

PSYCHOPHARMACOLOGY AND THE HISTORY OF PSYCHIATRY

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Could we begin with your recollections of the 1955 Paris meeting, which was effectively the first world wide meeting on chlorpromazine.

The meeting was organised in Paris by Jean Delay. It was supported by Specia, the pharmaceutical firm which had produced chlorpromazine, which was a branch of the Rhone Poulenc Group. For the first time people engaged in what was called psychopharmacology came together. They came from many countries, including the United States. The efficacy of the drug and the mechanism of action were discussed. However, at that time the biochemistry of the brain, as it exists now, was unknown. It was only at the beginning of the 60s, that we began to speak of the role of the neurotransmitters in the action of both neuroleptic drugs and antidepressants and of their potential abnormalities in the disease process. So in practice 1955 was only a meeting on therapy with chlorpromazine.

I have always been very much impressed by the fact that chlorpromazine, which had been introduced only 3 years before, was already used all over the world. Theoretical ideas take usually a very long time to travel from one country to another, and sometimes they never make it. I quote always, the case of Karl Jaspers' General Psychopathology, which is considered in the German speaking world as one of the basic books of psychiatry. This was published in 1913 but appeared in English translation only in 1963, 50 years later and, even then, a paper published in the American Journal of Psychiatry wrote ingenuously that, until this publication, many psychiatrists in the United States had not realised that Jaspers was not only a philosopher, but also a psychiatrist. It takes a very long time for theoretical ideas to travel but in the case of new techniques of obvious practical value, the transmission is very fast. It was the case with ECT and it was even more striking with the neuroleptics because at the time psychoanalysis had an extremely strong influence, especially in the United States, and psychotherapy was considered the appropriate treatment of the mental illnesses.

There was some paradox in the fact that psychodynamically oriented psychiatrists, when confronted with psychotic patients in hospitals, could admit that, after all, drugs were useful. At the beginning of the 60's I visited at Yale University an extremely well organised Department, in which a young British psychiatrist, psycho-dynamically oriented, specialised in the psychotherapy of schizophrenics. The programme combined intensive individual and group psychotherapy. At the end of the discussion, I asked my colleague "but do you use any drug?" "Of course" he said "we give them chlorpromazine 200 mg a day but just for facilitating the psychotherapy".

At the 55 meeting was the issue of who had discovered chlorpromazine an issue?

No. The meeting had been organised by Professor Delay who had published on it. It was certainly not an issue. In the case of chlorpromazine, the problem is extremely complicated. At that time, there was already a great hope about the possibility of psychopharmacology. In order to put the events in perspective, I must return to the life and career of Professor Delay. His father was a well known surgeon in the South of France and, as fathers are, wanted his son to become a surgeon. Professor Delay came to Paris to study medicine and became a Resident of the Paris Hospitals by competitive examination. At that time, this was a necessary step if you wanted later to attain an academic position. Professor Delay went through the entrance examination brilliantly - he has always been considered as one of the most brilliant physicians of his generation. His father was convinced, by one of Delay's friends, to let him to give up surgery. So he

became a resident in medicine and went to neurology which was - and still is - in France, and possibly in the UK, considered an "aristocratic" speciality, being reserved for the best medical students. At the end of his residency he became "Chef de clinique", a position more or less similar to that of a Senior Registrar. It's the first step in an academic career, followed eventually by the assistant professorship, and then by the full professorship. Professor Delay was Chef de Clinique at the Neurology Department of the Salpêtrière, but, at the same time, he studied psychology at the Sorbonne. All his life he had both psychological/literary and biological/scientific medical leanings. During his stay at the Salpêtrière, he was co-author of a book on EEG, an expression of his keen interest in biology and during the same period of his life, he became a PhD with a thesis on memory and its pathology. He was to write other books on psychopathological themes, especially one on mood disturbances which was relevant to his later ideas in psychopharmacology.

After leaving the Salpêtrière, Professor Delay entered psychiatry. This was a tradition in Paris. For a long time, in fact since the creation of a University Department of Psychiatry at the end of the 19th century, the Professor has been originally a neurologist of the Salpêtrière who had later specialised in psychiatry. At Sainte-Anne Hospital, the seat of the Department, Delay became assistant Professor and then full Professor and Head of the Department. Because of his dual background he was interested in both psychopathology and in biological psychiatry. His first interest in biological psychiatry was ECT, at that time the only really active biological treatment in psychiatry.

In the UK they were also using Insulin coma ...

Yes that was also used too, but it was technically complicated - there was a special unit at the University Clinic. The efficacy was at best marginal, but at that time we had nothing better for schizophrenic patients. One used a technique which came from the United States and Great Britain during the War, psychotherapy with patients whose state of consciousness had been lowered by a slow intravenous injection of amobarbital. It was called narco-analysis and was considered as combining in some ways psychological and biological components in the treatment. As soon as he became Head of the Department, Delay had encouraged his co-workers to develop research in biological psychiatry. At the end of the 40's, I was personally involved in research on amphetamines. The drug was not known to be addictive and it had been used in England intravenously in combination with amobarbital to produce abreactions, considered to be powerful therapeutic tools. During his period the general concept of "shock" - an ill defined term which implied that a rapid change in the state of consciousness could stimulate a recovery - was widespread: one spoke of insulin-shock, cardiazol-shock, electro-shock and of other now forgotten shock-techniques and, for that reason, Delay proposed the term amphetamine-shock.

In 1950 the first World Congress of Psychiatry was held in Paris, Professor Delay being President. As I have said, the main and practically only interest in biological therapy was shock treatments: the inventors of the three best known techniques - Sakel, Meduna and Cerletti presented the main papers. The same year, Professor Delay had collected all his previous publications on biological psychiatry in a book: "Biological Methods in Clinical Psychiatry" which gives a good idea of his interests and of the situation existing just before the birth of modern psychopharmacology. The book contains, among others, chapters on insulin therapy, electro-shock, narco-analysis, amphetamines, and interestingly, the first mention of drug therapy as we understand it today. Delay had published with Sizaret and Deniker the year before two papers on the action of a dinitrile preparation in depressive states. Dinitriles had been studied previously in Sweden by Caspersson and shown to have allegedly "stimulating" actions in nerve cells. Delay had various types of dinitrile derivatives prepared, and made a clinical trial with one of them.

I mention this fact to give a general idea about the atmosphere. The attitude at the Clinic was that, if we tried hard enough, we would find a drug with therapeutic properties.

At that time Chlorpromazine appeared. It has been synthesised at the Specia Laboratories. They had already created a series of anti-histaminic drugs, some of which, like phenergan, had been used in psychiatry because of their obvious sedative effect. But chlorpromazine had different and, much more complex properties. After it had been synthesised, its pharmacology was studied by Mrs Courvoisier at Specia Laboratories and it was then put at the disposal of Laborit. He was a navy physician, an anaesthesiologist. On the basis of a theory of the action of drugs in anaesthesiology, he proposed to use it in a combination he called a "lytic cocktail". During his work he discovered and published the fact that chlorpromazine, used alone, had a very specific action. The consciousness remained normal, but the patient showed a complete lack of interest about his surroundings. Laborit suggested that because of that type of action, the drug could play an important role in psychiatric treatment. Others had received supplies of the drug: Hamon, Paraire and Velluz the psychiatrists at the Central Military Hospital in Paris, the Val de Grace, and Pierre Deniker who used it at the Clinic under the direction of Delay.

They also published in 52 and this is one of the points of discussion. There were 3 groups involved. There was Laborit, who made the first clinical observations, who did of course not use the drug on mental patients, but who discovered its psychotropic action and suggested that it could have a special interest in psychiatry. There was the group at the Val de Grace, which used it on mental patients and published the first psychiatric paper and there was Delay and Deniker whose publication came immediately after. The debate has been very heated. The Lasker Prize was given in 1957 to Laborit and Deniker. Delay and Deniker have always considered that they were the real discoverers of the clinical properties of the drug. Their argument is that Hamon, Paraire and Veluz, even if their paper was the first, had used chlorpromazine in conjunction with barbiturates in manic states to potentiate the sedative properties, whereas they had used the drug alone. The American author, Josephine Swazey, a supporter of Laborit, wrote a book on chlorpromazine in which she portrayed him as the real discoverer of the properties of the drug. I have heard - but did not see the documents - that the New York Academy of Sciences made a detailed enquiry in France and concluded that Delay and Deniker were the discoverers of the clinical properties. However, the representative of the Army medical services still claim that their role was decisive.

In September last year a ceremony took place for the 200th anniversary of the foundation of the Val de Grace, an old abbey which became a military hospital in 1794, during the French Revolution. A large scientific meeting was held in the wonderfully restored building and, at the end, a marmor plaque was unveiled on which was inscribed: Hommage to Laborit, Lasker Prize 1957, and to J Hamon, J Paraire and J Velluz for their discovery in 1952 of the therapeutic effects of chlorpromazine in psychiatry.

From 1952 on, Delay and Deniker contributed enormously to the subject, whereas Hamon and colleagues did not pursue that direction, and Laborit, not being a psychiatrist, did not work directly in psychopharmacology. The momentum came from Delay and Deniker, who had realised the importance of the new field, and in this respect they were the real discoverers. This is my personal opinion but I believe the discussions about the precise role of the various persons and groups involved have had an unfortunate consequence. I have always thought that the Nobel prize was never given to chlorpromazine, when it should have been, because of this. Only two Nobel prizes have been given for psychiatric discoveries, namely for malaria therapy and lobotomy and chlorpromazine was just as important. My impression - but it is only a guess - is that our Swedish colleagues were afraid of being involved in an argument about the roles and the priorities - they had already had bad experiences in this respect - and preferred to abstain.

Is it possible to tease their respective contributions apart? Was Deniker simply acting under the direction of Delay ?

It is very difficult not to say impossible to tease the respective contributions of Delay and Deniker apart. As I have said Professor Delay was deeply interested in the potential possibilities of drug therapy in psychiatry well before chlorpromazine appeared, and he encouraged his assistants in that direction. Deniker was then assistant in charge of the men's wards, and had under him as resident Harl who is mentioned in the original paper. Of course Deniker was closer to the patients than Delay - and for that matter Harl even closer - but, just as Harl discussed the results with Deniker, so Deniker discussed them with Delay. It was certainly not a one man job.

At the 55 meeting, Linford Rees reported on the evaluation of chlorpromazine using a randomised clinical trial method and he recalls you asking him about the English obsession with clinical trials?.

I probably meant - and it is still my opinion - that in cases where the changes produced by a treatment are of such a magnitude that they appear obvious to a naive observer, we do not need statistical proof. But it is fairly ironical that Linford Rees mentioned this episode, since I was already considered in France as a strong supporter of statistics. My training had been both in psychiatry at the medical school and in statistical psychology at the Institute of Psychology at the Sorbonne. I had published a book on mental testing and I had close connections with British psychologists and psychiatrists with the same interests. The British tradition in those matters was strong, and from the beginning, I had a leaning towards measurements in controlled trials. I am more or less considered in French psychiatry as the man who has been responsible for the introduction of quantitative assessment methods, both in psychopathology and in psychopharmacology. Indeed, I have been much attacked at that time by my colleagues for taking this position.

The French attitude was the result of a serious historical development. Statistical methods were born in France with Laplace and the mathematicians of the "Ecole Polytechnique" such as Fourier, who developed the theoretic basis and the first great medical statistician was in the middle of the 19th century, a French physician, Louis. When the Royal College of Physicians started, about thirty years ago, a section of statistical medicine, the first session was significantly an outline of Louis' work. However statistics lost later any prestige in medicine, probably under the influence of Claude Bernard. Claude Bernard was, of course, a great scientist but in his field, experimental medicine, where a single well planned experiment was sufficient for a discovery, statistics were of no use. Unfortunately, in some of his writings, he ridiculed statistics. The result was that, because of his considerable influence, the medical profession took a negative view on the method. It was seen as opposed to the traditional and allegedly typically French clinical approach, which rested on the accurate observation of a single case. Statistics were confined to psychology and, in medicine, were looked down on until the Second World War.

It came back mostly through the influence of the medical publications we were receiving after the end of the War from the United States, but its progress was very slow. A few years after the end of the War, Robert Debre, at that time the most influential medical man in France, organised a meeting on clinical trials and invited French colleagues and British statisticians. The lectures of the proceedings are very revealing. Debre's idea was to promote clinical trials in France but the reactions were, on the whole, not very positive: it was only conceded with some difficulty that statistics had some place in medicine. Debre managed, several years later, to have a mathematician, Daniel Schwartz, nominated in a newly created Chair of Statistics at the Medical School.

Although Professor Schwartz was a brilliant statistician of engaging personality, who had a great talent for making complicated concepts understood by people without mathematical training, it took a long time to convince the traditional clinicians of the value of the methods. It was the same in psychiatry as in the rest of medicine: statistics and controlled trials were looked down as alien to the clinical spirit.

Hanns Hippus suggests that when the drugs were first introduced in Germany they weren't of any great interest to German psychiatrists because therapy was not considered to be part of science. The use of the drugs or the interest in the drugs would have been to see what they revealed about how the mind works rather than in terms of trying to get people well. To some extent, it was a little bit the same within the UK, in the centres of excellence like Oxford and Cambridge and The Maudsley. The idea that it might be a good idea to try to get people well has come from outside the big centres. Is that the same in France?

Not to the same extent, I would say. You must remember that in France, the Paris University Clinic was considered the centre of excellence, and that Head of Department, Professor Delay, had already shown a great interest in drug therapy, as I have mentioned earlier. On the other hand it is true that, in so far as you can speak of German, French or British schools of psychiatry, the German one had always been considered in France as mostly interested in theories. Since Madame de Stael, Germany was seen, especially in the 19th century, as a country of philosophers and thinkers, producing beautiful but sometimes obscure theories. Two years ago I wrote a paper on the history of German psychiatry as seen by the French authors of the same period. The German school had always fascinated the French psychiatrists because of its theoretical points of view, so different from the French attitude prevailing since Pinel, which was basically clinical and descriptive. Of course the atmosphere in those relations has been influenced by external events. During the First World War, German psychiatry, as represented then by Kraepelin, was attacked violently and considered as fundamentally aggressive, as aiming at imposing its ideas to the world, as the armies of the Kaiser were doing. But, even during this short episode, the main argument used against Kraepelin - of course wrongly - was that his concepts were of a basically theoretical nature and had allegedly no connection with the clinical facts. Even if one leaves aside the role of national stereotypes which colour the judgements on another country, it can certainly be said, as Hanns Hippus mentioned that the German psychiatry has always shown a great interest in theoretical issues and in psychopathology, whereas the French had a more pragmatic, descriptive and clinical bent. This emphasis on the clinical approach probably favoured the interest for the therapeutic methods, but was at the same time responsible for the antagonism to the controlled trial. It was claimed that a clinician could realise better than any statistical method, if a drug was active or not.

Well this is what Roland Kuhn would still say to this day that he didn't need clinical trials to discover imipramine and what have all the clinical trials, done ever since, shown.

In France such an extreme position is no longer supported. It was probably originally an idea dear to many "classical" French clinicians, but nobody would defend it today.

When the antidepressants came in they looked very different to chlorpromazine.

Yes, but they were studied first in Switzerland. As soon as they were known, they were used in France too and found clinically very interesting. I shall mention in this respect a curious episode. Professor Delay had formerly developed a psychopathological model of disturbances of mood - it was the title of the book he wrote on the subject. He considered that mood could be altered by being pathologically either elevated or lowered. The

lowering was the central element of hebephrenia which was in the French tradition seen as the core form of schizophrenia. This point of view had already developed in France by Guiraud, who suggested the term "athymie" - absence of mood. On the other hand, there were states with elevated mood, the hyperthymies. They could take 2 different forms according to the colouring of the mood: it could be a painful hyperthymie, typical of the psychopathology of melancholia, or it could be a euphoristic hyperthymie, typical of mania.

When the antidepressants came in, their therapeutic action could be logically interpreted as a lowering of an abnormally elevated mood. Possibly under the influence of Delay's model, the first documents published by the Swiss firm Geigy, which had introduced Tofranil, described the drug as having a "thymoleptic" action - it lowered the mood. However, since the generally held view simply opposed the elevation of mood in manic excitement to its lowering in melancholic depression - as the term depression implied - the new word "thymoanaleptic" - meaning elevating the mood was rapidly substituted, and was used by Delay himself in a paper on Tofranil, published in 1959.

There is a 1959 paper by Delay and colleagues on isoniazid and iproniazid in which was indicated that they had the impression that isoniazid might have antidepressant properties. It seems that this work was being done around 1953/54 which would have been very early. What was the basis for thinking that isoniazid was antidepressant?

At the beginning of the 1950's, there was a great interest in the new treatments of tuberculosis which were tried near Sainte-Anne at the Cochin Hospital, where the Chair of Pneumology was located. Professor Delay had discussions with our colleagues there and thought that, may be, the general well being experienced by the patients treated with isoniazid was partly related to a psychotropic factor. He used the drug at relatively low doses with depressive patients and concluded that, especially in the less severe cases, a positive result could be observed, and he published those results in 1952 with Laine, who was then Chef de Clinique, and a resident, Buisson. On the other hand, being interested in statistical assessments, I proposed to control the changes observed in tuberculosis patients and arranged for a group of them to answer the MMPI before and after treatment by isoniazid in Cochin. The results showed obvious changes in the psychological MMPI profile. I did not publish it but they were incorporated in a paper by Delay and Buisson published in 1956. After the discovery by Nate Kline of the antidepressant action of iproniazid, Professor Delay tried the drug, and the first results were published, together with the results on isoniazid, in a paper with Deniker and Buisson in 1959.

Did the idea of antidepressant activity mean anything like what Kuhn later claimed to have discovered namely a compound effective for vital depression or did it mean something closer to a stimulant effect?

At the time concepts such as "vital" or "endogenous" depression essentially belonged to the German school of psychopathology. In the UK, if you look at a book which was a classic at the end of the 40's, the Textbook of Psychiatry by Henderson and Gillespie, endogenous, neurotic and reactive depression are mentioned, but there is no emphasis on the sharp distinction which you find later in the Clinical Psychiatry of Mayer-Gross, Slater and Roth and which was imported by Mayer-Gross from the Heidelberg school. We had, in France, and even clearer situation, the words endogenous and vital being never mentioned. As I said before, the prevailing psychopathological view was derived from Professor Delay's book on Mood Disorders in which no mention is made of endogenous-non endogenous distinction. The result was that the antidepressants, when they appeared, were seen as acting on depression generally and not, as Kuhn

suggested, primarily on the endogenous-vital type. Delay presented his position in 1957 at the second World Congress of Psychiatry in Zurich. He suggested that psychotropic drugs could be classified according to their three possible actions on the psychological functions: depressing-sedative, stimulating, and finally dissociating. The first class of drugs with depressing action - the psycholeptics - included the hypnotics, the neuroleptics and the tranquillisers. The second - the psychoanaleptics - included the drugs stimulating the awareness: the psychotonics like the amphetamines, and those stimulating the mood: the thymoanaleptics or antidepressants. The third - the psychodysleptics included mescaline and other so-called hallucinogenic drugs. From this classification it is obvious that Delay's point of view was that antidepressants were stimulants of a specific psychological element, the mood.

Where the idea of calling the neuroleptics “neuroleptics” come from?

It was Professor Delay's idea. It means that the drug is taking hold of the nervous system and depressing it. Delay's original model opposed shock therapy to chlorpromazine. In the book I have mentioned, and also in a later one which he published with Deniker on "Chemical therapeutic methods in clinical psychiatry" he held a dichotomic view opposing shock therapies which tend generally to stimulate the nervous system and chlorpromazine, which tends to act broadly in a sedative direction. Although the word neuroleptic is now widely used in Europe, its use has been strongly opposed, especially in the United States, where antipsychotic is usually preferred.

The French, I think more than any other nationality, tend to break the neuroleptics up into different groups of compounds. In the UK we see them as being all the same - a different profile of side effects maybe but essentially they are all the same.

There have been efforts especially by Lambert and also by Delay and Deniker to distinguish between sedative and stimulating or disinhibiting agents, some drugs having both types of action. Of course such distinctions have also been taken over by pharmaceutical firms for marketing purposes - just as they stress today the difference of pharmacological activities on the neurotransmitters in antidepressants - but many French psychiatrists are convinced from clinical experience that some neuroleptics are more stimulating - or disinhibiting - and some more sedative. You can find such a distinction in all recent French textbooks.

What relationship, if any, did or does Athymie bear to Janet's concept of psychasthenia. Was he still around in 1950?

There was no direct connection. Professor Delay was of course a pupil of Janet. His book on Memory was considerably influenced by Janet's ideas and Janet wrote the foreword. But the concept of athymie has another origin. It derived in part from ideas expressed in a book written by von Monakow and Mourgue which was very influential among French psychiatrists in the late 20's. Athymie was really created as a concept by Guiraud who was a very respected clinician at the Sainte-Anne Hospital in Paris. It has certain connections with the ideas of Bergson about the elan vital. It was later used by Delay in his general model of mood disturbances but it had no direct connections with Janet except the fact that it uses analogies with physical notions such as power, level of energy and so on.

Janet died in 1947 at the age of 88. Until the end he was very well preserved physically and intellectually. He came every Sunday to Saint-Anne where Delay gave a public lecture which had a very large attendance of young and older psychiatrists. I was, at that time, already an assistant to Delay and I remember having met him there just before his death. I was, of course, very impressed. He was a very charming old man full of humour.

Showing me a book which was on a table he said "something extraordinary has happened. There is a book, which is a marvel". At that time Jean-Paul Sartre had published his philosophical work, *l'Être et le Néant*, which had become a best seller. Very few had read it, of course, but everybody had to buy it to follow the fashion. Janet added "it is wonderful. This young boy- that was what he called Jean-Paul Sartre - is a genius. He has managed to do something which no other philosopher has managed to do - to sell metaphysics as the Americans in Chicago are selling corned beef cans". He was probably right in a way.

You raised the question of the needs of the marketing departments shaping the concepts that get used. One of the interesting things recently is that, with the introduction of the SSRIs, disorders like obsessive compulsive disorder are being - not resurrected in that they never go away - but they are being recognised as being 100 times more common than we thought. There is also a revision in our ideas of how extensive these concepts might be - in the case of OCD its not just people who wash their hands too much, it's a much broader concept - lets say the concepts have fallen on the fertile soil of marketing needs.

Nosological entities can become very popular for many reasons. Some, of course, as you mentioned, because of therapeutic reasons. It's obvious that obsessive compulsive neurosis, as it was called formerly, has become more interesting because it was discovered that a fair proportion of cases reacted well to clomipramine. Up till then it was really one of the most horribly incapacitating mental diseases. When it was severe, the only hope was that it would react to lobotomy - which it did in a very small proportion of cases. But even then one was afraid for various reasons to use the method.

So even the neuroleptics didn't work?

Everything has been tried. There have been claims of positive results with various methods, but nothing really worked. Then clomipramine - and later the SSRIs - was found to work and so automatically there has been an expansion of interest and, of course, an expansion of the limits, especially in the United States, where things tends to be pushed to the extremes. But there are other factors in the changes of interest for special categories of disorders. Right now there is an extremely interesting problem with the problem of multiple personality. Many psychiatrists in France have doubts even about its existence. Of course in the 1900s there was a huge and picturesque literature about the subject. I became acquainted with it when I was in the High School. We learned then some psychology - including its pathological aspects as part of philosophy, and I remember vividly that my Textbook included descriptions of multiple personalities. Claparede wrote a book "Des Indes a la Planete Mars" about a lady who claimed to be at some periods an Indian who wrote Sanscrit, at another a Martian, and so on. Her multiple personalities were extremely picturesque. Such cases belonged obviously to the same category as the parapsychological phenomenon of clairvoyance, so popular at that time, and have probably to be considered as the result of unconscious suggestions of the observer on a suggestible hysterical personality. But they have reappeared today, multiple personality disorder is now an official diagnosis of the DSM, and thousands of cases are described in the United States.

It is, however, interesting that the ICD 10, which because of its international character is more cautious, has accepted the diagnosis because of an agreement of compatibility with the DSM, but it clearly states that such a diagnosis is not accepted everywhere. Several interpretations have been proposed to explain this rebirth. It seems to be an indirect way of re-introducing hysteria, whose name has disappeared in the DSM. The claim which is now made that such a disorder appears generally in patients who claim to have experienced sexual abuses as children strongly recalls the stories told to Freud by his

hysterical patients at the beginning of his career, stories which shocked him very much, but which he rapidly interpreted as being fantasies resulting from unconscious wishes, and not real facts. But if historical social factors can play a role in the re-birth or in the expansion of diagnostic categories, it is true then in other cases, as in OCD, drug therapy has played a role.

Panic disorder.

Panic disorder also. Panic disorder was created in its present sense by Donald Klein on the basis of differential responses to drug therapy. He has written down in detail how he came to the idea that there were two distinct disorders in the anxiety neuroses, one of them, the acute episode he named panic, reacting to the antidepressant therapy while the other component, basic permanent anxiety did not. It is true that the importance of a new disorder has been later increased by world-wide trials of drugs, the results of which tended to influence key people. At the beginning, many French psychiatrists considered it as an uncommon disorder. But of course one finds a condition if one searches for it.

Yes, absolutely.

You must remember that before panic disorder was isolated by Klein, the word panic had been widely used in the American psychiatry. Homosexual panic, which was described first in 1920 had become an official diagnostic category which lasted until 1960. It was related to a psycho-analytic perspective of the pathology and it consisted in what we would call now an acute psychotic episode. Klein's concept has of course nothing to do with it. But I mentioned this now forgotten episode to suggest that the idea of describing a panic disorder existed already in the American psychiatry.

The latest thing to be created in this way is social phobia. In some respects this seems to be a way to bring on stream some older ideas about what some antidepressants may do, particularly the MAOI antidepressants. There's always been a theme that these drugs are in some way personality strengthening, that is not caught by conventional rating scales .

The MAOIs have always been a mystery. It is perfectly obvious that clinically there are patients who react extremely well to them and to nothing else. But nobody has been able to pinpoint in advance which patient will react. There have been a number of studies, some impressionistic, some extremely sophisticated and well controlled but, practically no convincing demonstration of a special target for the MAOIs.

More generally, the differential clinical efficacy of the antidepressants raises unsolved problems. If you survey the controlled trials of antidepressants, using the best possible methodology and the best clinicians, practically no single study shows in a statistically significant manner that one antidepressant is therapeutically more effective than another one whereas every experienced clinician is convinced that there are differences in efficacy. The controlled studies show, of course, very significant differences in side effects, but that is a different problem. The statistically naive clinicians and the pharmaceutical companies claim that, since you cannot find a statistically significant difference between the new and the old drug, both are equally effective. But that is a false statistical way of reasoning. The only thing you can say in such a case is that you cannot disprove the null hypothesis, that is that, with the method you are using, you cannot prove that the activity of one drug is different from the activity of the other. They may be different but you cannot prove it. Such results with trials of antidepressants are in sharp contrast with the results obtained with neuroleptics, which demonstrate often significant differences of activity between drugs.

But isn't this because the companies haven't been prepared to do the trials that would test these things out?

Maybe it's partly true, although I doubt it. After all the trials are the responsibility of the clinicians. The problem lies somewhere else, probably in the methodology. Years ago, the Japanese health authorities performed what is known as a meta-analysis, combing a number of studies done there, but restricted to depressions in bipolar disorders, the idea being that there would be as pure a clinical sample as possible. Even then the results show that you couldn't differentiate the level of activity of the different drugs, although you could differentiate on the level of the side effects.

Part of the problem, I suppose is defining where the concept of depression begins and ends. In your article in the British Journal of Psychiatry two years ago, you said that one of the problems we are now faced with is that it turns out that most psychiatric disorders seem to be co-morbid with other disorders.

My opinion is that right now we are going in the wrong direction and I am not the only one who says that. The DSM, which I acknowledge as an enormous effort is in some aspects excellent. It has improved enormously, for example, the reliability of the diagnosis. But the trend now is to define smaller and smaller entities, with the background idea that the more homogenous the picture the greater the probability that the category so defined corresponds to a real species, which will have a typical reaction to a certain drug and so on. It is perfectly obvious that it does not really work. When chlorpromazine and the antidepressants came in, the famous Dutch psychopathologist, Rumke, who was an admirer of Kraepelin, said that their action proved the rightness of the Kraepelinian dichotomy, chlorpromazine being active in schizophrenia, the antidepressants in the manic depressive psychosis. But, he forgot to mention that chlorpromazine was also active in manic states. From the beginning the idea did not really hold up and we know now that there is only a very rough correlation between drug action and our present categories of mental disorders - except maybe, to mention a category we have already discussed, the OCD which seems to react specifically to a precise pharmacological type of antidepressant, but even there the correlation is not perfect.

The dream of the nosologists - to describe homogenous categories corresponding to natural species - is still far away and, maybe, will never be attained. You mentioned in this respect the now very fashionable problem of the so-called co-morbidity. When one uses the present nosological categories, the level of co-morbidity is high. In no other part of medicine, can you have four diseases at the same time, unless you are a very old man and you have collected a few along the way. This means that there is something wrong with the trend which has begun with the DSM III and has been accentuated by its successors.

Where will it go? What's going to happen?

I don't know. There must be some other direction which I foresee only vaguely. The DSM destroyed the concept of neurosis because it considered it, with good reason, to be controversial. But it didn't propose anything to replace it. An interesting example in this respect is hysteria. Hysteria does not exist any more, the DSM describes dissociative disorders, somatoform disorders, histrionic personality disorders and does not connect them. I am not personally a psycho-analyst and I do not claim that there is a special psychodynamic relation between them, but the existence of a statistical link in the form of co-morbidity seems to be present. My opinion is there will be, in the future, a trend in the opposite direction - toward bringing the present categories together in some broader wholes.

In the early part of the psychopharmacological era it seems to me the psychiatric profession, to some extent at least, was in the driving seat. The industry came and asked us our views etc etc. I get the impression in more recent years, in the last 10 years or so, that we are increasingly being marginalised.

In my opinion, if you look at the history of psychopharmacology, since say 1964 - 30 years now - nothing radically new has been introduced. Perhaps the only original idea was the discovery by Japanese colleagues that a drug, used as an anti-epileptic, could be protective in manic-depressive disease. The activity of clomipramine on OCD was also something new, but the drug had been introduced in 1962. There have only been new drugs in the old classes of drugs - new antidepressants, new neuroleptics, new anxiolytics. It is, for example, admitted by most clinicians that no antidepressant is more active than clomipramine. The new drugs have less side effects, or different side effects, but more or less the same efficacy.

You have spoken with Hanns Hippus, who has probably told you about clozapine, which was in some ways a very original neuroleptic and even became at the beginning an object of a theoretical discussion. Professor Delay had originally made the hypothesis that there was a direct connection between the therapeutic activity of the neuroleptics and the extra-pyramidal symptoms and, of course, clozapine did not fit the rule. It had a very good efficacy but little or no extra-pyramidal side effects. But, as I said, on the whole, with relatively few exceptions, the differences between the older and the new drugs are small and there lie, in my opinion, the reason why the pharmaceutical firms have been compelled to increase their efforts towards marketing. For chlorpromazine there was very little marketing. I still in my library some of the first commercial literature on chlorpromazine. It was matter of fact and somewhat drab. But since the efficacy was so obvious and no other drug was available no necessity existed for what one would call today aggressive marketing. The same is true with the first antidepressants.

Yes sure but it seems to me that as a group, the psychiatric profession, could have taken the opportunity 20 years ago to say “look, the drugs we’ve got all seem to be much the same. We should be doing the kind of trials and the kind of research that would pick out which is superior or under what conditions do people respond to one rather than another” but we didn’t.

I wonder if the responsibility lies on the psychiatric profession. The public research organisations in Britain, France or elsewhere had relatively little interest in clinical therapeutic research. They preferred to leave to the industry, the chemical and pharmacological research on the new drugs and also the organisation of the clinical trials, since the industry was naturally interested in determining the clinical efficacy and the side effects of the drugs it had developed, in order to obtain eventually its registration. It was generally hopeless for a clinician to ask for a research grant in the domain, the public research organisations considering, possibly wrongly, that it was better to direct the money into other types of research, since the industry was taking care of the domain. There have been isolated efforts.

The German Ministry of Research funded a special programme endowed with a large amount of money to study the long term efficacy of various types of treatments such as the comparison of long term neuroleptic, social therapy, and a combination of both in a population of schizophrenics. But such a programme has largely remained an exception. The public research organisations have always favoured basic research such as experimental work on brain chemistry and neglected clinical therapeutic research which was left to the industry, which was primarily interested in the type of clinical research which produced the results requested by the public health authorities for the registration of a new drug. Relatively short term comparative trials were requested although, of course, the requirements are becoming more and more stringent.

It seems possible that the change in health care in the US could change all this. I wonder if the situation we've got doesn't depend to some extent on a socialised market-place in health care. In the US with the move toward large health care, there are indications that the purchasers of health care will be saying to companies "Well is there any evidence that your more expensive antidepressants are superior".

There is now obviously much interest in the costs of health developments. This is a very complicated field, and the cost of the drugs is just one of its many elements. There are now a number of good studies on this issue. As far as the drugs are concerned, it must be kept in mind that already the basic conditions for the registration of a new drug - eventually, as in France - and for its acceptance by the social security system - are either a greater efficacy than the existing ones, or a lower cost. but because of the scarcity of really new developments in psychiatry, I believe one of our goals should be to improve the use of what we have already, to select the best strategies of treatment. The example I gave of the German research programme shows, in my opinion, a way we must follow in the future.

Are you hopeful that we'll go down this road?

Yes, it will come, and not only in psychiatry, for a quite simple reason that in all developed countries the cost of health increases at such a rate that the Governments have to do something. One of the ways - but not the easiest - is to try to find the cost of the different strategies and to choose the best with the lowest possible cost.

We don't yet have a potent European psychiatric forum. Do you think we will have one.

I hope so. I was one of the founding fathers of the Association of European Psychiatrists just at the end of the World Congress of Psychiatry which took place in Vienna, in 1983. As President of this Congress I was impressed by the weight of the American psychiatry. I have a great respect for its scientific status and I have many American friends but I became convinced that such a disequilibrium was not sound, including for American psychiatry itself which was tempted to cut itself from other schools and, by doing so, to lose the benefits of interchanges of ideas. This is the reason why I supported warmly the idea of founding a European Association. It will certainly be a long and difficult process. There is no homogeneity in European psychiatry. Of course there is no more homogeneity in American psychiatry but our American colleagues are much more efficient when it comes to working together. We, Europeans, have only been able to build jointly the Airbus but fortunately there are many positive steps in that direction. If we could co-ordinate our efforts - I do not say homogenise, because I firmly believe in the virtues of a diversity of opinions - a European psychiatry programme, in a broad sense, could compare favourably with the American one. It would bring advantages both for the Americans and for us. The American psychiatrists are eager to have contacts with Europe and they show it repeatedly, but the interchanges would be much easier for them if we had some sort of co-ordination.

Who else was involved in founding the AEP?

As far as I remember, the idea also came from Peter Berner, who had prepared the Vienna meeting, and from Leonard Singer, who became the President of the AEP. He was the Professor of Psychiatry in Strasbourg. The original idea was to start from a German-French core, just as it had started in European politics, although we had no political model, and Strasbourg had, in this respect, a symbolic view. The others were

Dufour from France, Hippus, Ackenheil, Dilling, Heimann and Rein from Germany, Bobon from Belgium and Pull from Luxembourg.

Was there a problem starting up a new organisation at much the same time as the European College for Neuropsychopharmacology was starting up...

No. The European College was created a few years later. Maybe we indirectly suggested the idea of its creation since its basic purpose was, in their specialised field, probably very similar to our own in the larger field of psychiatry. It is true that its existence created problems for us because we had our meetings every two years and they also. We made a satisfactory arrangement in order that they did not clash.

Within groups like the American College for Neuropharmacology and the BAP, there's a tremendous and increasing strain between the clinical people and the basic scientists, even though these associations were begun in order to bring these two groups together.

The story did not begin with psychopharmacology. More than a hundred years ago, a new Professor of Psychiatry had to be selected by the Medical School of the University of Vienna. One of the competitors was Meynert, a world famous neuro-scientist to use a modern word. The clinicians claimed that his basic research had absolutely no relevance to the real problems of psychiatry and opposed his nomination, the result being that the University had to take the diplomatic decision of having two Chairs of Psychiatry, one for the basic sciences and one for clinical psychiatry. The situation is the same now and is even probably more sensitive. The work done by the neuroscientists is extremely impressive. I don't dispute that, but until now very little comes out of it in psychiatry in terms of clinical concrete applications.

Indeed and ironically we've gone down the scientifically rational route of producing purer and purer drugs and all of a sudden we find that it's an old dirty drug like clozapine which is more effective.

I have been struck recently by the commercial literature on a new antidepressant, which stressed the fact that it worked simultaneously on three different neurotransmitters, that it was impure, to quote the bizarre word you were using. I thought that it was an original marketing idea. but in our present state of knowledge we have no conclusive proof that the disturbances of the neurotransmitters which have been observed - and eventually corrected by our drugs - constitute the central biological mechanisms, whose end results are the behavioural disorders. I do not deny that they exist nor that our drugs modify them but it is possible that they are only witnesses and consequences of underlying and more basic disturbances. The concepts of "pure" and "dirty" drugs are based on simplistic models which, as the case of clozapine among others demonstrate, are unable to predict reliably the therapeutic efficacy. The only proof of it is given by the clinical trials. At the present time a large gap exists between the scientifically impressive discoveries made on the neurotransmission mechanisms and the facts we observe at the clinical level. The same can be said about genetics. Thanks to molecular biology we have made tremendous progresses in other fields of medicine, for example in neurology, but in psychiatry, we are only able to entertain hopes and the results remain disappointing.

I have the impression that many neurobiologists realise now that their theories and the results of their research did not have the clinical relevance they expected. I, of course, hope that they will become relevant in the future. But for the time being it has, as you mentioned, created a tension in groups where there are both clinicians and

neurobiologists. An additional factor is, of course, the technical aspects of neurobiological methods which have become so complex that clinicians like myself are usually unable to grasp their detail. They only try to understand the conclusion in so far as it has relevance to clinical problems.

When did you begin to come interested in the history of psychiatry.

I have always been interested in history. But, when you get older, you usually get more involved possibly because it allows you to put things in perspective, to discover that ideas you had thought were new had been defended before. It does not mean that nothing changes, as the French proverb "plus ca change, plus c'est la meme chose" implies. It would be a nonsense to say that psychiatry has not made any progress. Coming back to neuropsychopharmacology, it is fascinating to look from a historical point of view at its introduction. It is obvious now that it has been in practice, responsible for an enormous improvement in the care of the mental patients. I remember Sir Aubrey Lewis writing in the days of its birth, that if we had to choose between drugs and social therapy, the drugs would go. Nobody can contest the positive role of social psychiatric measures, but it seems historically clear that the primary role has been played by psychopharmacology and that many of the social measures have been made possible by it. What is fascinating in such interpretations is the discrepancy between the objective facts and the theoretical explanations which are obviously not satisfactory.

Not even satisfactory. There's no theoretical background. These things aren't actually derived from any theory at all.

It is also largely true in the discovery of new drugs. A Swiss pharmacologist said once that animal psychopharmacology was a retrospective science. One you had discovered a drug which clinically worked in a certain way, say as a neuroleptic, the pharmacologists searched for other drugs which had the same profile on a battery of animal tests. With such a method you could not hope to find a new drug whose therapeutic action was based on a biological mechanism different from the original one. The search is based on empirically observed correlations, not on any theory.

As regards the antidepressants, you have had an overview of how they've been introduced. You've known all the key players, Kielholz and others.

Paul Kielholz was already a personal friend before the birth of psychopharmacology. He didn't have a role in the introduction of the antidepressants but mainly in promoting their use among the non psychiatrists, especially in general practice. Initially, there was a strong resistance of the general practitioners for two main causes. The first was that the teaching of psychiatry was a very small part of the medical training and consequently a general practitioner had practically no serious clinical knowledge about depression. It may be added that if they had some, it was usually about the most severe melancholic type and not about the minor forms, by far the most common among the patients they were seeing. The second cause was their fear of side effects. At that time the usual antidepressants were tricyclics and they had cardio-vascular side effects and, perhaps more importantly from the point of view of the practitioners, atropinic side effects such as dryness of the mouth, dilatation of the pupilla or trembling, which can be very unpleasant. The result was that, even if by chance the correct diagnosis was made, the practitioner tended to prescribe anxiolytic drugs, usually benzodiazepines even if it was completely inappropriate. The main role of Kielholz has been in promoting a correct diagnosis and a correct treatment of depression in general practice.

Historically another key player was Walter Poldinger. He was an assistant of Kielholz, became his successor at the Chair of Psychiatry in Basel, and had just retired. I discovered his role in a curious way. Some years ago a symposium was organised in

Paris to commemorate the 40th Anniversary of the introduction of clomipramine and I was asked to preside the meeting and to give the introductory lecture on the history of the drug. I did an extensive bibliographic search and discovered that the first clinical trial had been made by Poldinger who presented the results at the World Congress of Psychiatry in Madrid in 1966, but the paper was not published in the proceedings. I asked Poldinger about it, but he had no copy. Fortunately, there was, shortly afterwards, a symposium organised by Geigy-UK and the Chairman, who was the medical director of the company¹, gave a detailed introduction in which he reported the contents of Poldinger's paper.

The story of clomipramine contains many curious episodes. For example, its synthesis was made by the biochemists of the Geigy Laboratories on the basis of an analogy of dubious scientific value. They reasoned that since imipramine and chlorpromazine was more effective than promazine, as a neuroleptic, clomipramine would be more effective as an antidepressant than imipramine. They were, at the same time, afraid that it would be more toxic but they took the risk and it worked.

If you asked the psychiatric profession generally which was the most potent antidepressant, they would probably pick clomipramine, even though there's no real evidence.

I absolutely agree. Any clinician who has worked with clomipramine is convinced of it but we are unable to present what is considered today a scientific proof. I still remember a patient taking part in our initial trial with clomipramine. She was resistant to imipramine and responded overnight to the new drug. There are many such anecdotes, but by our present standards, they prove nothing. A criticism one can make to the controlled trials is that they have been unable to demonstrate a statistically significant superiority of clomipramine.

Is it because we haven't done large enough trials, like the Isis trials in medicine. We haven't done this.

I don't agree. If you need a sample of say 10,000 patients to prove a difference, the difference, even if it is statistically significant, has no practical interest. If the present conviction of the clinicians on the greater activity of clomipramine rests on observed facts, then the difference must be large enough to be detected on a normal sized sample.

Is it because we've got heterogeneous groups of depressives.

It is an obvious idea. But, as I have mentioned, the meta-analysis made in Japan using only bipolar disorders did not bring concluding results. We believe that depressions in bipolar disorders constitute a homogenous group, but may be we are wrong. My opinion is that we have not yet a satisfactory nosology of the depressive states and possibly also no good instrument for the measurement of the intensity of depression.

What about, if we were to try and give up our ideas of trying to find the molecular biology of schizophrenia or depression and tried to look at the molecular biology of responsiveness to particular drug groups.

Some psychiatrists have hoped to base nosology on responses to drug. Sometimes it seems to work. I have already mentioned the work of Donald Klein on panic disorders.

¹George Beaumont

At the present time there is a trend to re-group trichitillomania, nail biting, and similar illnesses with OCD on the basis of their response to SSRI treatment.

From a theoretical point of view it's very nihilistic isn't. Recently, Herman van Praag, who's been very much associated with biological psychiatry, looking at dimensions of behaviour and trying to associate them with particular neurotransmitters, has taken a position that's rather like the position that Adolph Meyer took, over half a century ago, saying that what we've got in psychiatry is a series of reaction formations.

I am in agreement with most of the present ideas of van Praag on nosology as developed recently at the AEP meeting in Copenhagen. His evolution in this respect is striking because in his previous work on anti-depressants he supported the notion that two categories of the disorder existed, each being associated with a specific anomaly of neurotransmission and therefore responding to a pharmacologically specific type of drug.

Who have been the key figures in the last 40 years. What we've been focusing on until this has been the forces that shaped the period, but it's also interesting to speculate as to whether things would have gone the same way without certain key personalities.

It is an extremely difficult question. The importance of the role played by personality can only be judged after a sufficient period of time has elapsed and, even so, there can still be disagreements as every student of history knows. Everybody would agree that Freud has played an important role in the shaping of many modern ideas. But look at the conflicting opinions about the impact of psychoanalysis on our present psychiatric concepts. At the beginning of this century, Kraepelin had, in my opinion, a decisive influence on psychiatric thought. In France, in the generation before mine, it is clear that the two most influential people were Jean Delay and Henri Ey. The problem is more complicated in Germany because of the gap created by the War. Looking at the just retired personalities, Hanns Hippus and Hans Hafner, each in its own ways, had a leading role. In the UK it is obvious that, since the end of the War, and for twenty years, Sir Aubrey Lewis has been a key figure. His role has been discussed but nobody can dispute the extent of the influence he had. I could also mention the contribution made by Willy Mayer-Gross who, through the textbook he wrote with Slater and Roth, introduced to British psychiatry ideas stemming from the Heidelberg school.

Max Hamilton ?

Max was a very close friend. He used to point out with his well known sense of humour that we had the same scientific training, both in psychiatry and in statistics, but he added: "Look at the result. You are now the Professor in Paris, and I am at this dirty English town". Max has certainly been influential, but not in the way as Sir Aubrey or Mayer-Gross. His scale is now criticised on technical grounds but it was the right instrument when he created it. It is striking that, although we are now aware of its deficiencies, nobody dares to abandon it, even if, in modern trials, other scales are added. It has taken the value of a symbol, just as in another field in the BPRS.

I should have mentioned in the Scandinavian countries the name of Eric Stromgren, whose position was unanimously recognised. But he was not directly involved in psychopharmacology, mainly in psychopathology and in genetics. In Denmark I want to mention Schou because a comparison of his work with what Hanns Hippus has done illustrates the difficulty of comparative judgements. Schou's studies have concentrated on a single, but very important subject, lithium, whereas Hanns Hippus has acquired

great merits in promoting, against strong resistances, psychopharmacology in the whole of Germany. And despite these differences, both are undoubtedly key historical figures in the history of drug treatments.

In the United States where, because of the number of people involved, a choice is more difficult than in the European countries. I would select Nate Kline. He had a decisive role at the beginning of the new therapeutic era by discovering the unexpected psychotropic action of new drugs. Thanks to his activity, to his optimism, and to the expansiveness of his personality, he became in his time the best internationally known American psychopharmacologist.

What about the larger questions of how the production of drugs that affect behaviour influences the culture - which brings us to the agenda of people like Julien Offray de La Mettrie, who put it that "once the physician can reliably influence behaviour, he will replace the philosopher"

Since I am not a philosopher myself, I shall not discuss the opinion of La Mettrie, which has of course to be considered in the context of the period with it was written. It was "l'ère des Lumières" and the word philosophy was used constantly. The title of Pinel's book on mental diseases was "Medico-philosophical Treatise on mental insanity". The problems raised by today's drugs have always existed. I accept that we have more possibilities now and our drugs are more effective and so the social consequences can be different, probably more complex, but fundamentally the situation is not new. Of course, we now have, for example, the case of the consumption of anxiolytic drugs. But basically it brings us back to the definition of the concept of a disease and of its limits. There is no really satisfactory definition. Take the case of the so called sociological definition, so important for psychiatry. there is now a trend in the DSM's to consider as mental disorders - the modern nosologies are careful to use disorder instead of disease, because its definition is even more vague - behaviours like pathological gambling. but gambling is a fairly common behaviour. The DSMs consider this behaviour as pathological if it interferes negatively with the social adjustment of the subject: a typically sociological definition of the limits between normality and pathology. The discussion on the socially denied disorders in psychiatry goes back to Esquirol when he described, more than one hundred and fifty years ago, the monomanias. How can we prove that a behaviour recognised by society as negative, such as stealing, or provoking a forest fire, or for that matter ruining oneself gambling belongs to medicine by being called kleptomania, pyromania or pathological gambling. The whole problem of the definitions of mental disease is a subject which has been dealt with in an excellent paper by Kendell.

But all of that was worked out against the background of the psychotic disorders, the diseases that are found in hospitals. With the SSRIs do we need to re-work these definitions for the population at large.

All the discussions about the limits of disease in psychiatry have started when psychiatrists began to treat patients outside the hospitals. There's a universal agreement also in the so-called primitive societies, that somebody who presents manifestations which would be called in modern terms an acute schizophrenic episode is insane. Even the ethnologists who defend a relativistic position recognise that in all cultures some types of behaviours are considered pathological and it refers roughly to the psychotic states treated in hospitals. The problem of the limits is raised by the other and less severe deviations. Zarifian has recently written in France a controversial book on the subject. He analyses and condemns the trend to use drugs, according to him under pressure of the industry for people who have only ordinary life problems and therefore are not ill in the medical sense.

On the other hand someone like William Osler said a hundred years ago “human beings are the animals who self medicate”. The drive to take drugs comes from us. In a sense, we create the pharmaceutical industry to supply our needs rather than the other way around.

There is in my view a fundamental difference between people taking something spontaneously and doctors prescribing it. If we prescribe a drug, as physicians, we consider that the people to whom we give it are ill. We judge that they have some kind of pathology. If somebody drinks alcohol because he is sad, that is something completely different.

But let me give you the case of if they go into the health food shop and they buy vitamins or whatever; they do so because they’ve got a lay concept of disorder of some sort, a humoral model - Yin and Yang being the current fashion. Now with drugs, like the SSRIs, becoming safer and safer, they could be sold over the counter. You could remove the physician. This would seem to me to pose the possibility of a change in the concepts of mental illness completely. If the industry started to sell directly to the consumer would we revert to more humoral type of concepts?

It is true that in some cases drugs are becoming relatively safer, but there are obvious limits. It has been said that side effects are the price we must pay for efficacy. Without pushing this argument too far, it must be remembered that even the vitamins can be harmful when taken in the wrong way. We have seen it during the last War when mothers gave enormous doses of Vitamin D to their children and provoked kidney troubles. We have always, in such discussions, come back to the concept of disease. To take spontaneously something to make you feel better if you are not ill in a medical sense is basically different from receiving from a doctor a prescription and taking a drug to improve your state of health. A doctor has no right to prescribe if he does not consider the state of his patient to be pathological.

I am perfectly aware of the difficulties involved especially, but not only, in psychiatry. From its beginning and until now psychiatry has adopted the medical model: even if we call them now disorders, we consider the states we treat as diseases. There are, of course, people who consider that psychiatry does not belong to medicine, and that there are no psychiatric diseases. It was the position taken by some exponents of the anti-psychiatric movement. But, if we adopt the medical model as we do now, and as I believe we must do, we must look at the question of the use of drugs from the medical point of view - that is that the use of drugs is only appropriate to prevent or to treat a pathological condition. It is completely different from taking a product for your personal comfort or pleasure.

But in the UK you can get H2 blockers for heartburn and ulcers over the counter, you don’t need to go to a doctor.

Today the rules defending the drugs which can be sold over the counter are made by Governments and are, at least, in part, related to the fact that in our countries the State supports cost of medical treatment. Confronted with the increase of this cost, it authorises the over the counter sale of drugs whose use is considered as not belonging to the treatment of "real" diseases, and in such a case is not financially involved. The health authorities have coined in France the word "comfort drugs". We are coming back again to the definition of the limits of pathology. The State, being financially involved, decides the limits. We have here to do with a typically social definition of the concept of

disease. If you get older and need glasses to read, the cost in France will be reimbursed by the social security system to a very small extent, which is equivalent to saying that presbyopia is not a disease.

But this comes back to the social engineering element of it, in that it is clearly useful for society to give you a pair of glasses that improves your eyesight. The same arguments have been made about the SSRIs - without them people are myopic, on them life suddenly looks much much better and clearer.

Even if you are a perfectly normal person, you may feel better by taking a small quantity of alcohol.

But headaches and aspirin. This is presumably closer to an illness but the treatment is in my own hands. I can go to the pharmacist and ...

Yes. But the sales over the counter depend on a combination of general factors. One, I have mentioned, is the link between disease and discomfort, another and very important one is safety. Aspirin has for a very long time been considered as a purely symptomatic analgesic drug - that is a comfort drug - without important side effects. But we now know that taken regularly at a low dose it has a protective effect against cardio-vascular diseases. We know also more about its side effects. It can provoke haemorrhages in the digestive tract and, at very high doses as it is sometimes taken for suicidal purposes, death by kidney failure. For that reason it is a common saying among the pharmacologists that, if aspirin had been discovered in our days, it would never pass the stringent tests requested by the FDA. This is, of course, a good story, but I doubt that it has any sense. Considering the extent of its consumption, aspirin is a remarkably safe drug and it is the reason why it is still sold over the counter.

Do we not have an issue of whether we are prepared to trust the populace with their own health care. One might argue that the situation is rather like the situation we had about trying to decide whether to give people the vote 100 years ago, with some people saying no you can't really trust people to make sensible decisions. In the same way we now say you've got to keep control in medical hands, but if you go to Asia, almost all the drugs short of the cancer therapies are sold over the counter. And people presumably learn how to manage the system.

But in the countries of Asia you mention the death rate is much higher than in ours. I would suggest, instead of your provocative comparison with the vote, to use a more relevant one. People, provided they have the money, can eat the food they want. It is clear that many do not make sensible decisions. Some statisticians claim even that in the western countries life expectancy could be increased by five years if people had a correct diet, if they had made the right choices of food. If the people need to be informed, as they are fortunately more and more now, by the specialists on the types and quantity of food, it is right to take to preserve their health, the same can be said about the drugs used to treat illness. There is, however, a difference. Whereas the choice of food is only related to the general purpose of maintaining health, the choice of drug is related to a specific situation, the existence of an illness. People without the special medical competence acquired by long training are, in most if not in all cases, unable to determine the nature of their illness and the right drug to treat it. If they are often unable to make the relatively simple choice of the food which is right for the maintenance of their health, how could they be able to make the much more difficult choice of a drug? The trend to self-medication is not new, but I consider that to support it is basically harmful. Social forces may favour its extension and some sociologists may claim that physicians are

opposed to this in order to preserve control but to approve of drugs to be sold without medical advice and control would be, from our part, a completely irresponsible attitude.

Can you account for the general hostility there is to psychotropic drug treatment? This was most clear in the States when these drugs were introduced but there is still a widespread popular prejudice that talking is the appropriate treatment for human beings in distress. I fancy that such attitudes are not without links to several of the big controversies in neurobiology such as the controversy at the turn of the century as to whether neurones were continuous or contiguous and the controversy during the late 40's and early 50's as to whether transmission in the nervous system was chemical or electrical. There's generally been a resistance to a particulate view of things and perhaps to the mechanical implications of such a view. Being particularly fanciful, one could suggest that there are connections all the way back to La Mettrie, when he proposed a radically material view of man and drew down the hostility of virtually everyone on his head and found himself consigned, more or less, to oblivion. Am I being too fanciful or are there other explanations?

There are, in my opinion two distinct problems. One, very simply, was the initial hostility of the psychiatrists who were psychoanalytically trained, and who had a dominating position especially in the United States when psychopharmacology appeared. They claimed that the drugs had only a symptomatic action, and did not really cure the patients as they did by allegedly reorganising the personality along normal lines. The same hostility and the same arguments existed, when behaviour therapy appeared, especially in France among the clinical psychologists who were, contrary to the situation in the UK, usually psychoanalytically oriented. But it belongs now to the past. Another problem is the hostility of the general public which has, as shown by many researchers on the popular concept of disease, a model about the causes of the disease and about the method for preventing and curing them. In psychiatry the basic idea is that mental disorders are of the same nature than normal psychological reactions, that they are the result of psychological or social causes, and consequently that they are best treated by psychological or social measures. The present fad for the so called natural food is possibly another expression of this popular model of disease. In this respect our drugs, which are the result of chemical syntheses, being non natural, must be harmful. It is probably one of the main ingredients of the resistance of many people to pharmacological treatments.

Many of those that I've interviewed, particularly people from Europe when asked about the climate of hostility to drug therapy have cited the movement that led to the events of 1968. When I think of 1968 I think mainly of what happened in France and hence I wonder whether you might be interested to comment on the events of 1968 and the relationship to trust or distrust in the idea of scientific progress. In some respects may be this question comes back to La Mettrie's L'Homme Machine but whereas La Mettrie was all for scientific progress since 1968 perhaps the idea of L'Homme Machine has not been received sympathetically.

There is no good explanation of the origin of the 1968 events in France or, if you prefer, there are too many brilliant ones proposed, from the murder of the father suggested by the psychoanalysts to André Malraux's crisis of civilisation. But whatever the causes, one of its expressions has been obviously the dream of a golden age, where life would be free without obligations and control in a world allowing a supposedly natural life. Since you mention the 18th century author La Mettrie, I would suggest that some of those 1968 attitudes had more to do with a concept of the same period, the myth of the good savage, who was supposed to live a harmonious natural life. I think that, if one wants to find a

relation between the popular hostility to drug therapy and the 1968 events, one has to consider that in both cases a contrast is affirmed between the natural things which are intrinsically good, and the others, represented by the industrial civilisation and its products, the drugs, which are bad.

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