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The place of chemical pathology in psychopharmacology

Why did you go into psychopharmacology?

I didn't even realize I was a psychopharmacologist until many years after I had become one. It's strange but true. I started among the monoamines long, long ago and by chance. The chance was that David Hay, now Sir David, Alan Goble and I were on the house together at the Brompton in 1954. I was doing a short-term research job after a house job there, mostly involving paper chromatography. David and Alan moved to the National Heart Hospital and there saw one of the first cases of carcinoid to be diagnosed in the British Isles; they phoned me at the Brompton and said they needed a bit of biochemical assistance.

So we set about investigating this poor lady, almost draining her of blood. We tried all sorts of bizarre things like doing platelet stickiness tests, borrowing a special machine from Helen Payling-Wright (who died only recently). Principally, we measured 5-HT in body fluids, compartments and blood cells and surprisingly interesting data emerged from this one patient. The main finding was that there was a higher concentration of 5-HT in the right side of the heart, as you would expect from the massive liver secondaries, than on the left. Putting two and two together, we speculated that maybe that was the reason why such patients developed right-sided heart disease. It seems so obvious now but it wasn't then.

So, there I was with an interest in monoamines, when suddenly Michael Pare who was my chum from the Army got a job at the Maudsley; it just seemed that everything at that time, in depression and schizophrenia in particular, had a monoamine dimension – you remember the pink spot . . .

This was when?

Our Army service was 1951–53. Michael Pare was the medical specialist at Shorncliffe and I, having done one year in pathology before I went into the Army went in as a specialist in pathology knowing virtually no

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pathology – can you imagine it? I was given a path lab and 15 technicians and almost nothing to do; well there were about 15 investigations a day including haemoglobins o I really was bored out of my mind. Anyway Mike and I became friends. We had very many wild ideas – we were both terribly untrained in research methodology and made many mistakes. We started off and wrote four papers, doing heroic things like starving for three days and trying to work out a new liver function test. We kept our urine and found odd chromatographic spots in it – nothing at all to do with liver function but somehow connected to starvation. That was our very first paper, called 'Starvation Aminoaciduria'. And then there was a lot of marching backwards and forwards for the poor bloody infantry over 50-mile routes so cases of 'March Haemoglobinuria' came our way. Soon we wrote a second *Lancet* paper 'Aminoaciduria in March Haemoglobinuria'. We started off in style I suppose.

As I said, when I came out of the Army and got a job in the Brompton, Mike went to the Maudsley and found that schizophrenia and pink spot were all the rage. Gaddum had pronounced in 1953 that maybe it is the 5-HT in our brain that keeps us sane and that became our signpost in the sky. So, I had the chromatographic techniques for measuring 5-HT and its metabolites. I didn't develop an interest in catecholamines until about 1957. I used to be and still am, I suppose, a voracious reader of the literature. I would work through, for instance, the Spring Edition of Federation Proceedings, with its several thousand abstracts. It was like telling beads, soothing and a bit mindless. And it was there that I spotted that very first abstract of Marvin Armstrong describing how adrenaline is broken down to VMA – its fate had been a complete mystery up till that time.

Very quickly Colin Ruthven and I jumped in and developed the first quantitative colorimetric test to measure VMA in urine. There was a postal strike at the time and I delivered our paper by hand to the *Lancet*. The *Lancet* was really quaint in those days. Very Dickensian. High desks and men standing up and writing at them. You expected to see a quill pen. But that's by the way. They published it within a few weeks, so that was a coup really.

Phenylketonuria had also come along by then – wherever 5-HT popped up Michael Pare and I chased it. I'm trying to remember the sequence of events. I wrote my very first paper on monoamine oxidase in 1956 with Alan Davison – that was monoamine oxidase in carcinoid tumour tissue. I had become a sort of oneoman carcinoid reference laboratory at that time. With Alan Davison I'd been looking at inhibitors of aromatic aminoacid decarboxylase and found that phenolic acids of various kinds to a greater or lesser extent decreased 5-HT production by inhibiting 5-HTP decarboxylase; and of course, a clinical condition which produced vast amounts of a range of phenolic acids in the body was PKU. So we approached Sam Stacey, Professor of Pharmacology at St Thomas', who

had a good *in vivo* assay system for platelet 5-HT. The speculation came off. Because of the overproduction of whatever it was, there was a deficit of 5-HT in platelets and, of course, we suggested that there might be a similar deficit in the brain, which might be the cause of the mental deficit. But, anybody can speculate. That's what I've done mostly over the years – it's been my favourite occupation.

In order, then, to test Gaddum's 5-HT hypothesis that I mentioned before, we got a series of volunteers – Maudsley registrars – and gave them LSD because of its effects on 5-HT. On another occasion, we gave them 5-HTP, the -5HT precursor, together with LSD. We worked with a German psychologist called Brengelmann, who actually had fought against Britain in the War – this was only a few years after the War. I always felt very uneasy in my relationships with Brengelmann but he had a set of measuring instruments and questionnaires for quantifying the changes with LSD which were the best available at the time. And indeed, there was a significant attenuation of the LSD effect after pretreatment with 5-HTP. But the fifth or sixth Maudsley registrar we dealt with had a bad trip on LSD. He had to be sat on by six male nurses and he didn't recover fully for a few months. This put the fear of God into us. We wrote off to our Medical Defence people but we were very lucky that nothing permanent happened. Those were the days before Ethical Committees. If you thought up an experiment, you just did it and nobody asked any questions. You used your own common sense.

So that was my first toe in the psychopharmacological water. Because of our PKU experiments, we got a bit of drug company assistance, I can't quite remember how, but I think it was probably through Mike being a clinician. It's always been more difficult for those of us in the lab to get money from drug companies than for chaps who actually give drugs to patients. I think Mike had contacts with John Marks, from Roche Products. A splendid fellow and a good doctor. Don't know how he got into drug companies. They were pretty down market in those days. He ended up as Senior Tutor at Girton, having been Managing Director of Roche Products. Anyway, John Marks sent Mike and me to Rome, to the very first CINP meeting in 1957. I'd never heard of the CINP. I didn't even know what the initials stood for when I went to the meeting. Neuropsychopharmacology or whatever they called it hadn't reached my consciousness as a possible discipline – it made no impression at all.

Was that in 1958 – when the Pope gave a talk?

Yes the Pope gave a talk and if you say so it was 1958. We all heard the Pope and he died 12 days after. I thought this was what always happens at international conferences. The Pope gives a talk, he dies – not that that counts. Yes, we were all bussed out to Castelgandolfo and Pope Pius XII made some significant pronouncement in Latin, it may have been broken English – can't remember.

Who was there from the labs, how many clinically, how many from the industry?

I can only think of outstanding personalities that I met there for the first time. Hannah Steinberg was there, perpetually drinking coffee with Philip Bradley and Arthur Summerfield. I remember very distinctly, they seemed so senior and grown up with strong opinions about everything. You always admire these grown up people. I still do.

Michael Shepherd was there.

Michael Shepherd was there, very much so. Aubrey Lewis was too but I didn't get to know him. He was developing Parkinson's disease and had a bit of a fixed stare. He looked a bit like Rasputin. I subsequently used to see him walking on the river bank at Richmond, with his wife, and tried to acknowledge him but he never knew who I was. Different from Sir Hans Krebs, whom I always used to see at the Biochemical Society and he'd call me Sandler in his precise Teutonic manner. The last time I saw him was at a meeting on aggression in Windsor Great Park. I knew I had arrived because, for the first time Krebs called me Merton! Then he died twelve days later. I seem to have this effect on people.

Really, I rode in to Rome as it were on the back of Michael Pare. We had our first drug company dinner. God, was it an eye opener. In the villa of Mussolini's mistress, Clara-somebody-or-other – was it Petacci? It was splendid. Roche had really pushed the boat out. This taste of the *dolce vita* and the faint whiff of corruption was the thing I remember most about that Rome meeting. There were some nice buildings around too.

Why do you say an eye opener?

I'm a little provincial Jewish boy from Manchester, of immigrant stock. I was the first one in our family to go to University. There was no question of Oxford or Cambridge or anything like that because there wouldn't be kosher food and there would be nonoJewish girls. So I went to Manchester medical school and lived at home. I led a narrow and cloistered existence. It was the Army really that opened my eyes to life outside provincial Jewish Manchester. Does this explain this eye opener stuff?

Yes. On what areas did the first CINP meetings focus?

I can't remember the topics of the symposia at all. Probably over my head. I remember giving my own paper. It went all right, not too many questions.

Who do you recall as being the key people? Who made psychopharmacology . . .?

Joel Elkes was very much there. Very smooth, very much an operator. Thought of himself as a philosopher and he gave this appearance of being an elder stateman even though he was quite young. He was a figure that I remember. I never got to know him properly until, I suppose, 10 years

after that. He never replies to my letters. It's a great character defect. Or perhaps I keep forgetting to put on a stamp . . .

I think I met Seymour Kety first in 1961 when I first went to the United States of America. Seymour, at that time chief of the lab of clinical science at NIH, gave me lunch and had all his disciples around him – what a galaxy they were. Julie Axelrod, Irv Kopin, Joe Schildkraut, Sol Snyder, Dick Wurtman, Joe Fisher, all now famous names in their own right or even Nobel laureates or Nobel candidates. It was funny because sitting round the table, there were 11 or 12 of us and we were all Jewish. I don't know what attraction psychopharmacology or neuroscience has for this group of chaps. Even out of the 10 Presidents to date of the BAP, I calculate that 5 have been Jewish which is a much higher proportion than their representation in the country. I've no idea why. Have you any speculation?

No. Of all of them who has had the most impact?

Well, I think there are two kinds of bright chap around. There are the mathematical or analytical chaps who go deep into one thing but almost invariably lack creativity and the other is the sort of not so mathematically bright individual who sees connections between things. I suppose I think of myself as a hanger-on in the second group.

Now Sol Snyder, even though he's been wrong many times, I'd put almost at the top. He probably combines the best of both groups. He's the exception. Then there's Julie Axelrod, slower thinking I would say but he just gets there, strips down concepts and sees through to the heart of them, sees what is real and what is mythology. I think this is a Jewish trick, as a matter of fact, this ability to see through to the reality, but I may be wrong.

What about Brodie?

Brodie, who was born in Liverpool incidentally and who many consider to have been the father of biochemical pharmacology, was a distant relation of mine as a matter of fact. He was a crazy man. He used to take uppers and downers all the time. He used to take amphetamines in the day time and barbiturates at night to make him sleep. He worked frenetically with the amphetamines – he would carry on until 2 am, 3 am in the morning and get his co-workers along to the lab at that time – it was nothing for Brodie to ring people up at 12 o'clock at night but he never got in until late morning or early afternoon. One way and another, I saw a lot of him but I never got on the same wavelength. Axelrod, in fact, was for many years Brodie's technician and he treated him like it. Axelrod is a sweet man.

I met Axelrod at that same seminal CINP meeting in 1958. How could I have forgotten this, when you asked me who struck me most. Well, I got on this bus back from Castelgandolfo or one of the outings and I sat

next to a rather shabby and self-effacing man, wearing a sort of flasher's mac even though the sun was beating down. One of his eyes was covered over. We started to chat about our work. I was cocky. The PKU work and 5-HTP work was going rather well. And he said 'Oh, I'm working on adrenaline metabolism and it's not going well at all'. I thought to myself that if ever anyone was cut out for failure, then this little guy was. He seemed to have nothing going for him. Twelve years later of course he won the Nobel prize.

I thought the same the first time I heard Hans Kosterlitz at the Physiology Society, probably some time late in the 1950s. Kosterlitz used to give what seemed to me terribly boring papers on the action of morphine on the gut. But this was the springboard for his discovery of endogenous opiates. I'm always wrong about these things – mixing up personality with talent. Axelrod was still Brodie's technician when I met him. He eventually got his PhD at the age of 45 and after that he gradually untied the shackles. Some say that Axelrod was responsible for many of Brodie's key experiments. It's difficult to say. I'm sure Axelrod himself would make no such claims because he's so decent and modest.

Some people say all the good work in Brodie's lab got done when he was on holiday.

Well, that may be. Brodie did have many flashes of insight and was a flawed genius I would say. You can't knock him completely. There was a lot that was good about him, but he did tend to exploit people and pick the young one's brains. Perhaps we all do.

Seymour Kety now is a very different kettle of fish. Very charming and diplomatic and formidably influential. He was also very brilliant. Perhaps the KetyoSchmidt approach to bloodflow measurement in the brain, which is where he made his scientific name, wasn't a big enough problem, as far as Nobel prizes were concerned. Given the right problem I'm sure he would have won one. He's still working at NIH, even though he's over 80.

Do you think in the end Kety's role was more an organizational one . . .?

His main achievement possibly was as the brilliant head of the Laboratory of Clinical Science in its heyday although you must remember he was deeply involved in the Danish Schizophrenia project and that was very important stuff too and he was the founding editor of the prestigious and influential *Journal of Psychiatric Research*. I always swore I would never edit a journal because it was a mug's game but after \'be of an hour of Seymour's blandishments across the transoAtlantic telephone, I was talked into being his successor. Thank God I've just managed to pass it along after 10 years. Joe Schildkraut was my co-Editor-in-Chief. Joe had published his monoamine hypothesis of depression to a fanfare of trumpets, in 1965,

but this theory had been foreshadowed by work Mike Pare and I had done in 1958.

Yes. Now tell me about that. I've always wondered about it. You seemed to have the amine theory all worked out at that point – at least implicitly?

Well, Mike Pare and I were the first to give 5-HTP and DOPA intravenously anywhere to anybody. We used them to try to cut down the lag period of response to MAO inhibitors in depressive illness. We did a trial of iproniazid because it was bright and spanking new, you see, and we reasoned that if it was just blocking monoamine oxidase, the action must be because of the excess amines that were produced. The only ones we knew of, of course, were noradrenaline and 5-HT. So, we got hold of some of the precursors because we knew that the neurotransmitters wouldn't cross the blood – brain barrier and we treated depressed patients with them. During the lag period, the 2–3 weeks until the MAO inhibitors started to work, we gave them 5-HTP or DOPA intravenously to see if we could shorten the timie before response occurred. It didn't work. In retrospect we didn't use enough. Thank goodness because we would have probably sent their blood pressure over the top.

We published our clinical trial of iproniazid in depression. Our amine ideas, disguised under the title of 'A trial of iproniazid in the treatment of depression' languished but Joe's got the full PR treatment and prospered

I've always thought it all comes down to good PR, what do you think?

Yes, yes. Joe's paper is one of the most quoted papers in the world now. Ah well, you win some, you lose some.

Do you want to comment more on the role of PR in the whole thing. because it does seem to me that people who coined the snappy phrases Type I, Type II . . . who market their ideas, get places where others don't – even if they're wrong.

You are absolutely right. I agree with you all the way. The Americans have lived in a marketing climate for longer but we seem to be getting used to it now. We no longer have to talk ourselves down to the same extent and British understatement still needs to be banished. Nate Kline, perhaps the most prominent American psychiatrist of his day, called a press conference even before he gave that first paper to the American Psychiatric Association on iproniazid in the treatment of depressive illness.

Nate Kline, who died in 1982, was a great romantic. He liked reciting poetry and had an inexhaustible supply that he would quote at the drop of a hat. Everybody seemed to like him but I felt uneasy with his flamboyance. Perhaps because of it, he had his face on the cover of *Time* magazine as one of the 10 best known men in America – not one of the 10 best known psychiatrists. When he wanted to reduce his private practice because it was getting out of hand, he doubled his prices overnight to $1000 a throw. His private practice increased substantially when he did

that. It was quite incredible. I owe a lot to Nate Kline. I owe about 10 Caribbean holidays to him!

Tell me about that. That was the Denghausen Group . . .

Yes, Mrs Denghausen was a depressed upstate New York millionairess and Nate Kline was her psychiatrist. I think, from memory, he had her on tryptophan and it seemed to work for her. One day, when she was slightly less depressed, Mrs Denghausen said to Nate 'What can I do for medical science' and Nate told her that doctors need to meet with other doctors without being worried about leaving their wives. So for fifteen years, she funded this meeting and 12 or 15 international chaps, of Nate's choice, plus their wives, met on the beach, on a different Caribbean island every year. It wasn't a joke. It was a proper meeting. We started at 8.30 am and carried on until 1, when drinks were brought out on a tray.

There was just a blackboard on the beach under the palm trees. We all took turns to make our presentations, interrupted all the way. We couldn't get away with a loose sentence or phrase – a pretty high calibre bunch. I set up a lot of research collaborations through this Denghausen meeting and got lots of ideas. I came in five years after it all began. Arvid Carlsson joined the year after me. I remember Bernie Wagner, a pathologist, and Biff Bunney there. Sol Synder was asked but he never turned up. Jules Angst was there – a bit like Eugene Onegin. Linford Rees and Alec Coppen had been there from the start.

Tell me how did the BAP come about?

The BAP came about almost casually. We were all lying by the side of a swimming pool in Palm Springs, where that year's ACNP meeting was being held, when I remember David Wheatley saying to Alec Coppen and me what a wonderful thing it would be to have a British College of Psychopharmacology. David Wheatley was the guiding spirit. He liked to go abroad; he loved the sun and foreign beaches and was captivated by the ACNP, which always met in exotic places. So was I. That was in 1971 or 72. We thought about tactics and how to organize things and the name of Max Hamilton cropped up. I don't know who spoke to him. Max certainly wasn't there at the meeting. I don't even know whether Max was allowed into America at that time.

Why?

Max had been a communist party member, though he resigned after Hungary. All his organizational strength derived from his party training so for many years he could not go to America. With Max it was policy rather than personality. He learnt this directly from his party days. Although Max could be an abrasive fellow, it was probably because of his political colouring that he was unpopular with the British psychiatric establishment and never made it on the London scene. In the opinion

of many, Max should have been the successor of Aubrey Lewis at the Maudsley.

Who else was involved in the start?

Anthony Holden, Ronnie Maggs, Philip Connell who did such a model investigation of amphetamine toxicity. Everyone thought before that time that amphetamine didn't really do you any harm until Connell published his monograph. Really a fine piece of work.

You said Max was the person that pulled it all together.

I say that David Wheatley was the driving force. He had the intelligence to know he had to have a front man. David was only a general practitioner – and you know how hierarchical we tend to be in Britain. A very successful general practitioner. He was well in with the drug companies because he used to mount very successful clinical trials for them. He was slightly flamboyant but very capable. To my mind he was the driving force. He got his people into place and must either directly or indirectly have spoken to Max. He later did a magnificent job as BAP secretary.

I wanted to talk to you about the great schism in the BAP.

I was on the very first council. A lot of bitterness emerged and the situation became polarized between the non-medics and the medics. The non-medics – as now – thought of themselves as pure, good scientists who don't get besmirched by drug company handouts or anything like that. To some extent the tension is still there in the background and is always liable to re-emerge.

Max brought us all together with his cunning ploy as I said before, of policies before personalities and he was right, I suppose. He'd had a vast experience at manipulating chaps in the party. He talked it through with us at great length and somehow he did weld us all together. But it was a pretty close thing. We had extraordinary general meeting after extra-ordinary general meeting, well two or three, and they were dismal. The West Hall of the RSM, long before the RSM had been upgraded to its present splendour, was a shabby place, especially on a Saturday morning. I seem to remember the lights weren't on, for some reason.

I seem to remember, too, that Philip Bradley led the revolt, ably assisted by Ian Stolerman and to some extent Malcolm Lader. After the armistice, the second president, by agreement, was Alec Coppen. And then for the only time in the Association's history, there was a fight for the third Presidency between Philip Bradley and me and I lost. After that bitter lesson, we agreed the Presidency should be decided by tacit collusion between past presidents.

One of the other things that happened was that 'Academy' or 'College' were thought to be bad names and so we became an Association for Psychopharmacology.

Was the election bitter?

Well, perhaps I remember it being bitter because I lost, I don't know. Anyway Philip Bradley and I are good friends and I duly became the President after him.

David Wheatley never featured prominently in office, was that because he would have been seen by the non-clinical people as the kind of person who was too associated with the industry?

Well, people are very status conscious and would rather see a professor as president than a GP. But David was secretary at a crucial period and did a magnificent job. In my opinion our symbiotic relationship with the pharmaceutical industry has enriched us and has never got out of hand.

There are virtually no general practitioners in the BAP now

David was special. He was a member of the Royal Medico-Psychological Association before it turned into the College. So he automatically became a member of the College.

He says you were the person who brought the BAP together. It actually began poorly, as you've said, and it took some putting together, a taking by the scruff of its neck and he points to you as the person responsible.

Well, that's extremely kind. I did work hard at it. It was a bit of a ragged nest after the fighting and there were still a lot of ruffled feathers and sourness. I myself started off in the opposite camp to Philip Bradley and it took time to feel as we do today about each other. I still pull his leg, about Birmingham mostly, which isn't my favourite place in the world.

What did you actually do to sort things out?

I don't know what I did. I suppose that a touch of enthusiasm and talking to people on a oneotooone basis helped. A sense of humour. I think I tried to stop people being so bloody pompous and intense.

There was a period during the 1980s when the BAP was a fun group between yourself and Sid Levine

Yes. Sid is marvellous, isn't he. I think that's important. I think it's been good for the membership. I hope we don't become too serious ever.

One of the other ways things could have gone, of course, would have been if Philip had organized a branch of the CINP here in the UK. If he had, would we have ever had a BAP?

No, there wouldn't have been a BAP. Many people say we made the wrong decision anyway, to start off with the BAP. We should have started a Biological Psychiatry Society. The conceptual focus on drugs to the exclusion of biological psychiatry in general was really a bit of a misnomer

for a society that in some respects has really been a Biological Psychiatry Society. There are still people now who would prefer a Biological Psychiatry Society.

What about the 1984 meeting and the fuss over the St Pierre Park Hotel? There has been this issue with all psychopharmacological organizations that if they go down the large conference centre route, they become just a club for clinicians.

Oh, that's something that really worries me quite a lot as a matter of fact, the hold of the drug companies on academic psychiatry. We all know about free lunches.

Do you want to talk about that?.

No, not very much, because I too have many mouths to feed, alas. Without the drug companies we would not be able to conduct our research. Until the last phase of the Thatcher period, I was usually successful in taking money from drug companies without strings, but you can't always do that. You've got to produce the stuff they want sometimes, especially if you want larger sums. It's a great bind. I'm perfectly aware of the ethical arguments but what alternative is there? The universities are bankrupt. The MRC is broke and the Wellcome people are peremptory and idiosyncratic, or at least they were with the old regime.

If you think of a group like the BAP, there are at least six different groups in it – a clinical group, a psychology group picking up the kind of work that someone like Hannah Steinberg was doing back in the 1950s with healthy volunteer work, the industry and the basic scientists, particularly the animal people. Then there's been your area, chemical pathology, and the chemists, the people who have the time and imagination to be able to see receptors and what drugs will bind to them. Any thoughts on which groups have been most influential?

No, no because they've all blended very well. It's remarkable really that it has worked. Our industry representatives have been selfoeffacing and discrete to a man. The Americans, the ACNP, were also well aware of the problem but they had the good idea of making the industry pay through the nose for corporate membership. It's good. The CINP, of course, has been heavily infiltrated by trade and commerce which is sad. Of course you can't have a meeting for 5000 souls without someone actually paying for it.

What about blind alleys? The field has tended to be dominated by people who sell ideas well – Schildkraut and the amine hypothesis for instance. To some extent the way it came out and the impact it had, stultified things, I think. Take your work for instance. My impression is that what you were doing during the 1970s increasingly became orthogonal to the mainstream and it seems to me that was because the mainstream suddenly didn't seem to be going anywhere any more. It

seemed to me anyway that if there was going to be any development it would have to come from without.

In my long research career the only lesson I've learnt is not to get too fixated on ideas. It's very easy to start thinking about ideas as something of your own and you try to cling to them then and not see the bad spots. Come to think of it, I've learned one other lesson: a rat is not a man! If you really want to know about man, you can get some pointers from the animal world but only pointers. Yes, I think we have had many blind alleys because strong personalities hold ideas too long. The famous Spanish histopathologist, Ramón y Cajal, once said, 'I wish to warn young men against the invincible attraction of theories which simplify and unify seductively'.

In terms of this field, can you pick out people and ideas which you think have been counter-productive?

Yes. Starting with Henry Dale and his oneocellooneotransmitter hypothesis, that held everything back for ages. And then there's Freud and the whole psychoanalytic movement, which is still hanging around.

What about the amine theory. Do you think I'm being a bit harsh on the amine theory?

No. Obviously the monoamines have a role but . . . the thing is you've got to be humble and you've got to realize just how little information there is. There is a jigsaw puzzle but with only two or three pieces of the whole picture in place. You can turn them around one way and you get one picture and if you turn them another way you get another. It's easy to link this to that if you have a vivid imagination. But it may not be true.

The industry has a role in imposing orthodoxy, hasn't it? It prefers to produce drugs for example where it knows what exactly they are going to do rather than produce something dramatically innovative.

Yes, industry is conservative. Of course, meotoo drugs are the safest financially. I think most people within the industry understand this and that the way forward lies via getting a new drug quickly into man, then watching like a hawk for unexpected side effects as pointers for new types of drug action. Because one man's sideoeffect is another man's new drug action.

Who else has been of importance?

Another important chap who never got into this clinical area at all, who is still alive and well, a neurochemist to whom we all owe a great debt to was Derek Richter. A shy retiring man but very talented. One of the very early neurochemists.

Why do you say you owe a lot to him?

I was talking both on a personal level, because I have been a friend of his for some years, and on a biochemical level because he was one of the original workers on monoamine oxidase in the 1930s with Blaschko who died only very recently. And then there was Judah Hirsch Quastel who had a major impact in the early days of neurochemistry. Quastel worked on many fundamental aspects of neurochemistry and biochemistry, on the conjugation of benzoic acid, for example. Things that are now taken for granted. And the same with Richter.

You've been a very public figure in psychopharmacology. Any particular reason?

The reason I suppose I've been involved in so many meetings, national and international, probably stems from the scientific isolation that I've lived in all the years at Queen Charlotte's and this isolation, in a way, has been beneficial because it means that I have had to look elsewhere for intellectual stimulation in a way that I wouldn't have had to do had I worked in Cambridge or Oxford or wherever.

My great regret is that the fax wasn't invented earlier but even so, I have been a pretty inveterate traveller and have made a lot of telephone calls. All this activity has resulted in many international friendships, particularly in the United States, I suppose. So I think of myself not necessarily as a scientific citizen of Hammersmith but just as a scientific citizen. I still talk science into the middle of the night with the same excitement wherever I am wafted by the scientific winds.

Of course, I'm terribly grateful to Queen Charlotte's. I've been a neurochemical cuckoo in their nest but they've been extremely kind to me over the years.

Why did you end up there?

Oh, expediency and opportunism, my dear boy, purely that. I was a lecturer in chemical pathology at the Royal Free Hospital. I had already started on my monoamine way in those days, of course, but my chief said 'well, there's a consultant job going at the Queen Charlotte's, you won't get it, you're too young, but show them that you think yourself up there with the toffs' and so I got my application together. Ridiculously, I got the job, although at the interview, I did everything to wriggle out of getting it. They asked 'are you interested in obstetrics', and I said 'not really'. When they asked 'What are you interested in?'. I said 'I'm interested in monoamines', but I also said 'I just follow them wherever they go and if they go down into the uterus, then I will follow them into the uterus'. They took me at my word.

In fact, I came up with a monoamine hypothesis of toxaemia almost immediately and I don't completely disbelieve that even today. It's just that more exciting things cropped up soon after I got to Charlotte's.

Although we found a deficit of monoamine oxidase in human placenta in toxaemia even in those days, it may well just be secondary to fibrotic changes in a toxaemic placenta – I don't know. We never really pursued it further, I'm sorry to say. Anyway the papers came tumbling forth – our department produced twice as many as the whole hospital put together – perhaps more.

At the Cambridge meeting on the History of Psychopharmacology you threw out some very provocative comments about the MAOIs, that some of them are MAOIs but aren't actually antidepressants and there are related compounds that may be antidepressants and aren't MAOIs – do you think MAO inhibition is necessary to their antidepressant action?

You are right, of course. I suppose I have never accepted revealed truth in anything and just because a compound has been dubbed a monoamine oxidase inhibitor and because it does have monoamine oxidaseoinhibiting properties, it doesn't necessarily mean that it works because of that monoamine oxidaseoinhibiting ability. Take deprenyl, for instance, the monoamine oxidase B inhibitor now used extensively in the treatment of Parkinson's disease because of its possible neuroprotective properties. Well I'm quite convinced that its neuroprotective ability doesn't derive from MAO B inhibition. Other selective MAO B inhibitors don't seem to possess this particular action. The point is that every individual drug has multiple properties and abilities, despite its official classification. We have shown with deprenyl, for instance, that there's a significant increase in superoxide dismutase activity in patients or rats treated with it. I can put up a good case for superoxide dismutase being neuroprotective.

But that's another story. I have argued over the years that the beneficial effects of the monoamine oxidase inhibiting drugs in depressive illness may not depend completely on their ability to inhibit MAO A. Their effect on this enzyme is maximal within hours but lightening of affect may not be observed before several weeks have elapsed, so there's something else there.

What about the tyramine conjugation deficits that can be found in people who are depressed.

That's very interesting and the finding has held up well, although we still don't know the mechanism. It's not for the want of trying, I have to tell you. I can give you a long list of things that it isn't. It isn't a deficit of phenolsulphotransferase. As a matter of fact its very interesting that we stumbled on that because it led us to some really hard science. We were able to show for the first time that the human phenolsulphotransferase enzyme had multiple forms – PSTM, M standing for monoamines and PSTP, for which dilute phenol was the first substrate we identified. We found that the two forms had different substrate specificities, different

inhibitor specificities, different pH optima; just like monoamine oxidase A and B.

Do you think it was the lack of a Bethesdaotype PR campaign that prevented the tyramine test being more widely known? It has always hit me that it was a very clear piece of work – one of the few biological findings we have and nothing has been made of it.

Well, it's quite difficult to do. Even the most intelligent patients – even doctors – have difficulty collecting accurately timed 3-hour urine samples. You have to be supervised and there's no way round this – otherwise mistakes are made. That's probably the main problem. Other people have confirmed it of course – Donald Klein and his group, for instance, and others, but people still sort of sniff a little bit, don't they?

Why? Is it just a matter of timing? The idea of a DST test in a sense was there before Barney Carroll but somehow it clicked into place at that time and bingo there's this industry that grew up out of it.

And it doesn't mean a thing that test, yet it still persists; ah well, never mind.

Do you think it comes back partly to the idea that there was a US sales component?

Yes, I think so. Really the new generation of psychopharmacologists have to learn to be their own mouthpiece, their own trumpeter, their own PR man. I think this is important. We tend to be diffident and hide our light under a bushel over here.

Another area you've been involved in, indeed led the field in, but which hasn't received as much outside attention as it perhaps deserves, has been in trace amines. Can you tell me something about trace amines?

Alan Boulton, in Canada, and I myself, on this side of the Atlantic, have both been a bit obsessed, over the years, with all the monoamine substrates of monoamine oxidase that weren't catecholamines or 5-hydroxytryptamine – I mean the tyramines and octopamines, phenylethylamine, phenylethanolamine, tryptamine, etc. They are all present in the brain in low concentrations but that's only because they haven't got specific storage mechanisms. The turnover of octopamine, for example, seems to be just as large as that of noradrenaline. Both our teams have identified a number of changes in these systems in different types of mental disorder but we've only scratched the surface. There's plenty of room for further study. Alan wanted to call them 'microamines' but Earl Usdin and I thought that inappropriate and put forward the name 'trace amines' which stuck.

One of the other areas you've been involved in the last 10 years that I've always thought looked awfully interesting and I've been surprised it hasn't had the impact that I thought it would have, is the whole story from tribulin to isatin.

Well, tribulin is a bit of a tangled skein. You see although we have identified the main MAO Boinhibiting component in tribulin, there now seems to be at least one major MAO A inhibiting component too. We've recently found, in addition, that isatin, the MAO B inhibiting component, has a strong action on a quite unrelated receptor system in the body and we're trying to get to grips with the implications of this too.

Another complication with isatin is that it's generated endogenously in the brain but it is also produced in large amounts by the gut flora. Our crucial experiment was in germofree rats, which excreted relatively small amounts in their urine compared with conventional controls. I've been interested in gut flora all my life. They're terribly under-rated things, gut flora. If you ever have any bizarre or anomalous effects or unlikely compounds in the urine you should immediately think of drugs or gut flora. My colleagues in the lab smiled when I said we've just got to do these experiments with isatin in germ-free animals but then these beautifully clean data emerged. It's a very expensive business – breeding germ-free animals – but it's difficult to approach certain problems in any other way.

So, we've been involved with that but one thing that I would have liked to have spent much more time on, because I think it could have been so desperately important in our overocrowded society is aggression. You probably don't remember that we did a study which got a lot of media coverage on prisoners from Wormwood Scrubs in 1977 where we found an increased production of phenylethylamine or, rather, of its major metabolites, in aggressive psychopaths. Now, most of the phenylacetylglutamine and phenylacetic acid in the urine, in fact, comes from gut flora so we don't know, even now, that these patients had an overproduction of phenylethylamine as such. If you block phenylethylamine degradation with a monoamine oxidase B inhibitor like deprenyl, you get a very substantial increase in urine output of phenylethylamine, from 2, 3, 4, 5μg per 24 h – it's as low as that you see – to something like 80 or 100μg per 24 h. A very respectable increase but not when you consider the amounts of the major metabolites, phenylacetic acid and phenylacetylglutamine, in the urine – something of the order of 100 mg per 24 h. So, this is another aspect of the gut floraness of things and it just makes life that much more difficult.

So whether our Wormwood Scrubs multiple murderers with large amounts of these metabolites in their circulation really did produce larger amounts of nature's amphetamine, phenylethylamine, is still an open question . . .

They weren't on MAO B inhibitors.

No, we didn't get a chance to put them on MAO B inhibitors. We speculated and proved that it was true, that the aggressive alpha male in a monkey pack, the pack leader, had a high circulating phenylethylamine metabolite level. We still don't know what it means, but we had a nice

trip to St Kitts in the Caribbean to perform the experiment. I'd be terribly interested to pursue it. It may just be that they get more constipated – the aggressive ones for all I know.

Anyway, there is a phenomenon here that needs further investigation. We would have needed the full collaboration of the prison services at the time but they were very difficult. Did I ever tell you about this? The very first paper on the aggressive psychopaths from Wormwood Scrubs came about by accident. I had to go to a very boring dinner at the Royal College of Physicians and I got stuck at the end of a table. The chap opposite me hadn't turned up so I only had the chap sitting next to me to talk to. I asked him what he did and he said he was a psychiatrist at Wormwood Scrubs. So I plucked from the air a fact I'd read that 80% of the murderers in North Carolina had been taking amphetamine at the time they committed their murder.

Really.

Yes, well in fact it was very obvious in retrospect but I had never heard of amphetamine psychosis at that time. They must have been amphetamine junkies who flipped and became paranoid amphetamine schizophrenics. Anyway the Wormwood Scrubs psychiatrist started to get interested and I remembered that we had a test for phenylacetic acid and that phenethylamine is closely related to amphetamine. If you block phenylethylamine degradation in a rat – if you give them a monoamine oxidase inhibitor and administer phenylethylamine – you will get a typical amphetamine-like response.

So I started to generate a hypothesis, you know, as one does after the second drink and he said 'well, perhaps we should test this' and I said 'I'd love to, and can you get some blood'. So he got a dozen of these bloods from a selection of homicidal maniacs and a dozen samples from meek and mild controls and, lo and behold, we had a paper. We sent it off to the *Lancet*. My collaborator promptly got into trouble from the prison service because he hadn't had proper permission to do it. They were scared stiff because experiments on convicts are tricky things.

When I tried to go back to Wormwood Scrubs, the doors were closed. I couldn't get any more samples. Anyway, three or four months passed. I happened to find myself at a dinner party and there was a very brash but personable young man sitting opposite. I was reciting the story and the frustrations of science and all that and this young man, whom I vaguely recognized, said 'well, I might be able to help'. I said 'do you have any useful contacts' and he said he was in the Cabinet and the Home Secretary was his friend – it was Norman Fowler, looking terribly young, like a school boy, in 1977. And he said 'send me the documents of the case, send me everything you've got, and I'll promise to have a word with Willie Whitelaw'. He was quite fired by all this, really.

Anyway, nothing happened for another three or four months and I

despaired. Then all of a sudden, a phone call came and he said, 'It's Norman Fowler – you're all right, just apply'. So we got another set of samples with the same result but then our psychiatrist retired and it all got difficult so we went to the monkeys in the Caribbean instead, hoping some time to get back to Scrubs but we never did. But aggression, it's such an important thing isn't it and with these so-called anti-aggressive drugs being developed, I don't know if I believe in them or not. The serenics and all that. Terribly interesting.

Eltoprazine?

Yes, I've been interested since it started and I know quite a bit about it. Eltoprazine may be serenic; at least in a peculiar rat model, the rat maternal aggression model, it's very good. It also has one other unfortunate action, however. It not only blocks aggression but it blocks the sex drive too. And I think Barry Everitt will tell you that these two drives seem to be very closely related. I always remember Barry giving a brilliant paper at a Sardinian meeting when he was trying to disentangle them by producing suitable brain lesions. He never could do so though. I can't remember the details of his experiment except I think this was my first very positive impression of Barry Everitt. A beautiful experimentalist.

Oh yes, aggression is so important. I'm sure if I'd have been able to take the blood of Adolf Hitler or James Jones in Guyana or what was this nutter in Texas called, David Koresh, they would all have had high circulating levels of phenylacetic acid. In terms of aggression, Robert Maxwell, for example, might well have been an example of this. Robert Maxwell was such a charismatic man. As I told you I edited the *Journal of Psychiatric Research*, a Pergamon journal, for 10 years. This meant meeting Robert Maxwell. Well I had first met him in 1973 . . .
I liked him tremendously.

This was the problem, wasn't it?

Tremendously likeable man. I first met him in 1973, at night time, in Strasbourg Castle. I think it was the third or fourth Catecholamine Symposium. It was a very Shakespearean scene in the courtyard, with torches blazing, a crowd of extras milling around. Somebody took me and half a dozen others along to introduce me to this great big chap. Of course, I remembered our meeting clearly because he was famous or notorious but it never crossed my mind that he could possibly remember me.

Well, in 1982, having taken over the editorship of one of his journals, I found myself invited to one of his annual jamborees in June at Headington Hill Hall. They were great affairs with brass bands and drum majorettes and he used to arrive in his helicopter. Well, there he was sitting outside his tent literally, with nobody whispering in his ear and I went up to make his acquaintance and said 'You won't remember me' and he said 'I

do – you're Merton Sandler, you've just taken over the *Journal of Psychiatric Research* and I remember meeting you in Strasbourg in 1973'. I was impressed by that.

Hearing you go through the range of things you've done, is how little chemical pathology I know or was trained in and how much risk, I think, the rest of us nonopathologists run, as a result, of re-inventing the wheel. I'm sure that in five years time people will trumpet things they wouldn't be trumpeting if they knew about gut flora. But it's not a fashionable area at the moment is it?

No, it's not a fashionable area. I think one has to have a lot of luck in science and suddenly some big finding will come. A lot of luck. You're right, who has heard of what I do except for a few specialists in the area really. I suppose we were the first with the multiple forms of monoamine oxidase and that sort of thing. But I'm not a popular folk hero like Marie Curie or Brian Leonard. I don't think cults of personality have much to do with science, though.

What about your interest in migraine?

Ah, yes . . . migraine has played an important part in my professional research life, purely by accident as most of these things are. It happened by chance – I got a phone call one day from a lady called Edda Hanington who was Assistant Scientific Director of the Wellcome Trust and she was passionately interested in migraine. Now it had been known for centuries that certain foods can initiate migraine attacks in certain susceptible people. She pointed out, in a seminal paper, that cheese was one of these triggering substances and suggested it did so by virtue of the tyramine it contains.

She was wrong, of course, about tyramine. It doesn't seem to initiate a headache attack, according to work that was subsequently done over the years. However, my mind is not completely closed. When my colleague Richard Peatfield gave tyramine intravenously to certain migraineurs, some of them did get a headache.

But it was an important question in 1967 and even though Hanington is likely to have been wrong, a lot of people took up the baton and became enthusiastic about the whole chemical background of migraine. As Popper has said, 'Fertility is the result not of exactness but of seeing new problems where none have been seen before, and of finding new ways of solving them'. One of the most important things about Hanington was that she worked for the Wellcome Trust, so when she got on the phone to me and said biochemically speaking 'Help help', it was important because there was money to prime the pumps. So that's how I got into the biochemistry of migraine.

And. in fact, following this lead, we were the first to find that there's a platelet monoamine oxidase deficit in migraine. Two kinds of platelet deficit. as a matter of fact. During the acute attack there's a transitory defi-

cit but about 25% of males have a permanent decrease in platelet enzyme activity. There's been intense activity once more in the past year or two in this area, spearheaded by us but also by Kathleen Merikangas in Yale and Naomi Breslau in Detroit because it turns out that there is a substantial increase in psychiatric morbidity in migraine and up to about 20% of patients have a major depressive illness at some time in their lives. This has now been put on a quantitative basis and studies of the genetics of this phenomenon are proceeding with full molecular biological cooperation – maybe some answers will now emerge.

Do you not think the whole fuss these days about the 5-HT is something of a 5-HT bubble?

Of course, my dear boy. 5-HT is important, I've never said that it isn't. I've earned my bread and butter from 5-HT over the years and I wouldn't really knock it. Even so, 5-HT is all right in its place but there are many other things that the seven groups – so far – of 5-HT receptors connect to. What has amused me over the years is the sheep phenomenon in science. Everybody follows my leader in science. Some American publishes a new paper and it gets the full Bethesda PR treatment and all round the world, the little chaps in their journeyman laboratories follow and write their safe papers and of course the safe papers are accepted. It's the papers that change science that we all have difficulty in placing. Most science, unfortunately, is safe science.

You have to have safe science to get a grant, alas. I really mean that. If you want to get a grant, then you must not stray too far from what the last man has produced. I don't blame the referees when they've had no experience with a new concept – or rather, I don't know if I do or not! If you haven't got enough knowledge of an area and if you're spending public money then to be safe, you turn the project down. Where Leonardo would get his money from if he were alive today rather worries me. That's a big problem David.

Select bibliography

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