate animal work on tryptophan and on the interactions between cortisol and tryptophan. It makes a lovely story doesn't it. You get emotionally disturbed by the environment; this causes a burst of cortisol and this interferes with amine synthesis and it goes round in a vicious circle. There may be something in it.

But people now aren't aware that it's been around before.

Well, I think basically we are still living on the intellectual capital of the 1950s .

Do you want to expand on that? .

Well how were psychotropic drugs discovered. We all know they were discovered by accident. People doing funny things because they had a bright idea and they tried it. Now I think I was probably one of the last to do that with tryptophan and monoamine oxidase inhibitors. The way to discover things is actually to try things out. This is what we did in the 1950s and 1960s but of course we can't do that now because we're so heavily regulated. You can't have these ideas and it's notable, isn't it, there haven't been many new ideas in psychopharmacology in the last decade.

What about the origins of the BAP?

This really came about because a few of us thought it would be a good idea and we wrote a letter to the *Lancet*in 1974.

The first thing I knew was from old Max Hamilton because I knew him and I knew David Wheatley – he was a general practitioner. I suppose what it all revealed was the sort of problems between specialist pharmacologists and people in clinical situations like David Wheatley.

Yes there was this big row; how do you read it?

Well, I never really knew. I know that people like Malcolm Lader, Philip Bradley – they were professional pharmacologists and somehow it seemed to them it was the clinical people who were trying to take it over. I don't think that was ever anyone's intention. far as I know, they just wanted to simply get it going as a multidisciplinary forum. That was certainly my idea – a CINP-like group really. And as you know there was a fuss about it because we didn't put the letter in *Nature*and we did put it in the *Lancet*and obviously clinical people are more likely to read the *Lancet*. All that sort of thing but I think there was just a bit of paranoia. But Max really helped a lot to diffuse on that famous Saturday morning meeting at the RSM.

Tell me about that.

Oh, it went on for a long time. Max was a very good Chair because he had a lot to do with trade unions and he knew how you should put motions and amend motions and that sort of thing, which by the time figured it out, it had taken the steam out of the situation. I remember Philip Bradley was very against it but I think he and others were pretty reassured at the end of it and in a way because of the suggestions that they had made we became a very democratic society. No one was allowed to be in Council for very very long. So, it was a very transitory Council. You go on, you do your bit and you're kicked off. I think it's one of the most successful organizations I've been associated with. I think the prob-

lem is going to be getting the balance right because I don't know how you see clinical research in this country but I feel that the interest is declining among psychiatrists.

By clinical research do you mean clinical trial work?

Not only clinical trials but clinical pharmacology and basic biochemical pathology in patients; I think that's the most important thing. I think as I say the use of drugs is very important. People like to smear drug trials but in fact good drug trials, good evaluation of therapy, is extremely important. i've been really impressed by the ISIS trials in cardiology. They're wonderful, aren't they. Could one do that sort of thing?

We need it but these haven't been industry run and I think there's a failure to appreciate that we need trials other than the ones that are being done by the industry. The MRC at one point during the 1960s did that kind of thing.

The MRC trial was actually a very bad trial. I was in St Ebbas' and I always remember seeing these yellowing piles of forms going round. I suspect the most junior psychiatrist in most places was told to do it. It wasn't carefully done. I think there should be properly established ways of doing these. But it's not being done in this country. I think in the United States they are more aware of this need.

Yes, but even there someone like NIMH should be taking on this but they are not.

Well, the NIMH has its advantages and disadvantages. It's a very bureaucratic place. place I have great respect for is the Cochrane Centre at Oxford. Everyone should be looking at their outcomes. It's not difficult to do now, with the NHS central registry, all computerized now. You should be looking to see what's happened to your patients say in 10 years time. In mood disorder trials, you've got the acute trials which are not difficult to do but there are also the continuation trials, which some drug companies are doing now but there are also the long-term trials. The most urgent thing to investigate is the proper long-term treatment of depression and no—one is doing that at the moment. Drug companies I think find that maybe the dangers of doing it are too great – some awful thing might come out and they think well why should they risk their short-term profits.

I think the SSRIs could be the good long-term antidepressants. David Kupfer's trial was interesting. It cost a lot of money to do but at least one has some idea of the three-year outcome. The short-term six-week trial, of course, is still necessary but it's the long-term trials which are now important. The results of six-week trials are more or less the same for most drugs but in continuation trials, there's this enormous difference and I would think that a five-year study would be even more clearcut.

One of the curious things about the BAP has been that it was an organization of small groups. It hasn't been dominated by the Maudsley. Somehow the Maudsley didn't really contribute to British psychopharmacology.

A lot of the questions I've been interested in the Maudsley hasn't contributed to. Malcolm Lader has contributed a good deal to the anxiety area but on a lot of the big questions I think the Maudsley hasn't been there, although they have contributed to genetics.

Why did they miss out on a revolution?

They went very heavily into social psychiatry and actually what has social psychiatry shown that reduces morbidity and mortality? What social psychiatry has done is that it's shown that you if send schizophrenics home to a place where people are unkind, they don't like it very much. I don't know how important social events are in depressive illness. Maybe for the initial episode. I did a study with Gene Paykel, which I never published, on life events in patients on long-term lithium. The bottom line was that even big life events don't cause a relapse in a patient on long-term lithium.

You've risen to the top of the CINP as well. Do you want to chart your career through that?

Well, I've been on the CINP for a good many years. Early on the most dramatic thing I remember was that we were going to have meeting in Prague but when the Russian tanks came in, we had to decide whether we should carry on having the meeting there or not. At that stage it wasn't possible to change the venue so we would have had to just cancel it altogether. Our Czechoslovakian colleagues begged us to go and we went actually and I've asked them since then whether we did the right thing and they all said yes. We weren't going there to prop up any regime. We were there as scientists meeting other scientists. It was a very sad place too. But I think we did the right thing.

I was on the Scientific Programme Committee of the CINP initially and then I was asked to become President-elect. It must have been 1986. I enjoyed it actually because I never canvassed for the job or even thought about it actually; they just asked me to – the nominating committee – and I said yes and I found it a very interesting job to have.

Why?

Well, I was interested to get the best people in the world together and where else to do that but at the CINP, which is a world meeting. Secondly, I had the opportunity of taking CINP to Kyoto – I felt, as a world organization, it was an omission that we hadn't been to Japan. So I put all my weight behind it and it was a very good meeting. It was well attended considering it was so far away for a lot of people and also we

had a lot of Japanese contacts. It's very important to realize that America and Europe are only part of a world science club.

I started two new initiatives in the CINP when I was President. One was to start a programme of postgraduate teaching in developing countries. This we did in conjunction with WHO. I asked Brian Leonard to be the Chairman of the Education Committee and he has organized a fantastic programme in Africa, the Middle East, Indonesia and Korea for example.

My second initiative was the President's workshop. The idea was to discuss a subject in depth for two and half days with a number of fairly brief papers and lots of discussion. The CIBA Foundation meetings were our model. As it was my workshop, the first one was on 5-HT. The discussion was recorded and a very good volume was sent to all our members. Merton Sandler was very helpful in the organization and publication of this meeting. I am glad to say that both these initiatives have been built into the cycle of CINP programmes. Since the CINP has become so busy, I felt it was necessary to have an office with an Administrator and Gill Houston has filled this post with distinction. I think the CINP has now become more useful and stimulating.

Can I just ask you about that. A point that can be made is that in a sense psychopharmacology has been a means of spreading US/UK cultural imperialism where psychiatry is concerned. Because of English becoming the language of psychopharmacology all the major journals in this part of the world have had to adopt it so that whereas before the War German psychiatry had been dominant; now it has become an Anglo-American thing.

I think a lot of it was the European actually. I always thought the 5-HT theory of depression developed around the North Sea in a way. George Ashcroft up North, us, even though we're not quite on the North Sea but we're not far away, and Herman van Praag. People say this sort of thing but I don't think it's true. The French publish in English now because they realize this is necessary in order to be read. The British scientific paper has become the normal way to report science.

Yes, but you could argue that the creation of things like DSM-IIIR, etc. have formed a mould in which all of the other cultures have fitted. Japan in particular. You've got these pharmaceutical companies over there now having to make drugs for indications that culturally aren't theirs.

But the Japanese say they are. I mean I agree the Americans are trying to push their DSM-IV but I prefer the ICD-10. Its a bit annoying but I've been surprised how well these things do fit into other cultures. Not relying on our own judgement but that of other people. You know we all say the orientals are very calm and so on but you know they suffer from psychiatric illnesses similar to ours. I've been out in the Middle East, talking to Royal Princesses, and their problems are very much like the ladies of West Ewell actually. Exactly the same – unsatisfactory spouses,

boredom, etc. I think it's universal. But, one of the things you have got to realize about oriental peoples is that they have a different metabolism so their dosages may need to be quite different to ours. We had a bit of a problem about a 1 mg dose of dexamethasone in the Japanese, when using the Dex test, and I think they've probably reduced it to half a mg. Their dosage of antidepressants is also less. Another thing is that other cultures may not have our high intake of food and so on. For example, to get a proper response to antidepressants, you've got to have a normal folate and this isn't so in some countries. So I don't think it really is scientific imperialism. I just think that it's evolving. But I think the Europeans and the Americans got there first on this one.

Talking about psychiatric nosology – you've left your mark there in the form of the premenstrual syndrome.

Yes, Neil Kessel and myself looked at this (Coppen and Kessel, 1963). We certainly didn't invent it but we put it on the map. We carried out the work in the early 1960s, which was before the pill, which has made all this kind of work unrepeatable since. Or sample was a group of 500 women randomly selected from their general practitioner and we sent a questionnaire to them. We tried not to suggest that there was a pre-menstrual syndrome but we asked about pain, irritability, depression and other symptoms and whether they occurred before, during or after.

What came out very clearly was that pain occurred during and depression and irritability and all the rest of the symptoms occurred before. It was associated with neuroticism. There was no difference between North and South of England or between country and town. Parity made a difference to menstrual pain but it didn't make any difference to the pre-menstrual syndrome. I can tell that in those days people didn't talk about menstrual periods. Women could never discuss with men whether they had a menstrual period or not because they found it terribly embarrassing. Your generation probably can do that but I can assure you it wasn't the thing then. Anyway when the results came out there was a lot of interest in them. The *Sunday Times* did a big spread about them but at the last moment the medical editor rang up and said 'Well, the editor doesn't feel the public is quite ready for this'. But at least it got around. It got on the news and I think onto radio as well. The reaction was actually that I had a lot of letters from women saying well thank God someone's described it, because it was common it was not recognized at all.

There had been Franks in the 1930s and some work by Katerina Dalton, Raymond Greene and Linford Rees. Katerina Dalton's studies were fascinating. She used to go to boarding schools where they recorded the menstrual periods and girls did less well in the exams during the pre-menstrual time. But ours was first epidemiological study. found that 10% of women complained of severe pre-menstrual syndrome. But it could

never be repeated because people went on the pill and you can no longer get the natural history. Then we looked at the premenstrual syndrome in psychiatric patients. wasn't very much difference actually – they were like other people. Then we got to nuns, who presumably didn't have much to do with men and they were much the same as anyone else. I also helped to organize a study in Spain. At that time, in Spain, upper class girls were very virginal and they were also the same as in Britain. So we weren't bringing any menstrual imperialism into Spain.

You said that the field has been very small in this country – if I was to ask you who influenced you, would it be more useful to ask a question on a world scale?

Well, let's see. I think of Mogen Schou, Herman van Praag, Biff Bunney, Fred Goodwin, Ed Sachar, who's dead now – a very good friend of mine, I think his death was a great loss. Who else. Well I suppose people like Joe Schildkraut – we were old sparring partners – and a man I have great respect and liking for is Arvid Carlsson.

I don't think we've been inferior to any group actually. We had this habit of doing several things at the same time, which always used to irritate some people, but I never felt over-stretched. I think our 5-HT things were a success. I think our long-term treatment studies were a success. We certainly drew attention to the pre—menstrual syndrome or whatever they call it these days. I think we contributed quite a bit to psychopharmacology as regards plasma levels and therapeutic response and the development of new drugs. I think we were the first to demonstrate that mianserin had some antidepressant effects.

I think the Maudsley has really been a bit a disappointment in the last 20 to 30 years, especially in the field I've been working in which is the biochemistry and the management of mood disorders. It raises the question of which is the best way of conducting research. I think there's a lot to be said for the old MRC idea of selecting a Director and backing him for a good period of time. I think, though, that our small Unit which never consisted of more than a few people at any given time bears quite reasonable comparison with any other unit. I think the thing that is most important, the only things that are important, really, are ideas and the ability to promote those ideas and to put them to practical use in research terms.

Picking the right people also helps.

Picking the right people, and that's a matter of luck really. You know you get awful people, you get good people and some people are shy and don't show themselves. I must say that most of the people with whom I worked were very good and we had a lot of fun. The best days have been when one's just sort of sitting down talking with a bit of scrap paper in front of you putting forward ideas and so on. I think it must be very difficult to

work up long term programme ideas because you stumble on all the really new and really good ideas as you go along.

In a sense psychopharmacology really doesn't lend itself to long-term programmes – new drugs are turning up new phenomena and you've got to change to accommodate the phenomena rather than . . .

Yes, you've got to change your ideas in view of what is happening. I gave a talk in France at the Pasteur Institute some time ago and I said that since we can no longer try new things so easily, we need to keep an eye on the side effects of drugs in other areas. They say the best way of finding new oil reserves is to sink oil wells – I mean geology studies are one thing but the main thing is to be sinking lots of wells and see what comes out. But we can't do that so easily anymore.

Ole Rafaelsen used to say that all movements are over in 30 years whether it is Elizabethan or Jacobean drama or painting. The whole thing happens in the first and second wave who have the exciting ideas. After that something dies and something else has to take its place. I think maybe with research projects if you get a very large organization you get into the problem of self-promoting bureaucracies and so on which maybe doesn't produce very much work.

It would be nice really for something really new to turn up but in the interim we must stop research being very conventional. I think I was very fortunate in being in the work at this time. All my colleagues who went into the research side say it would be so awful to try and do that again, given the present circumstances. People today, though, don't realize what a tremendous impact the antidepressants, neuroleptics and lithium have had on the terrible morbidity of mood disorders and schizophrenia, however imperfectly these drugs have been applied by clinicians. When I go to West Park now I find about 400 patients suffering from dementia. What a contrast to 40 years ago when there were 2000 very disturbed young and middle-aged patients, many of whom are now leading ordinary and rewarding lives thanks to these advances.

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