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The place of clinical trials in the development of psychopharmacology

Can we start with why you were interested in medicine and what then led you to do psychiatry?

I came from a family of teachers. My father was a teacher, my grandfather a headmaster, my uncles and aunts either teachers or directors of education. They were all teachers. When I was at Llanelli Grammar School, I found that almost everyone in my class intended to become teachers. Wales exports teachers in fact!. In view of the competition, I decided to think of something else. I therefore wrote to the Welsh National School of Medicine for a prospectus and was very attracted by the curriculum. I applied for entry and went through the medical training there. I was fortunate in the course of my training to win a variety of prizes in anatomy, physiology, medicine, and months as a resident student clinical assistant at Whitchurch, which gave me my first real contact with psychiatry. I enjoyed it tremendously. Of course, the irony is that I entered medicine to avoid becoming a teacher but ended up becoming on just the same.

What year was this?

This was 1937/1938. We were given a variety of types of work. For example, if the social worker was away on holiday, we would carry out the detailed social histories of outpatients as well as inpatients. Similarly when the pharmacist was away we did all the dispensing. It was very good experience. I used to do two rounds each day, accompanied by the senior nursing staff, who treated us with great respect and made us feel very important.

We also attended the outpatient clinics at the Cardiff Royal Infirmary and were given patients to treat. There is nothing like being given clinical responsibility to stimulate the interest of a medical student. I enjoyed the work and this gave me my interest in psychiatry.

After I qualified and after a period of house jobs and general practice I went to Worcester County Mental Hospital in Powick, where my first post was to look after the annexe containing 800 chronic patients. I examined all these and found a number of cases of general paresis which hadn't been diagnosed. During that time, there was a great interest in Birmingham and in the

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Midlands in the role of focal sepsis in the production of mental disorder. This was treated by surgical procedures including tonsillectomy and washouts of sinuses and the removal of any other focal sepsis. I had to give the anaesthetics. One or two patients seemed to get better, but it was probably the non-specific effects or the stress of the operation which helped.

What other treatments were in use at that time?

I was the first to introduce convulsive therapy at Powick, using intravenous Cardiazol. The first patient I treated by this method was a chronic schizophrenic, who surprisingly showed considerable improvement. At that time, it was given for schizophrenia because of the belief that there was a biological antagonism between schizophrenia and epilepsy. Other treatments included producing pyrexia by TAP injections or by the intramuscular injection of a colloidal solution of sulphur in oil, which was called Colsul, which would also produce a temperature. These obviously were very empirical non-specific methods of treatment.

Were they used for general paresis only or would they be used for anything else?

Anything, really. In the case of general paresis, there was malaria therapy of course. But some people improved with Colsul. I think it may have mobilized the acute immunological system in some way. Anyway they weren't very scientific treatments but they were the only ones available. ECT hadn't come in at that point. Intravenous cardiazol was used to produce convulsions but it was frightening for the patient, much more frightening than ECT.

When did you move to London?

I came up to London to the Maudsley, to do a Diploma in Psychological Medicine in 1940. I was appointed to The Maudsley Hospital, which was at Mill Hill in 1940. At that time, there were a lot of famous people there – Aubrey Lewis was the Clinical Director, Walter Maclay was the Medical Superintendent and Aldwyn Stokes his deputy. Other distinguished people included William Gillespie, Russell Frazer, Maxwell Jones and others. Maxwell Jones started his Therapeutic Community there.

I found Mill Hill very stimulating. During the War, we took about 500 service people suffering from neurosis from the army, the navy and the airforce and from the women's auxiliary armed services. There were also some civilian casualties. One interesting thing was that although London was being bombarded at that time I, a young psychiatrist, looked after nearly all the outpatient clinics for the whole of London. What that shows of course is that there wasn't a tremendous demand for outpatient treatment. I had clinics at St Mary's Highgate, Mile End, St Charles and one or two other places.

It was during this time that the future Institute of Psychiatry was planned. We had meetings on a Monday evening to discuss what was required for the future psychiatric services at the Maudsley Hospital and the needs of post-graduate psychiatric training. Aubrey Lewis brought these plans to fruition



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after the War and the new Institute subsequently led to a tremendous expansion of research, with new Chairs, new Departments and a great expansion of postgraduate training.

You did some early work with Eysenck

I was the principal psychiatrist who worked with Eysenck. We did a great deal of work on the effects of narcosis produced by nitrous oxide and other agents on suggestibility. That was our first collaboration. Subsequently, I did a lot of work with him on physique using anthropometric measurements on various groups of psychiatric patients, people with effort syndrome and various normal control groups. I did most of the work and he helped with the statistical application of factorial analysis. We devised various indices of body build including Rees-Eysenck Index for men and there's another for women called the Rees Index. These studies were all based on measurements of patients at Mill Hill.

What were the findings?

I think the work provided precise methods of assessment and therefore helped to standardize the assessment of physique. We showed that there were two main factors accounting for variations in physiques; the first factor was a general one of body size which affected all measurements, and there was a second bipolar factor which governed the shape of the person's body – whether it was narrow or broad. The broad type correlated with manic-depressive disorder, whereas schizophrenia was associated with a variety of types of physique. There was also a correlation between hysteria and anxiety states with totally different kinds of physique. Our findings only supported Kretschmer's views in part. There was, as I have said, some correlation between manic depressive disorder and a broad physique but this was partly due to age – a lot of the manic depressives were older and one tends to put on weight as you get older.

I also studied physical constitution in effort syndrome. I worked with Paul Wood on that – he was a cardiologist, whose recommendations that the syndrome be called Da Costa's syndrome were widely adopted. It was also called neurocirculatory asthenia. What I found was that the narrower the physique the greater was the constitutional predisposition to effort intolerance, autonomic instability and so on, whereas the broader types of physique were correlated with external stress such as bombardment and other forms of battle stress or sometimes precipitated by infection.

Is effort syndrome the same thing as M.E. ?

No quite different. Although in some of the Da Costa's syndrome patients, infections played a precipitating role, most of them were in ongoing military service and the clinical picture was quite different. The ME syndrome is characterized by intense fatigue and muscular pains, whereas Da Costa's syndrome is characterized by intolerance, autonomic dysfunction and various neurotic symptoms and is quite different from ME.



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I worked very closely with Aubrey Lewis, who took a great interest in my research on physique. He used to come with me to the Mill Hill barracks. I would carry out the measurements on various groups of soldiers and he'd record them. We also worked closely in studying involuntary movements in post-encephalitic Parkinson's disease. This interest stimulated by a patient who presented as suffering from what seemed to be an obsessive compulsive symptom – tongue protrusion. This involuntary tongue protrusion had developed after eating Ryvita bread with ants on it.

Ants?

The insect – yes! The ants stung his tongue and the referring military psychiatrist thought that being stung on the tongue by ants was the triggering or precipitative mechanism for his obsessive compulsive symptoms. I noticed that this man's pupils reacted to light but didn't react on accommodation which gave me the clue that this was a post-encephalitic type of neurological disorder.

Aubrey Lewis then arranged for us to visit Winchmore Hill Hospital, which was a center for post-encephalitic Parkinsonian patients. We examined a number of these patients and found in addition to general features such as rigidity and tremors, a number did suffer from involuntary movements such as tongue protrusion. We filmed a number of these patients and it was interesting that occasionally we detected oculogyric crises, which had not been observed clinically. It should be remembered that this was before the introduction of the phenothiazines and other neuroleptic agents and this was a rare phenomenon. Now of course, it's commonplace to see tongue protrusion. It was very interesting.

In addition to looking after the soldiers, I also looked after units of women, who were members of the auxiliary armed forces from ATS, WAAF, and Wrens. I was told I was given this particular assignment as I was married and they thought it was safe to have me in charge of these beautiful young service women from the forces. I had to do a round everyday, inspecting these lovely girls. It was very pleasant.

Another of my units was devoted entirely to conversion hysteria. This was very interesting. There was a whole range of conversion symptoms affecting special senses and various other functions. Physicians had no experience of these severe hysterical conversion symptoms had tended to discount hysteria as a diagnosis and referred to it as illness behaviour. All these patients were thoroughly investigated neurologically as well as physically and I found no evidence to support the view of Elliot Slater, who considered that hysteria did not merit consideration as a separate nosological entity and that in his experience it tended to occur on the basis of somebody having a pre-existing neurological condition. But that's because he worked in the National Hospital, Queen's Square. If he'd worked in Mill Hill he'd have seen clear-cut cases of all types of hysteria – paralysis, blindness, and all the classic symptoms, without any underlying neurological disorder. The underlying disorder sometimes was a depression or occasionally schizophrenia but very frequent anxiety states with no evidence of neurological disorders. In addition to having all varieties of

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conversion symptoms we also had dissociative states, including fugues, amnesias and hysterical fits.

When Mill Hill closed down, I then went to the Southern Hospital, Dartmouth with Maxwell Jones, where we were in charge of units of re-patriated prisoners from Japan, the Far East or from Europe, suffering from a variety of psychiatric disorders. This was interesting work, but the service was only needed for a limited time until the patients were sufficiently improved to be discharged. I was still on the staff at The Maudsley Hospital, and was asked by Aubrey Lewis to undertake continuing postgraduate training full-time of a group of fifty ex-service psychiatrists at St Ebba's Hospital, Epsom.. This was one of the most exciting and stimulating posts I have ever held. Teaching consisted of individually supervised clinical investigation and treatment of patients, the presentation of patients at case conferences and daily seminars covering the whole field of psychiatry. The group greatly enjoyed the course, were highly motivated, worked very hard and were extremely diligent. It was a great success and I am still in touch with many members of that group, some of whom achieved high eminence and leading posts in the health service and academic institutions.

The next step in my 'career' was to go as Deputy medical Superintendent to Whitchurch Hospital. I enjoyed teaching undergraduate and post-graduate students and at the same time began research on Schizophrenia and on the evaluation of treatments for it, including deep insulin therapy, electronarcosis which was a new thing then and electroconvulsive therapy.

Electronarcosis?

Yes. It was introduced at that time as a new method of treating schizophrenia and it consisted of bilateral application of the electrodes, which gave a continual stimulation of the brain over a period of seven minutes. It was a bit frightening for the patient and for the rest of us, with lots of funny noises, stertorous breathing.

Did they actually have a fit?

Oh yes, but it was an inhibited fit. It came on right at the end. They were kept in a state of tonic contractions during most of the seven-minute period and then the clonic movements came at the end. It was not a very effective treatment for schizophrenia – no more effective than ECT. At that time deep insulin therapy seemed much better and I know the reason now. Research in this field needs a prospective, random allocation of patients by controlled methods. But at that time, the advocates of deep insulin therapy recommended that patients should have a good previous personality, a shorter illness and acute onset florid symptomatology, and these in fact were features indicative of a good prognosis anyway. Therefore, it was bound to be better than the results for other treatments. I published results controlling all these various factors in schizophrenia and matched groups by these means and insulin achieved better results than ECT or electronarcosis, but the main reason for this still lay in the initial criteria for the use of insulin treatment.

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What about Harold Bournes' article that questioned what was actually going on?

Yes. I had many discussions with him, and arguments. His views were empirically derived. Later at the Maudsley they did a prospective study, which threw doubt on the value of deep insulin therapy for schizophrenia. So insulin went out of favour.

How big a role do you think randomized controlled clinical trials has played in the development of the treatments we now use?

A major role really. I'll develop this in the context of talking about the early days in psychopharmacology. The beginning of the era was in 1952 when chlorpromazine was used in a French hospital called Valdegras. As you know chlorpromazine was different from the previously available drugs treating psychiatric disorders. Anyway, from Valdegras its use spread throughout France and in 1955 Pichot, Jean Delay and Deniker held an international congress in Paris to discuss chlorpromazine and other neuroleptic medications. This was the first conference on chlorpromazine and other neuroleptic medications. This was the first conference on chlorpromazine and I had the honour of presenting three papers on it detailing three studies in which strict double-blind control methods had been used. Pichot showed a great interest in this methodology development, partly, it must be said, because he was interested in this British 'preoccupation' with double blind clinical trials. It may be a little unfair but the French favoured a more 'impressionist' approach.

I had carried out a double blind controlled trial in anxiety states in the first place because when I read about chlorpromazine and its actions it appeared that on pharmacological grounds it might be useful in treating anxiety states. I was working in South Wales at the time and I was running a number of out-patient clinics. It didn't take me long to get a hundred anxiety states. Colleagues in London were flabbergasted but it was different there because I had an unlimited supply of patients. So I carried out this double-blind control trial, and although it helped anxiety to some extent, its value was strictly limited because of the anticholinergic and hypotensive side effects and also because people with executive or responsible positions had their anxiety relieved but it also eroded their enthusiasm and motivation.

Then I tried it out on asthmatic patients who had severe anxiety. These were patients that I collected from St David's Hospital. I was working there with D A Williams, a distinguished expert in allergies. I found that it helped the anxiety but it didn't help the asthmas very much and the dryness of the bronchi was disadvantage. That was a double-blind randomized controlled trial. The third paper was a study on autonomic functions as a prognostic aid in the treatment of patients with chlorpromazine.

Not many people realised that this first international conference on chlorpromazine was in fact the beginning of the science of psychopharmacology. I think there were about 150 papers submitted. Mine were the only double blind control studies. The next step was at the World Congress for Psychiatry in Zurich in 1957, where Nathan Kline organised one session in collaboration

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with Denber and others. This was the first time that the World Congress of Psychiatry had sessions devoted specifically to drug treatments. That then stimulated people to form an International College of Neuropsychopharmacology and its first meeting was held in Rome in 1958, where I presented a paper on a fully controlled trial of iproniazid in the treatment of depression. Since then the CINP has met every two years in different places.

I think my contribution to psychopharmacology is in the field of scientific controlled trials. I wrote a chapter in a book edited by Nathan Kline entitled *Factors in Depression* and there was an article in *Nature* in 1960, which gives you all the methods used in controlled trials at the time. The iproniazid trial for instance was a cross-over trial.

How did that work, you'd cross people over from iproniazid to placebo?

That's right, yes, by random allocation of active drug and placebo and cross-over.

It must have been pretty well the first trial on antidepressants in this country?

It was yes. Then I did the very first trial of phenelzine (nardil) in the world with Brian Davies. Although these were severely depressed inpatients, the results were very good. But the dose we used was comparatively high. It was 90 mg a day, which was also the dose that both helped depression but suppressed REM sleep. In the Medical Research Council controlled trials on depression, unfortunately a dose of 45 mg was used.

I also did a trial on imipramine – not the first but an early one. Then it so happened that Brian Davies and I did the first trial of haloperidol in this country on mania and schizophrenia. It wasn't a fully controlled trial but it was the first trial. We also did the first trial on amitriptyline but the results were very disappointing, but I think, had to do with the severity of the depression we studied. A certain proportion improved but quite a lot of them didn't improve. I will come back to this point later. We later did a double blind control trial with nortriptyline and that showed better results than placebo but not very dramatic. I did the first double blind controlled trial of dothiepin with Maurice Lipsedge and a statistician and we then compared dothiepin to amitriptyline, which was a very interesting trial. Dothiepin came out better. Less side effects than amitriptyline. Then I did another trial comparing the full daily dose of dothiepin at night compared with a divided dose during the day. Giving the full dose at night was as good as divided doses.

As a result of all these double blind trials on tricyclics and monoamine oxidase inhibitors, we had an immense number of probands and a big number of first degree relatives, so Michael Pare, Peter Sainsbury and I carried out a pharmacogenetic study. Taking the patients who had participated in double blind trials as the index cases, we studied the development of depressive illness in the first degree relatives and the outcome of their treatment. The results were very interesting. There was a high correlation between the results in this group and the first degree relatives in the following ways. If the index case responded to

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monoamine oxidase inhibitors, the first degree relative did so also. There was a similar response correlation with tricyclics. If they responded to both or neither, the same correlation held. This was a very clear cut result. Jules Angst in Zurich and other people have carried out similar pharmacogenetic studies. So it seems there may be a genetic basis for responding to a particular group of antidepressants.

Another study was to carry out a sequential design trial on diazepam compared to amylobarbitone. The sequential method of studying became available only at that time. This gave a potentially quicker method of detecting differences between treatments. We also studied diazepam by a new method of assessing anti-convulsant therapy in relationship to convulsant therapy – with EEGs and a range of other measurements.

After that we were involved with the Beta-Blockers. In my department at St Bartholomew's Hospital the first trial of propranolol in anxiety states was carried out by Granville-Grossman who worked with me, and Paul Turner. It was a double blind controlled trial and this was the first trial to demonstrate the beta-blockers had a role to play in anxiety states. John Bonn did a similar trial with other betablockers, some of which have now been withdrawn because of the adverse side effects.

Then we did another study comparing oxypertine with a placebo. That showed that oxypertine was an interesting drug. It's an indole derivative produced by scientists at Winthrop for the treatment of schizophrenia but it never became popular – there were so many other agents available. We used it in a trial for anxiety states and it was found to be better than diazepam. But when they promoted it for anxiety generally, the response was not favourable because people had been on diazepam. They were taken off diazepam and put on this and of course some of them then were suffering from withdrawal symptoms of various sorts.

Where did you get your interest in double-blind placebo controlled trials from?

Well looking back Ralph Picken, the Professor of Preventive Medicine in Cardiff, taught us the pitfalls of uncontrolled trials. He was talking about controlled trials in hygiene and in treatment, when I was a student, and I think that's where the seed was sown. Before I did any work with chlorpromazine, when I came back to Cardiff after the war I did a number of controlled trials in schizophrenia, a lot of them with Dr King in Caerleon – evaluating treatments which the Americans had recommended such as cortisone in the treatment of schizophrenia. It was ineffective but somebody had to prove this. Desoxycorticosterone acetate was another one as was hydrocortisone. So they required a double blind trial. I think the very first one I did was a study on the substance betasyminine in the treatment of anxiety. There were theoretical reasons why this could be helpful in depression or anxiety. So I organised a double blind study but the results were totally negative. I think we should have published that, but people were reluctant to submit negative results. It's important to publish negative things but a lot of people don't want to waste time. That was one of the earliest trials.

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That was when?

That was about 1950.

So these were pretty well the first placebo-controlled double blind trials of any sort in psychiatry?

I think probably that's right. Yes in psychiatry. Then the drugs came later. The comparisons of insulin, ECT and electronarcosis, were not fully controlled studies but they were partly controlled because I managed to match groups for all prognostic and clinical features. What was missing was the initial randomisation of treatments. Anyway, it at least showed that electronarcosis was not effective. This paper was presented at a meeting of the RMPA, at which Spencer Patterson enthusiastically advocated electronarcosis. I gave my studies which contradicted these claims. The response to my paper was one of great interest. Most people there hadn't heard a paper given like this before in which all the prognostic factors were controlled and evaluated. I don't call that a properly controlled study but it had quite a big impact.

Did the industry help at all in terms of organising such studies?

The industry came on board for the phenelzine study. I told them how it should be done. I was ahead of them I think then. I don't think they were at all au fait with the principles involved. Later in some trials they helped by funding the salary of a research assistant.

Obviously when the first compounds were introduced, this didn't happen through double blind methods. When do you think the industry got the message that they should be doing them?

Oh I think after the initial trials of chlorpromazine, iproniazid and so on. They realized that in order to get through the Committee for the Safety of Drugs and later the Safety of Medicines committee – I was on both committees – results of double blind control trials became obligatory.

Let me put this to you – Roland Kuhn would say that the industry now spends billions of pounds on all these controlled trials, but they don't discover anything new; that, taking the impressionistic approach that he took, he was the one that discovered antidepressants and most other psychotropic drugs.

Well that's all right. I think that the drugs are discovered by basic research, animal experiments and then from the profile that emerges – there is a feel for whether this drug is useful for depression, anxiety or schizophrenia. So, that's got to be true, but the only way you can prove it then is by proper controlled trials. Controlled trials only prove whether a compound is efficacious or not for a particular condition – they don't discover the compound. But even if new agents are discovered by other means they still have to be tested. There are different varieties of controlled trials but you cannot dispense with randomised double blind trial.

Now, I think one fault with these double blind controlled trials, is the heterogeneity of clinical conditions. You see, they're all heterogeneous – schizo-

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phrenia, depression and anxiety – so that's why you allocate at random. What you're doing is expecting that unknown factors are equally distributed in the two groups. But you don't know. That's the best you can do really.

I have advocated many times, that we still need is to be able to identify sub-groups of depression, sub-groups of schizophrenia, which are specifically susceptible to different treatments. I mentioned this to Aubrey Lewis in 1955. He agreed, but it still has not really been resolved. Once we are able to identify sub-groups with specific susceptibility to particular treatments, much better results will be achieved. The same thing applies with neuroleptic drugs in treating schizophrenia.

Can I take you back to 1955. What was the mood as regards new drugs. What did people make of chlorpromazine?

Oh, I think people got quite excited. Because here was a drug which seemed to alleviate psychiatric symptoms without making patients fall asleep and from the basic sciences viewpoint it was interesting in that it had a wide range of novel pharmacological actions. Chlorpromazine enabled people to be discharged from hospital earlier and more frequently.

Now I don't think it was entirely due to chlorpromazine. I think there was a change in the composition of the patients going on at the time. A lot would have probably been discharged anyway. The therapeutic enthusiasm of the staff also undoubtedly contributed and chlorpromazine must take some credit for that.

Michael Shepherd's study published in 1956 seems to suggest that it was as much a question of changing patient-staff ratios as anything else?

Oh yes, but you see even then reserpine was available.

Yes, on that point, there's a paper by Davies and Shepherd, a prospective trial using reserpine to treat people who were anxious and depressed – showing that it was quite good.

Yes, this trial was carried out.

Which is all very odd given its reputation for causing people to get depressed.

Ah yes, but reserpine was really not suitable for a number of reasons – you do get a tranquil phase, due to the release of the biogenic amines, I suppose, but then there is a reactivation phase in which all the symptoms get exacerbated. It was very interesting. It occurs about a week or two after starting reserpine – if you're treating schizophrenia, all the symptoms can get worse before you get a resolution, but the other danger of course is severe depression – very severe, sometimes needing ECT. So I think there was a great deal of enthusiasm. And really the enthusiasm was something new and useful even though it was really not based on proper controlled trials.

Who were the key players in 1955?

Well, before that we shouldn't forget the work of Cade in 1948, who introduced lithium. But that really didn't shake the world at the time. It only became much more important when Mogens Schou found it to be of value in

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preventing recurrences of affective disorder. Anyway, to some extent it contributed, but only in retrospect. The other drug was lysergic acid (LSD) which was the most powerful drug available. It was active in minute doses, producing profound changes in perception, thinking, feeling and so on. Bradley in Birmingham did very important work on this. And then later Sanderson and a few people utilised lysergic acid to facilitate psychotherapy. So I think the three drugs which stimulated my main interests were lithium, chlorpromazine and lysergic acid, all in different ways. But the main boost to the start of the whole science of psychopharmacology was the use of chlorpromazine in France.

Did people at the 1955 meeting know that they were at the start of a new era?

I think so, yes. There was no doubt about the efficacy of chlorpromazine or about its wide range of pharmacological and clinical action – that's why they called it Largactil. So then attempts were made to find new phenothiazines with equal efficacy but greater safety in terms of side effects and adverse reactions. A large number were then produced and I wrote an article for the BMJ on phenothiazines. Most of us just tried the whole lot of them in an ad hoc manner.

I was also asked to write an article for Nature on the use of drugs in the treatment of depression. That was a new idea at the time. For Nature to invite this article showed they were very perceptive. They could see in the treatment of depression, the shape of a new era emerging.

This was when?

1960. The new antidepressants created a lot of enthusiasm because there were no useful drugs before the discovery of imipramine and iproniazid for depression.

It takes a particular kind of personality usually to get a field going – one thinks of a person like Nate Kline – he was obviously an enthusiast..... who were the other people in the field that you felt were the ones who were actually responsible for contributing a certain dynamism to what was happening ?

I think Nathan Kline especially. He discovered or at least popularised reserpine and later discovered the antidepressant iproniazid. Heinz Lehman of Montreal was another one. Bradley certainly in his own specialised field, and of course Paul Janssen introduced lots of new drugs early on – haloperidol, droperidol, pimozide, and many others and he is still producing. But you're really talking about clinicians who contributed to the excitement.

What about Axelrod?

Well, Axelrod was a pioneer in basic research on monoamines. Kety was also important in the area of basic research and genetics. Biff Bunney was another – he was partly clinician partly basic researcher. Then there was Derek Richter and his team who carried out important research on many fundamental areas relevant to psychiatry. More recently there has been people like Jules Angst and Julian Mendlewicz, who have both been very prominent in the areas of clinical, epidemiological and genetic research. Alec Coppen worked mainly on the

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electrolytes early on and later on antidepressants and someone whom I mustn't forget is David Shaw.

Mogens Schou and his team were very important and they did very good research, but they more or less restricted themselves to lithium and its prophylactic actions. Another name I should mention is Stuart Montgomery. He's carried out a great deal of work in the field. Hans Hippus from Munich was also a leading figure. There was an Anglo-German symposium in London in 1956 and Hippus and I gave papers on psychotropic drugs and that is where I met him for the first time. He is one of the people who discovered the efficacy of Clozapine, now marketed as Clozaril. He's been using it for years and he found it to be effective in schizophrenia and relatively free from extrapyramidal side effects. I was on the committee for the Safety of Medicines when we considered it and were put off by these reports from Finland – although this may have been a selected group of people who were genetically susceptible to agranulocytosis. One still has to pay attention to these things but under the special monitoring scheme they seem to be controlling it.

What weight would you put on the contribution of clinical people, basic scientists and the pharmaceutical industry to the way things have gone.

I think the pharmaceutical industry must take credit for the introduction of new compounds because they increasingly have to steer new drugs through complex and long and vigorous procedures – animal toxicity, human pharmacology and trials – before submission to the Committee for the Safety of Medicines or the FDA. Sometimes, ten or fifteen years of intensive work and expenditure goes into development of a drug by a pharmaceutical industry. Now I think in the application of drugs, clinicians have played a much bigger role than the scientists, the biochemists, the pharmacologists, because they can do clinical trials and these provide essential information on efficacy, clinical applications, side effects etc. On the other hand, scientists like Arvid Carlsson have been outstanding in actually discovering new types of compounds – zimelidine was a very good antidepressant; it was

a pity it had to be withdrawn – but he was exceptional. He developed a lot of new things and he had also done a lot of relevant research on receptors and biogenic amines, so I think his contribution has been very important. Another person to mention in this regard is Paul Janssen. But apart from those two I would have to give most credit to the clinicians.

The operations of the CSM and the FDA now mean that drug companies have to come up with vast amounts of money in order to bring a drug to the market and because of that they are less inclined to look for unusual uses of a drug – they only want drugs for the larger conditions like schizophrenia and depression where they are guaranteed to bring their money back. Do you think we've come to a point where perhaps because of the GSM and the FDA we're inhibiting the development of the field?

I think that drug development takes far too long, really. I think we could speed up the whole process. You see, once they've done the basic tests and trials I

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think then the Committee of Safety of Medicines should accelerate things and try to allow a new compound to go to a limited trial rather than hold it back until everything has been cleared. For instance, the new reversible monoamine oxidase inhibitor, moclobemide, was waiting for a terribly long time to be released. But having said that, there has got to be a regulatory machinery, otherwise all kinds of drugs would be brought to the market. It must be there for public safety.

It seems to me that for ten or twenty years after the introduction of the first new drugs, there was great hope of progress and there was co-operation generally between all concerned in the enterprise. Things though have gone a bit sour of late partly perhaps because there aren't any truly new drugs, partly because the public has become more concerned with the risks of treatment. Have you any thoughts on whether the whole thing has gone sour, and if so why?

No, I do not consider that the situation has gone sour. Valuable and exciting new drugs are still being produced. The 5HT reuptake inhibitors were one such; risperidone is another, as is the resurrection of clozapine. But there is a public aspect to it. Nowadays when the public are given a drug they want to know is it safe, has it got any drawbacks or dangers ... and of course they are entitled to know this. But they are tending to prefer alternative medicine, which they feel is much safer without knowing anything about its efficacy and safety.

Why do you suppose they prefer the alternative treatments. This is quite a mystery in a sense.

Yes, but I think many people are reluctant to take drugs. There's resistance even to take an aspirin and therefore when they read about adverse effects or the risks arising from drugs, they tend to go for herbal medicine or homeopathy, which is relatively speaking even safer than herbal medicines. Then of course, the teratogenic effects produced by thalidomide were disastrous. Because of that the Safety of Drugs Committee was formed.

When the Prince of Wales was made President of the BMA, the mentioned in his Presidential address that we as doctors don't own patients but yet we give them drugs without necessarily knowing how they work and we haven't given sufficient attention to the alternative methods of treatment. The BMA took this seriously and formed a working party on alternative therapy. I was a member of the working party which met for four years. We interviewed representatives of all alternative methods of therapy, including acupuncturists, psychotherapists, hypnotherapists, reflexologists, all kinds of therapists. Anyway, we concluded that the attraction of alternative methods of treatment was the relationship between the therapist and the patient. They would listen to the patient – spend time with them – they'd touch them and they were sympathetic and they provided some symbol of treatment which the patient was willing to accept but on analysing the evidence we concluded that there were only three methods of treatment which had any scientific basis of true value. One was osteopathy – of certain specific skeletal abnormalities; acupuncture because of its role in producing endorphins and hypnotherapy which is effec-

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tive but which isn't really alternative medicine. The other therapies we felt were based on other factors, mainly to do with the interpersonal relationship – because the therapist was a nice person.

I think the other thing is that apart from the 5HT reuptake inhibitors which have had an interesting development, freedom from the anticholinergic side effect, no cardiotoxic effect and are effective, there have been as you say no other truly new compounds. Although there again you see with fluoxetine you get scares from America that people who take this commit suicide. I think what the American psychiatrists forgot about was people with severe depression are at suicidal risk and the greatest risk for putting this into action is when they start feeling better. And then there's another example recently. Somebody took a huge dose of fluoxetine and murdered someone. I think all of these reports can put people off.

Then of course the embryonic effects produced by thalidomide – that was a frightener. Because of that the Safety of Medicines Committee was formed. But, I think the real reason is that we haven't really discovered entirely new effective and safe drugs. All current drugs have got certain disadvantages – side effects and adverse reactions. I gave a lecture the

other day on Executive Stress and Alcoholism. One physician got up and said what we need instead of alcohol is a drug which relieves our anxiety and stress, stimulates our brain and enables us to work better. I said 'yes it'd be lovely if a drug could do all of those things' but will there ever be such a drug?

In Barts between yourself, Michael Pare and your links with people like Merton Sandler, you were a very strong group of people.

I should have mentioned Merton earlier as a research person who has done an immense amount of work in the clinical field as well as in the lab. Then, of course, there was also Trevor Silverstone whom I should have mentioned, he also contributed a great deal, so much so that he was given a title of Professor of Human Psychopharmacology.

Was there any reason why the department you had there was so strong in this area. It was probably the strongest department in the country.

Well, my interest in psychotropic drugs started in Wales before I came back to the Maudsley first of all in 1954. I joined Barts in 1958. I did a lot of the early trials in the Maudsley and the Bethlehem. So, I had a strong interest in all this and I suppose was fortunately joined by Michael Pare, Trevor Silverstone, John Bonn and Paul Turner later, all of whom had similar interests. I suppose the fact that Pare and I had been enthusiastic and keen on research into these drugs, probably stimulated more general interest.

My links with Merton Sandler were first through Michael Pare and then later as a member of a research group called the Denghausen Group. This was founded by an American family that suffered from recurrent depression. Nathan Kline knew them and he suggested that they ought to finance a group of leading people doing research on depression to meet once a year to discuss

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their researches and to discuss the implications for practice and treatment. So the first meeting occurred in New York about 1958.

How large a group?

It was a small group then. It consisted of Nathan Kline, Heinz Lehman, Biff Bunney, Karl Key Westergard who worked in Nathan Kline's laboratory, Jose Delgado who worked on animal experiments and myself – we were the first. The first meeting in New York was devoted to factors which determined cyclical activity and Karl Richter who worked a lot on rhythms attended the meeting.

After that we usually met in one of the Caribbean islands and later on Alec Coppen and Merton joined on my recommendation. Mogens Schou, Jules Angst and L Gjessing were also members. We used to meet at 8 o'clock in the morning in our bathing costumes with a blackboard underneath the coconut palms and then each one would present his work and results from the previous year. It was all informal, but we worked continuously from 8 in the morning to 1 o'clock and then had the rest of the day off. It was an ideal way of running a scientific meeting.

Talking about the BAP, is there any particular reason why you haven't been very involved with it.

I did join it. I was a member from the beginning and I think I was asked at one time whether I'd be prepared to stand for President, but at that time I was so busy with other commitments that I had to decline. Max Hamilton became the first President, which was an excellent choice.

These days it's all a question of time. The meetings are always held in July and in Cambridge and I'm always on holiday then. That's nothing against the Association; as a society I think the BAP is very good – it's purely in terms of the timing that I have problems. It's funny, when I was working before I retired I managed to find plenty of time to do research and teaching and go to conferences. But once I retired I found I didn't have time. It's very strange that, isn't it? But when you work at the University, you've got a big team, Nathan Kline, who was often away, was once asked who did his work when he was away and he said the same people who did it when he was there. There's a lot of truth in that.

What role do you think the BAP has had in this country?

Oh, I think it's had a very important role in fostering and encouraging proper scientific studies and presenting them in an acceptable and scientific way.

Where do you see it fitting in with the Royal College of Psychiatrists? Is there room for the two groups?

I think there is because there isn't really a proper biological psychiatry forum within the Royal College. There's a group for addiction and alcoholism and so on, but there isn't one specifically for psychopharmacology. So I think the BAP serves this purpose. Special interest groups are encouraged to develop by the

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College and if such groups grow and become well established they can be converted into sections of the College. There is, in my opinion, room for psychopharmacology to develop on these lines.

Before we finish, I'd like to bring you back to something you mentioned before we started the tape, your article that's buried in New York?

Yes, I was approached about one of my articles by the Academy of Sciences in New York as to whether I would be happy to have it included in a time capsule. This was buried in New York in 1965 and is to be opened five thousand years from then. As English is unlikely to be in use in 5,000 years, they have converted the contents of the capsule into mathematical symbols. They have also copied the contents to various parts of the world, including the tops of mountains, in order to keep them safe from nuclear explosion, for instance. The capsule contains work of Einstein, Churchill and others as well as a contraceptive pill, a polythene bag, a Beatles record and of course my article.

References

see: Rees W Linford and Healy D (1997). *History of Psychiatry* 8, 1-20.