

THE MYTHS OF PSYCHOPHARMACOLOGY JULES ANGST

You began training in Zurich when Jung was still there.

Yes C.J Jung was in Zurich. He lived with his wife in Küsnacht at the lake of Zurich. He had a wonderful villa, which I believe was built with the money of his wife, who came from a wealthy Schaffhausen family. Jung's father was a clergyman in Basel. His academic career took him to a Chair in Psychology at the Zurich Institute of Technology, but he started out at the hospital where I am, at the Burghölzli in Zurich, where he became, under Eugen Bleuler, PrivatDozent, which corresponds to Reader in Psychiatry. I knew him personally of course.

What was he like?

Well, he was very much as his biographers describe him, a big bear. A very tall, strong man, always surrounded by a multitude of women,. There were very few men around him - one was C-A. Meier, who was one of his most important students. He was admired by everyone and I too admired him for his encyclopedic knowledge. He had such a brilliant, wide scope of interests covering all aspects of culture, the history of religions and anthropology and this attracted many sophisticated experts from all over the world, experts in Egyptology, Taoism, Zen Buddhism, mysticism and cabbala. I attended his lectures and was also a discussant at them; he was always very brilliant, able to relate esoteric concepts to his theory of archetypes.

I was a student of Jungian psychology over many years. Originally I had started by studying Freudian psychology when I was in the gymnasium at age 15 or 16 but then I went on with Jung and with Adler and others. The Jungian school was quite strong at that time in Zurich. In the second year of my medical studies I began attending presentations on psychotherapy by psychotherapists: Boss, Banziger, Bjerre, Brun and Herbert and Kurt Binswanger. Then I underwent a Jungian analysis and attended lectures in the Jungian Institute, which had been founded by then. Interestingly enough, Jung did not sympathise at all with the Jungian Institute. He did not attend either its foundation or its opening. He was very suspicious of a school being made out of what he did. I find that rather a healthy reaction, because the more scholastic a movement becomes, the more rigid and less productive it gets. I think that may have been his concern, too. Later, of course, he was not at all hostile to the movement. Anyway that was how I came to study psychology.

Later, I was a guest member of the Psychological Club for many years. The Psychological Club was an interesting idea. Jung founded it because he wanted to organise social events for patients together with their analysts. Papers were presented in the Club by good people from all over the world and these talks were attended by both patients and therapists. There was also another group, the SGPP, the Swiss Association for Practical Psychology, of which Jung became President. The SGPP membership consisted of psychologists and psychiatrists. Jung's aim was to provide a special forum to bring the two groups together - this goes back to the old development of psychoanalysis by Freud. The SGPP was in existence until 1994. Jung was its first President, Meier the second and I was the third. I was also a founding member of the Jungian Analytical Society.

Originally then I was a Jungian analyst to a certain extent; later I was also trained in existentialism and psychoanalysis by Medard Boss and Gustav Bally, in supervision

groups mainly. With time, I have become increasingly eclectic and when I became Professor of Psychiatry at the University, I didn't stick any more to schools. But I continued to give psychotherapy until very recently. I have never given it up completely.

How did Jung react to the introduction of the first psychotropic drugs?

That I don't know. I was a young hospital assistant at the time and I remember that Jung invited the young hospital psychiatrists to his home, in order to discuss psychotherapy and schizophrenia. He still maintained his original hypothesis that schizophrenia was an inner intoxication - an idea which was not in itself absurd. Nowadays it might be expressed as a disturbance of dimethyl-tryptamine (DMT) metabolism, which was also one of my hypotheses for a while. Although he thought that schizophrenia had some organic background, he was convinced patients could be treated by psychotherapy; whereas my experience with the psychotherapy of schizophrenia had convinced me that it was not very efficacious and had led me to abandon it. Indeed that was my main reason for giving up being an analyst in the hospital. The psychotherapy of schizophrenia was carried out under Professor Gaetano Benedetti in Zurich, and I was one of Benedetti's students at the time. Follow-up studies of the results were published by Christian Müller and showed no difference in course and outcome between patients given psychotherapy and the non-treated sample described by Bleuler in his monograph on the course of schizophrenia. So I think Jung was wrong in his psychotherapeutic optimism. He expected too much originally, as many other analysts did, I think.

But I never heard him comment on drug treatment. Jung attended the 1957 World Congress of Psychiatry in Zurich at which he gave a presentation on schizophrenia; this dealt with its causation by strong affects inducing an endotoxin and resulting in psychosis and he also spoke on the psychotherapy of schizophrenia. At this Congress he was also Honorary President of a Symposium entitled "Chemical Concepts of Psychosis". I helped edit the 4 volumes of the Congress report, which was an enormous job and took me about a year.

What was the mood of that conference? Because that was the time...

I did not attend the conference itself because I was in the Army. Nathan S. Kline from the United States helped organise a big symposium on psychotropic drugs, the first of its kind to my knowledge to be held at a general psychiatric Congress. The report was later published by Rinkel and Denber (1958). Nathan Kline became a very close friend and told me something about that conference. I can only speak about the attitude of Manfred Bleuler, my teacher, because he organised the congress. He accepted the offer to host the meeting, but his main concern was how to sponsor it. Of course Nathan Kline was an expert in fund raising and had no difficulty financing this symposium.

But drug treatment won through and of course became very important. Bleuler, himself, had played an active role in the field of psychopharmacology from the very beginning. The Burghölzli Hospital was the first to test reserpine in '53. So by the '57 Congress we already had four years of intensive research behind us in the field; but we didn't do primary research on chlorpromazine. That, as you know, was carried out in France by Hamon and colleagues and by Delay and Deniker in 1952.

There were quite a few people from Switzerland, who were involved in the early days - Kielholz, Staehelin, Poldinger. Was that because the companies who introduced the compounds were largely Swiss?

Yes, in Basel there were John Staehelin, Paul Kielholz and Felix Labhardt, who was one of the first investigators on chlorpromazine in Switzerland. In Zurich, there were Bleuler and Mielke. Mielke, who is probably less well known, conducted the first very large studies on reserpine in schizophrenia. All the trials at that time were open but were as conclusive as double-blind studies, as history has subsequently shown. The development of reserpine, and later of tetrabenazine, a derivative of reserpine, was quite interesting. At that time, the idea was that these drugs worked by inducing a kind of a curative sleep. So patients on reserpine were kept in large 15 to 20 bed dormitories, where earlier the insulin shock treatment had been carried out. The curtains were drawn to encourage sleep. This strategy of keeping patients rested in bed was in contrast to later ideas. We now know we shouldn't keep patients in bed because of the danger of thrombosis. We lost quite a few patients by this treatment at the beginning. We also had sleep therapy with high doses of barbiturates, sometimes together with scopolamine, which was very dangerous, especially in females. I saw patients who had died in the night from an embolic disorder.

That original strategy was later reversed to one which aimed merely to repress the psychotic symptomatology and to activate patients as much as possible, giving them all sorts of occupational or work therapy. The earlier strategy probably arose from the way in which chlorpromazine was detected. Chlorpromazine was detected in anaesthesia where it was used as part of a cocktail, originally in the sedative treatment of manic patients in France by Hamon even before Deniker and Delay. The underlying concept was that of inducing a kind of hibernation sleep, which is healthy. Now this was obviously a myth, which hasn't been confirmed by subsequent developments.

Were you able to get to any of the early CINP meetings with your Army duty?

I was not at the first meeting. The first one I attended was in Basel in 1960. I became interested in the CINP because Werner Stoll, an associate professor of psychiatry in our hospital, was the son of A. Stoll, a great collector of paintings, who as the Director at Sandoz was involved in the development of LSD. Together with Rothlin, also from Sandoz, he had founded the CINP in 1957. So drug companies played a major role in the CINP's foundation. I was invited by Stoll to present on imipramine at the CINP in Birmingham in 1964. In 1974 I became a member of the CINP executive committee and was the secretary under Pierre Deniker and Leo Hollister. For a while I was very active in testing drugs but then delegated the task to one of my co-workers, Brigitte Woggon. Lately I have become more active again in the field.

I remember one CINP meeting, in Munich in 1962, at which Mogens Schou stood up in a discussion dominated by talk of neuroleptics and antidepressant drugs and spoke about the prophylactic properties of lithium and was greeted with loud laughter. People simply didn't believe that lithium was active. Schou stressed the efficacy of lithium very early on, on the basis of his own experience, but his view was not accepted. There was also no support for the development of lithium because it was not produced by a drug company at the time. In the early days there were no tablets available on the market. When we prescribed lithium it was as a natural product in powder form, which had to be made up by the pharmacy. It was of no financial interest to the drug companies, because it couldn't be patented. Mogens Schou was in an uncomfortable position and showed considerable courage. Lithium is very interesting. You may have heard of the Denghausen group.

I have yes.

The sculptor Denghausen, whose wife suffered from a bipolar or schizo-bipolar disorder, sponsored many meetings in the Caribbean. The first was in Haiti in 1966 and was organised by Nathan Kline. That was where Mogens Schou and I met. He hadn't yet published his paper with Baastrup on lithium. I had been invited by Nathan Kline because of my monograph on uni- and bipolar disorder and my studies on the course of affective disorder, using multiple regression analysis. When Mogens Schou presented on lithium, I offered to do the statistical analysis of his data, which were purely descriptive. He had an impressive number of single cases, before and after lithium treatment, but no statistics. So we did intra-individual statistical analyses, which became a point of controversy, because when Blackwell and Shepherd in 1968 tried using the "mirror method" they didn't obtain the same results on the spontaneous course of depression as I had.

I'm a strong believer in intra-individual comparisons in disorders, such as schizophrenia, which are known to have a poor prognosis. If you had a drug like lithium that would change the course of the disorder dramatically, you wouldn't need many statistics. Intra-individual statistics would be sufficient without any control groups, as in carcinomas with a pure outcome.

So Mogens Schou, Paul Grof, Baastrup and I published these papers together, analysing the data we had collected in Denmark, Czechoslovakia, Germany, Canada and Switzerland. It was a wonderful collaboration. We published three papers on our results in the British Journal of Psychiatry and received the Anna Monika award for our work, as it was considered to be good evidence for the efficacy of lithium. But the point I want to make is that we didn't operate with control groups. All these major drug developments in psychiatry came about without controlled trials by using accurate observation, by open trials with good observers and by intra-individual comparisons. There is a comprehensive historical review of the development of lithium written by Gattozzi for NIMH which includes early interviews with several investigators in the field.

You've also been involved with the development of clozapine?

Clozapine was developed here in Switzerland by the Wander company under Professor Stille, a pharmacologist working on the dibenzodiazepines; it was from this line of development that dibenzepine and clozapine came. It is interesting to note that it was a very small group of pharmacologists, doing excellent work, who produced the important drugs. Today we have big institutions, which are no more productive than the small labs they had at that time. Clozapine was then tested in open trials. One of the main investigators was Engelmeyer in Germany. You will have heard of the Fünfer Ring from Professor Hippus. The Fünfer Ring consisted of five German investigators: Bente, Engelmeyer, Heinrich, Hippus and Schmidt from five different universities, who were the real pioneers on the continent of the methodology of anti-psychotic drug assessment. They developed a symptom checklist. In Switzerland we were especially interested in depression: our five university hospitals were linked together a little later. We developed a checklist, or rather a rating scale, for depression and hypomania. The German and Swiss groups then joined and together developed the AMD and AMDP systems for Methodology and Documentation in Psychiatry.

By the time clozapine came to be tested, the ten of us were already cooperating and we were later joined by Peter Berner from Vienna. Clozapine was tested in open trials in all the centres and incidentally found to be efficacious in treating insomnia. This was a very important finding. Clozapine worked for the insomnia of barbiturate-dependent persons -

barbiturates could be replaced by clozapine in very small doses. Clozapine was available in 10 mg tablets and you would administer 5 -10 mg only.

The main theme of course was clozapine's sedative and anti-psychotic effect, which was quite obviously present. We published an open study in 1971, of which I was the first author - only because the names were listed alphabetically. Then we in Zurich produced the first double-blind study comparing clozapine to levomepromazine, which we chose because of its sedative effect. We wanted to have a drug more or less equally sedative and with low extra-pyramidal side-effects. Clozapine's efficacy was clear right from the start. Its reinvention in America for the treatment of chronic schizophrenia with negative symptoms had great commercial and scientific impact.

But clozapine was recognised from the outset as being an important drug, even though we had a lot of trouble with it. The first problem was proving efficacy. We had a few double-blind studies and two or three open studies, when Wander was taken over by Sandoz. A big meeting on clozapine was organised in Bern; Sandoz completely rejected that it could be an anti-psychotic, especially the people from Canada, America and other English-speaking countries. They wrote it off as poorly investigated, having only side effects and no efficacy. Then the agranulocytosis risk appeared in Finland with deaths of patients. All the cases were traced and carefully examined by Dr Amberg, the internist at Wander, and clozapine was withdrawn from the market in most countries. It was not withdrawn completely here in Switzerland. It continued to be available, because it was known to be very efficacious not only by those who had investigated the drug but also by all the hospital clinicians with patients being treated with it. We had so many chronically schizophrenic patients who had shown significant improvement on clozapine that we put pressure on the company to carry on producing it. Dozens of individual letters were sent by the heads of the hospitals and others to the directors of the company - arguing that it was unethical to stop production. The company wanted to kill the drug off, but it was maintained because of our opposition.

In a second stage clozapine was reintroduced in all countries. It was not possible for psychiatrists to stop all clozapine treatment when patients were discharged and so it gradually returned as a post-discharge treatment. But the person really responsible for introducing clozapine into the United States was Nathan S. Kline. Whenever he visited me in Zurich he would enquire about new drugs; I mentioned clozapine or HF1854, which was the investigational number. I recommended him to try it and gave him some, which he took back to the United States where he prescribed it to his patients. When he was no longer able to get clozapine from the company, he sent patients to me; so I started to treat American patients decades ago when clozapine was in its early stage of development. Nathan S. Kline was the first person in the United States to recognise clozapine's value. But then he was always ready to try out new things.

Tell me about Kline.

Nathan S. Kline was an extremely dynamic man and a very good friend. I got to know him on one of his visits in Zurich. The range of his activities was very broad. You may have heard of the admirable work he did for immigrants for example; he supported 150 or more immigrants in the United States, providing them with work or financial support. That was just one of his merits. Another exceptional thing was his activity founding hospitals abroad: one in Liberia, one in Haiti and another in the Far East, I believe. He raised the money from the drug companies not only for hospital building but also for the supply of the drug treatment and for staff training in Canada or the United States as well.

I find that quite admirable; it shows just how energetic he was that he could combine all this with being Director of Research at Rockland State Hospital.

He was, to my knowledge, the first psychiatrist to build up a large databank on hospital patients and their treatment. He did this with Eugene Laska, who is still one of the leading mathematicians in the field. They had a large computer centre funded by the money Nathan Kline had raised. He was extremely active in the field of computerising psychiatry; he gave us all his computer programmes, programmes which had cost over a million dollars to develop. He was a very generous man. He was also very active as a practitioner. He not only did research at Rocklands, he also had a large drug practice. He had an initial long interview with his patients, which was frequently video-taped. After that the patients were seen by his assistants, and he saw them again if there were any problems.

But above all he was a man with a special nose for new things. He had enormous enthusiasm and was able to recognise what was important and new. His interests within psychiatry were very broad, and that's one of the reasons why he came to be such a pioneer in the field of psychotropic drugs. He was one of the very first in the world to use iproniazid, which is proof of his flair and interest. He was also an extremely trustworthy friend. He was very active, a bit hypomanic even and never needed much sleep. At 7 o'clock in the morning he would already be knocking at his patients' doors in order to visit them, after that he would drive to the hospital for his research and in the evening he would see more patients. He was a highly motivated doctor, there's no doubt about that. That's Nathan Kline as I knew him.

You said that he was one of the first to collect a large database of patients but you've also gone down this route with a view to tackling some of the myths that have been around psychiatry. One of the first myths that I heard you talking about was at the BAP guest lecture in 1987, when you suggested that there is a common belief that antidepressants can cause a switch into mania but that there is no evidence that this is the case.

Well I got into data processing very early. I had always been interested in statistics. In 1959 Bleuler gave me a research position for a year and a half, which was sponsored by Geigy in order to test imipramine. I started a large study covering 200 patients, (150 inpatients and 50 outpatients), all of whom I treated myself. For more than eighteen months I did nothing but treat depressive patients, which is quite an experience. I nearly became depressed myself. All the patients were drug-naïve, at least in present-day terms, although some had been treated with opium, amphetamines or barbiturates.

This study brought me into close contact with Geigy, where Peter Weis was in charge of documentation and statistics. Peter Weis was a chemist but had the task of computerising the data. At that time only the big banks and big drug companies had computers. The university didn't have one yet. I had the data punched in and computed in Basel by Peter Weis and in 1961 I published a larger analysis on imipramine dealing with predictors of response.

I then got involved in computerising the AMP, which was more or less a consequence of receiving the computer programmes from Nathan Kline. The big push for data processing in psychiatry at the time came mainly from psychopharmacology - statistical analyses, which required computers.

As to the myths of psychiatry, I don't know. The hypomania issue is certainly one of them. We are autistic in Eugen Bleuler's meaning of the word : we are full of wishful thinking; if we do something and something happens we are always tempted to think that we were the cause of what may in fact be just a chance phenomenon. So if you treat a patient and he gets better, it's a temptation to believe it is because of our treatment, while we know perfectly well that we have to control for the spontaneous course of the disorder, for the placebo effect and so on. This also applies to the switch to hypomania, which for a while was even taken as an indicator of a drug's antidepressant activity. It was maintained that if a drug didn't cause a switch, it wouldn't be a good antidepressant.

I was very sceptical about that from the outset because of other studies I had done on the natural course of the disorder with representative samples, where I had seen the switch occur very frequently without treatment. I had also seen such switches in patients on imipramine, but when I investigated their previous histories, I found that the majority were bipolar patients (Angst 1965). I therefore carried out retrospective studies going back to the beginning of the century, collecting hundreds of case histories from hospital records, prior to and after the introduction of psychotropics and ECT, in order to see if the switch rates had changed at all over those years. And they hadn't (Angst 1987, 1992).

W. Bunney's extensive 1978 review of multiple studies on the switch concluded that it was drug induced; but of course if you have an overall switch rate of 7 - 8%, it consists of uni- and bipolar cases taken together; however, if you split them, you find that a very low percentage of the unipolar cases and a very high percentage of the bipolar cases subsequently switch from a depressive episode into hypomania or mania. The main factor then in the studies he reviewed is the ratio of unipolar to bipolar patients, for which there was no control. Ideally the existence of drug-induced hypomania should be shown by means of placebo-controlled studies; however, I know of no studies which have established it by this method. Switching is also a rare event compared to other side effects, which makes it difficult to obtain reliable rates; this is probably a subject for meta-analysis. The problem is that even today there are methodological shortcomings in measuring the switch to hypomania. It's not on the rating scales usually applied for drug evaluation. Our ratings are one-sided - depression-rating scales measure only depression - and the spontaneous reports are, of course, not very reliable. I wouldn't rule out the possibility of a switch occurring. There may be a small percentage of cases which switch on certain drugs, amphetamine or whatever, but I simply do not believe that majority of switches are drug induced.

So it's not inconceivable then that the antidepressants may also be antimanic in that after all ECT is both antidepressant and antimanic.

Well, that is the other problem which is raised by this question. There are the studies on imipramine carried out by Akimoto (1962) in Japan. He used up to 400 mg of imipramine in the treatment of mania and reported successes and sedative effects, which is very interesting.

We've completely lost sight of this possibility - partly I suspect because the catecholamine hypothesis came along and very simplistically said that there is a lowering of amines in depression and therefore there must be high amines in mania and ipso facto, any drug which increases amines couldn't be used in the treatment for mania.

This question is dealt with in the monograph on imipramine which I wrote in 1970 with Theobald and others from Geigy. That monograph summarises over 4000 references, including something on the drug treatment of mania. Akimoto's success in treating mania with drugs was impressive and it hasn't been disproved. Such high doses of imipramine have been discredited mainly because of side-effects, such as epileptic seizures.

One of the other myths that you've been interested in more recently is the is the target symptom myth.

The target symptom concept was introduced by Freyhan in 1960, who was at St. Elizabeth's Hospital in Washington D.C. His paper on target symptoms was based on open trials with imipramine mainly. Of course the majority of depressives are retarded, not agitated and the general impression was that imipramine worked better in retarded cases than in agitated ones. Agitated patients are very difficult to treat anyhow; they respond well to ECT. So the concept of target symptoms was formulated solely on clinical grounds. Randomised trials were lacking, and it was more of a clinical intuition that a sedative drug should be given to an agitated and non-sedative to a non-agitated form of depression. This was the basis of Kielholz's idea of three components of the effects of antidepressants, activating, mood-improving and sedative effects. He classified antidepressant drugs accordingly. I don't believe in these three components. There is no doubt that drugs can show more activation or sedation from an experimental point of view, but that does not provide evidence for a differential indication of drugs, answering the question which drug is more suitable for which type of patient.

Paul Kielholz's recommendation now belongs to common-sense psychiatry and has spread world-wide. In my opinion, though, many of these ideas have not been soundly proved by empirical data.

What do you mean by that?

The common sense view is that an agitated depressive will respond better to a sedative antidepressant like amitriptyline than to a non-sedative drug like moclobemide and vice versa for a non-agitated depressive. But this is simply not proven. A meta-analysis we carried out comparing sedative antidepressants and moclobemide clearly showed that there was no difference in efficacy between patients with low or high agitation.

I'm not convinced about this whole matter of selective clinical profiles for antidepressants. An exception may be amphetamine. I have treated many depressives with amphetamines, as have others like Nathan S. Kline, Donald F. Klein and others. In the early fifties opium and amphetamine were the main drugs used to treat depression. The drug available on the market was pure dexamphetamine and a combination with a barbiturate in order to have a sedative effect. Some of us still use amphetamine pure or in combination with a standard antidepressant in refractory depression. Over the years I have certainly seen many patients who do not just show activation under amphetamine but also mood change, a clear elevation or improvement in mood, which points to a true antidepressant effect as well.

Anyway, we now know that all the standard and modern antidepressants have roughly similar efficacy; there is little evidence of a differential activity profile in the subgroups of depression; they all respond to the same extent. Indeed it is the syndrome of depression across a whole range of disorders and symptoms which seems to respond, while within the depressive syndrome there is no clear evidence of substantial differences between drugs. I therefore think the target symptom concept is a myth. It may be better to apply

non-sedative antidepressants; this has been shown by the findings of Ian Hindmarch on the unfavourable effects of standard sedative and anticholinergic antidepressants on cognition, learning, driving and memory. I think it is important to have non-sedative drugs and to use them. Today's SSRIs or RIMAs have great advantages over the standard antidepressants.

Given that the target symptom approach falls down and given also that the target neurotransmitter approach has fallen down, people like Herman van Praag have gone back to an Adolf Meyer type language, it's all just reaction formation. Do you take this kind of approach.

Herman van Praag and Leijnse developed the theory of a functional pathology in 1965, which hasn't so far been disproved. What is clear today is that all transmitter systems are interrelated, which doesn't lend credence to the simplistic views of the action of drugs or of the relationship between personality types and transmitters proposed by some. It may be correct to think along the lines suggested by Van Praag in a more dynamic sense, based on syndromes which cut across psychiatric classification.

Psychopharmacology stimulated a syndromal approach very early on. It has always been thought that the drugs work on core syndromes and not on disorders. This idea is now better founded. It makes little sense to stick to a rigid, static system of classification but might be more promising to look for general functional syndromes of behaviour or mood regulation. In these terms, I think I would to some extent agree with Herman van Praag.

The third group of myths you've taken on to some extent is one you've taken on through your involvement in the development of moclobemide. The MAOI's as a group of drugs have been more subject to myths than any other group of psychiatric drugs.

I was involved in research on iproniazid and isoniazid in 1956 before they were used in psychiatry. I carried out a trial on iproniazid and isoniazid in multiple sclerosis, which is published in the Swiss Medical Journal. At that time, these drugs were used in the treatment of tuberculosis. A paper from Vienna reported gram negative bacteria in the CSF of multiple sclerosis patients, suggesting that it was a special sub-type of tuberculosis and that it should be treated as such, which is what we did - but without any effect. Without any therapeutic effect that is but we did see a lot of side effects, which is the point of the episode. Iproniazid turned out to produce peripheral blood changes. We found extensive erythrocyte destruction. I made a lot of bone marrow punctures and looked at the findings together with a very good haematologist colleague; they were quite clearly a side effect of iproniazid.

All this was before iproniazid was introduced into psychiatry. After the first symposium on iproniazid in Zurich at which Roche Company presented its data Bleuler asked me whether we should introduce it. I advised against, because it was toxic. My scepticism was also based on the literature, which showed that it can create confusional states. Although we did use iproniazid to a minor extent, it was never really a major antidepressant drug and it wasn't a great success on the Swiss market. Subsequent drugs like parnate, tranylcypromine or phenelzine never broke through as antidepressants either.

The fact that the MAOIs had a restricted indication, being targeted at the syndrome of atypical depression, didn't make them great drugs. If they are only suitable for a

subgroup of patients - and an ill-defined one at that - one may well ask why they should be used at all. When I did use these drugs it was mainly in combination with tricyclic antidepressants in treating therapy-resistant cases.

I remained interested in the MAOIs because of reports from England and America. I ordered phenelzine and tranylcypromine from abroad for use in treating depression, but the results were never very impressive or were insufficient to offset the dietary and other problems such as interaction with other drugs. So the MAOIs remained second or third choice drugs. In the 80s the advent of the new reversible MAO-A inhibitor (RIMA) Moclobemide gave us a fresh opportunity in the field of MAO inhibition.

Looking at the MAOI story though the MRC trial which suggested that they weren't effective was probably a poorly done trial, with too low a dose of phenelzine; the liver problems that they caused may have been as much caused by co-prescription with the barbiturates - anyway you don't find these problems now - and then the famous cheese effect, even in the case of the older MAOIs, seems to have been something of a myth, in that it's very hard now actually to prove that there were ever many people who had a serious problem with the cheese effect other than those who were on tranylcypromine. But for whatever reason, this group of drugs got branded and it's very very hard now for

Yes, in 1965 I was at the Maudsley for a couple of months under Michael Shepherd where I did a retrospective record study by analogy with the MRC trial. Erwin Varga and I went over more than eight hundred records documenting the treatment results of phenelzine, imipramine and ECT. We confirmed the results of the MRC trial: phenelzine did not perform well compared with imipramine. ECT was the most effective. It is not clear what the poor response to phenelzine really means, given what we now know about moclobemide. The MAOIs should work, at least in adequate doses. It was probably a major error to recommend their use mainly for atypical depression.

Well, was the idea that it was specific for particular kinds of depression more a marketing ploy rather than anything based on scientific evidence?

My view is that we simply didn't have good clinical studies on the classical MAOIs, and the drug companies were not sophisticated enough at that time to attempt any really systematic investigation of them. The MAO inhibitors have never been investigated across all indications to anything like the extent we see for new drugs today. That's my opinion at least.

On that point, it seems likely that there's only going to possibly be one or two more RIMAs introduced into the market and even these compounds are ones that entered development some time ago, so in a sense they are part of an older generation of compounds. Is the golden age of psychopharmacology drawing to a close?

I don't share this opinion. Let's start with the antidepressants since we're on the subject. A ceiling has been certainly reached as regards side effects. The new drugs have so few side effects that they barely differ from placebo; there's not much further one can go. The ceiling may have been reached on tolerability, but there's a long way to go to optimal efficacy. There, too, we certainly currently have a ceiling effect, in that all antidepressants have the same limited, modest efficacy. We still don't have a truly powerful antidepressant. The potential for better drugs is vast. Good antidepressants, in my view, would be drugs which, like good hypnotics or good analgesics, worked within a

few days, if not hours and had higher success rates than 50 to 65%. However, it's my hypothesis that if a new drug really acted faster, it would probably also be stronger; with a higher response rate. The companies will have to look for quicker onset of action and will hopefully focus on non-sedative, stimulant drugs. They won't return to amphetamine but to similar substances.

In contrast to antidepressants, tolerability is still the main problem for antipsychotic drugs. On the other hand, their onset of action is rapid and their effect is more reliable, improving the positive symptoms considerably. But these drugs do not generally cure the condition, which means that there is room for improving action as well as tolerability. The development of receptor sub-typing is likely to play an important role. I wouldn't rule out improvement on both tolerability and efficacy by much higher specific and local action of the drugs in the CNS. So far experience at least shows that more selective action does not reduce a drug's efficacy. There is no proof, for instance, that the specific serotonin uptake inhibitors are any less active than the tricyclics. There may be some differential indications, although that's not really proved in my view.

But in the case of the anti-psychotics, arguably the most potent drug is clozapine, which is as non-specific as you can get, and the least potent are the highly selective D-2 blockers.

Yes, but even if that is the case, it doesn't exclude the development of more specific, less toxic and better-tolerated drugs. I think we are still in the early stages of development and I wouldn't be too pessimistic. The whole field of receptor sub-typing seems to be very promising for psychiatry from a dynamic point of view; and I think it could revolutionise psychopathology and pathogenetic theories, cutting right across all sorts of behavioural syndromes. There is some evidence at least for the assumption that certain regulatory systems cut across functional behavioural systems. So I repeat we shouldn't be too pessimistic, as was the case for benzodiazepines, where some drug companies wrongly to my mind decided to withdraw or scale back their interest.

The benzodiazepines provide a good example of how the whole issue of partial agonist or partial antagonist hasn't been sufficiently explored. For instance, we had access to oxaprotiline, developed by Roche, a drug which was a partial agonist but behaved clinically like an anti-psychotic. Now, if we had benzodiazepine-type anti-psychotic drug, avoiding all the extra-pyramidal problems, it would be just great. So, there is some potential left for new compounds with new pharmacological principles.

But aren't we in a climate where it's harder and harder for a company to recoup their costs. The pharmaco-economic prospects facing companies wanting to launch psychotropic drugs that do not differ radically from what has gone before are not good.

Yes, that is a enormous brake. Development has certainly been slowed down by the registration and safety demands and costs, for example. I think this has had a damaging effect of the strategies of the companies, making them over-anxious and unwilling to take risks. Risk-taking behaviour by individuals in the companies is not rewarded, and there's no doubt that to develop a drug has become a major financial risk. It's not that there is no potential. It's rather that society has an exaggerated need for ever more security.

Why do you think we've got so neurotic about drug development?

Well, it's a combination of factors. There is a hostile attitude against everything which is chemical - even though nature is chemical. This interreacts with the whole Green

movement, which favours an alternative, more natural way of living and food intake, avoiding all chemicals, which are defined as poisons. Then there's the distrust of science, scientific thinking and scientific proof, which stems from the '68 movement, and inevitably results in an irrational bias against scientific methods in proving efficacy. In Switzerland at the moment natural healing has a large following, with all sorts of unproven medication and natural products selling well. Medical science has partially lost its prestige in society, with more distrust than trust in scientific methods and overconfidence in all homeopathic products.

Its really odd that there should have been such a change in so short a period of time. When the drugs were introduced first there was the idea that nature and particularly disease was bad, or at least potentially hostile, and they had to be contained by man. Now we've gone to the opposite extreme. Nature is good. Man is the fly in the ointment. Where does that change in thinking come from?

To my mind it stems from the 1968 movement, which was romantic, mystic and irrational. That is why Jung's psychology, with its theory of archetypes and stress on emotional development, or the writings of Herman Hesse, who was treated by a Jungian analyst, had a special appeal. All the mystic experiences of the LSD movement to change what they called consciousness were irrational in a way. This anti-rational movement is still very much alive and partly explains the opposition to drug treatment, which is thought to be inhuman and merely chemical, as opposed to human and more emotional types of treatment.

Another factor is the belief that human beings are being increasingly poisoned by the environment. No-one would deny that there is environmental change and pollution, but current concerns are that our present life style and civilisation are far away from nature and must therefore be unhealthy. So we have this polarisation: on the one side advocacy of a return to nature, and drug treatment is one of the demons on the other side.

Yet another aspect in the rising costs of developing drugs, as I mentioned earlier, is an exaggerated demand for security. Switzerland is a good example. Increased wealth brings over-insurance. People would like to avoid having to take risks in their lives - up to death. As regards drug treatment, people want it to be safer than it can possibly be.

Let me re-introduce the question of psychotherapy here because psychotherapy is often put forward as being much safer than drug treatment. You began as a psychotherapist and recently, at least, there've been some claims that treatments like cognitive therapy and interpersonal therapy are useful for depression - although I know you are somewhat sceptical about claims for the efficacy of psychotherapy in depression. Do you think the vogue for therapies links up to this question of risk?

I was interested in both interpersonal psychotherapy - IPT - which was created by Myrna Weissman and Gerry Klerman and in cognitive therapy - CT - founded by Aaron Beck. I looked carefully at this development but am not entirely convinced that the evidence for the efficacy of these techniques would meet the requirements for registration as new treatments if the same standards were applied as for drug treatment today. There are not enough well-controlled studies proving psychotherapy's efficacy against placebo, controlling for severity of depression. For instance, the evidence from Irene Elkin's NIMH study - the biggest carried out in the field with about 400 patients - a very well-designed study using well-trained therapists, is not convincing as to efficacy : on conventional

measurements, at least, such as the Hamilton Rating Scale, neither CT or IPT was any different from placebo over eight weeks.

In 1989 I organised a workshop in Zurich, at which Aaron Beck represented CT and Bruce Rounsaville IPT. The results of the NIMH study of Elkin et al which were presented at the workshop showed no difference in efficacy between placebo and cognitive therapy on the Hamilton Depression Scale. Aaron Beck was disappointed and angry and maintained that the therapists had not been well trained, but he was contradicted by Brian Shaw from Canada, who had trained the therapists for the project. Moreover, Aaron Beck himself had been a consultant for the whole project. I therefore concluded that CT must be very demanding to teach and to learn, which would tend to favour the application of IPT, which has been shown to be at least as efficacious as CT.

So the big studies on the psychotherapy of depression are not convincing, and data analysis has shown drugs to be clearly superior in severe depression. Psychotherapy is frequently recommended in the treatment of minor depression, which is to ignore the fact that there is a lot of evidence that in minor depression it is not possible to prove efficacy either with drugs or psychotherapy. But despite the lack of definite data on the psychotherapy's efficacy, it should always be used. I would, though, recommend learning IPT as a first technique, because it is easier to learn and it gives the patient the necessary information about his disorder. It underlines the social roles and quality of life of the depressed patient and highlights important aspects of depression that lie outside clinical features identified by the rating scales.

Medicine's neglect of these aspects has damaged its reputation. This whole area of a patient's social roles, support and networks is extremely important, not only for depression, but for all disorders. So I am very much in favour of psychotherapy combined with drug treatment but would never advocate replacing drugs in the treatment of moderately or severely depressed patients by psychotherapy alone.

But there's another point I'd like to make. I am now predominantly an epidemiologist and therefore interested in the pharmaco-epidemiology of fluoxetine. The wide use of this drug is a very interesting phenomenon. I would say that there is a big natural experiment in progress, one which I'd be very cautious about judging. I would tend to the view that there's no reason why people should not take an SSRI if they get better. If they resort to cigarettes or alcohol for example, why should they not take a drug which is less toxic than nicotine or alcohol ?

From an epidemiological point of view, there's a high prevalence of mild depressive, sub-threshold syndromes; many people are mildly pessimistic, depressive, obsessional or hypochondriacal throughout their life time. We know from the lithium data that effective prophylaxis can decrease obsessionality. This may also be true for the SSRIs. A person taking an SSRI may have the impression that a character trait is changing, for example, that depressive traits, pessimism, joylessness or chronic fatigue, are diminishing. If these symptoms have been chronic, the subject may consider them as part of his personality. But there are no grounds for assuming that personality disorders are essentially different from psychiatric disorders. In some cases I would say they belong to the same spectrum; for example a person with a cyclothymic personality belongs to the bipolar spectrum and a depressive personality belongs to the depressive spectrum, in my view. There is good reason to assume that drugs will act on personality disorders if they belong to the target spectrum. We know that, across a certain spectrum, drugs are unspecifically efficacious.

So I would say that it's perfectly possible that many more subjects in the population could benefit from such a drug. And the number is far higher than you would think. New epidemiological studies show that depression as such is much more prevalent in the population than previously thought. There's extensive sub-threshold morbidity, which has been shown to be socially relevant. So I repeat I would be very cautious about judging the widespread use of SSRIs. How to handle such a possibility is a political, social or ethical question. I am not an advocate of flooding the population with antidepressants, but the whole field needs careful research, a scientific approach rather than just opinion.

Let me pick up on some epidemiological issues. While you've been here, Zurich has been a centre for epidemiology. Now one of the things that's come out of this is the idea of recurrent brief depression. Do you want to comment on how that came about?

The concept of recurrent brief depression was a by-product of the methodology we were using. When I started the studies, I hunted around for instruments for assessing morbidity in normal populations; the PSE was the only structured interview available, but it was not really suitable for that purpose. The PSE was designed primarily as an interview for psychiatric patients suffering from schizophrenia and severe affective disorders. Whereas we wanted to cover the whole field of functional somatic syndromes, together with psychological syndromes, including for instance gastric functional complaints, headaches and insomnia. So we created the SPIKE interview, which is comprehensive and picks up milder symptoms and syndromes. Applying the SPIKE interview, we assessed systematically the number, length and frequency of symptoms, and it emerged that brief spells of depression are frequent among treated depressives who do not meet the diagnostic criteria of DSM. The question was then: what frequency was needed for case definition and how that could be validated; we then came up with the concept of recurrent brief depression.

Our study contained other groups of non-recurrent and less recurrent brief depression, but these were just not as valid and would have raised the prevalence of affective disorders in the population to a percentage that would have been meaningless. So, we settled on recurrent brief depression. But that was not all. We found brief spells, of a few days, in hypomania, neurasthenia, anxiety and insomnia. There is, in fact, epidemiological data from England showing that in many cases the consumption of hypnotics is not chronic but occurs in brief spells, which is linked with brief insomnia. Fatigue, too, can occur in brief spells. The same is true for hypomania, something which I consider to be quite important clinically, because it means that such subjects belong to the bipolar spectrum. But these brief spells are simply not investigated or considered. So recurrent brief depression is just one brief psychiatric syndrome we have described.

Is recurrent brief depression distinct from the kind of brief depressive episodes that go with borderline personality?

Well there is no specific research on that. Two other groups, those of Montgomery and Staner, have been involved in the area of personality disorders. Stuart Montgomery started with a group of repeated suicide attempters, to whom he gave flupenthixol and a several SSRIs as a long term medication; he couldn't see much change against the measures he had used. Of course, from a phenomenological point of view, a group of frequent suicide attempters is bound to include many personality disorders. This may be true for about 80% of suicide attempters. Therefore, such a group cannot be

representative of recurrent brief depression and indeed Montgomery didn't define them as recurrent brief depressives at the beginning of his trials.

Staner from the Mendlewicz group studied intermittent depression and assessed personality diagnoses. They found a high rate of recurrent brief depression. They also showed that about 14% of major depressives received a diagnosis of a personality disorder in contrast to about 4% in the group of recurrent brief depressives. This finding does not suggest that recurrent brief depression can be explained by personality disorders. Those are the only data on personality disorders currently available. A study on personality disorders is being conducted in Zurich by Johann Walter Meyer, sponsored by the Swiss Science Foundation, with interviews of patients whom we had earlier diagnosed as suffering from recurrent brief depression or major depression. This will be the first epidemiological study to assess both recurrent brief depression and personality disorders. Although it involves a sample of males only, it will probably answer the question of the overlap between the two.

If we take a group who have recurrent brief episodes who don't have a borderline personality, any ideas what mechanisms could be causing recurrent brief syndromes, whether depressive or whatever?

I think it is an endogenous mechanism. These subjects are rapid cyclers, with brief spells, which are difficult to treat. If you ask them as we did in our interviews about life events, using standard instruments, they don't report the occurrence of life events in connection with these repeated brief episodes. Someone is more likely to make associations when he has had one or two major depressive episodes; the more you have, the fewer precipitating events you can find. The fact that fewer and less intense events are involved over time may also be an effect of kindling. The threshold for manifestation or the threshold for sensitivity to stimuli may change. This is the view of Robert Post, whose kindling theory may also be applicable to recurrent brief depression.

I have also looked at all the case histories of RBD subjects and their personalities and they are not very deviant from the norm. Many of them are living under considerable stress but performing quite well in life, in other words, many are quite strong, stable individuals, not borderline subjects at all.

Let me raise the other issue which comes out of the Zurich epidemiology work, which is that contrary to prevailing views that depression is much commoner in women than men, if you go out into the community, as you have done, you find that there's an almost equal prevalence...

Well, the sex ratio depends very much on co-morbidity. The analysis of pure recurrent brief depression shows that the prevalence is almost equal - close to 1.1 or 1.2. In the Zurich study we found this also applied to major depression if you exclude the comorbid cases. On the other hand, taking double depressions there is a several-fold preponderance of females. So the more complicated and severe the case is, the more common it is among the female groups. I don't know what this means. The hypothesis of Susan Nolen (1987), an American psychologist, is that the sexes have different coping strategies. It would appear that females ruminate, blame themselves and try to find subjective reasons for their depression much more than males do. Males would be more likely to act out, go out and try to forget, drink, or try to overcome their depression through sport. This male strategy might be better. The females may get trapped in a vicious circle, which intensifies the severity of episodes and increases their vulnerability to depression over the years. So a psychosocial effect may be involved. Another possible reason is hormonal. Androgens influence aggression and may also determine male coping

strategies. I do not think that the explanation for the sex ratio is to be found in the X-chromosome, something which I advanced in 1966 in my monograph but which I now consider too simple.

We lack a European forum. We've got ECNP and AEP but do they actually provide what we need in Europe. Compared to the Americans, who are so organised....

Yes the CINP has changed and declined since becoming a huge world congress. It has too many parallel sessions and has lost its coherence. Earlier meetings always ended with all the symposia Chairmen presenting a synthesis of their results in a plenary session; this gave an extraordinary overview of the whole field. This practice has been abandoned and forgotten. At a meeting nowadays you are confronted with dozens of parallel sessions and time-consuming choices between them.

The balance of ACNP has changed: as its clinical element has declined so has its interest to clinicians. While it may have gained scientifically, I don't think it fulfils its former role of bringing together basic science researchers and clinical scientists. I think the area of clinical research has been grossly neglected. I find that the development of ECNP, embracing clinical and experimental research, is currently more promising. Over the past few meetings it has developed well and has maintained a clinical course. This is interesting in view of the foundation in the States of an American Society for Clinical Psychopharmacology by way of reaction to the changes in ACNP.

As you say, the area of clinical trials needs development. We've had something of a hiatus since the 1960s. It seems to be only recently with the European Consensus Conferences on Methodology that there is any movement returning to the field.

Yes, little has been happening because the drug companies' main interest is in meeting the FDA requirements, and new methods are a lower priority. This is why we launched in Zurich the European Consensus Conferences on the methodology of clinical trials. In 1994 in the context of the ECNP Conference in Jerusalem, a full-day methodological meeting was organized by Stuart Montgomery attended by Paul Leber from the FDA and representatives of most of the drug companies. It was quite obvious that new methodological developments will be of great future interest. One example is the development of new criteria for the onset of action of drugs.

Another neglected area is self-assessment, for instance daily self-assessment by the patient. A new rating scale has been developed by John Rush, the IDS, a depression inventory of 28 items, existing in two versions, for self and observer ratings; the correlation coefficient between them is 0.95. If that is true, one could replace observer ratings for ambulatory patients by daily self-ratings and determine more precisely the onset of improvement. I would also recommend regular application of a global self-assessment of depression on the line of school marking systems. In Switzerland for example school marks range from 1 to 6 and I have started to apply such a scale in the daily assessment of depression. Because they feel immediately at home with such a measure, patients are able to define their ratings very precisely, right down to decimal points. The advantages of a familiar scale over an invented and artificial one are obvious. On the whole, the methodology of drug trials is a neglected area in psychopharmacology and deserves far greater attention.