Thomas A. Ban: They used to call it psychiatry
David Healy's Interview*

Chasing up the question of who discovered any of the psychotropic drugs or was responsible for the major psychopharmacologic organizations is a bit like watching Akira Kurosawa's movie Rashomon, in which someone is murdered and the witnesses and finally even the victim's ghost each give their version of the events and none of them tally. I had this impression very strongly after reading Towards CINP, which you and Hanns Hippius put together. Having collected all this material, though, you are in a better position than anyone to answer the question of who was responsible for the 1957 meeting in Milan that laid the basis for the CINP?

I don't know for sure, but probably Emilio Trabucchi. He had the necessary foresight. But, it could have been Silvio Garattini, still his first assistant at the time.

Silvio has proven his foresight —setting up the Mario Negri Institute.

There was a great need for Institutes like the Mario Negri. Universities, by and large, had lost their independence from the State and other vested interests by the 1950s. During the past decades, they have been less and less able to fulfill their role of generating unbiased information with the necessary speed about the steadily growing number of new drugs. In the absence of the necessary machinery to meet the need, education about how to use the new drugs had to be substituted by information disseminated by each company about its own product.

Recently several alternative possibilities are emerging with the capability of generating unbiased information - not just bits of information but all the information relevant to the development of a particular drug. But in the early 1960s a non-profit foundation, such as Garattini's was the only viable alternative. It was certainly more better placed than departments at the universities.

Who else were the key people in the development of CINP? What were the forces at work to produce it?

The ones who actually proposed the founding of an international organization were Corneille Radouco-Thomas, who became chairman of the Department of Pharmacology at Laval, and Wolfgang de Boor, the psychiatrist from Cologne, who just about a year before published his monograph on Pharmacopsychology and Psychopathology. They were the ones who picked up that psychopharmacology had come about - that an important new discipline was born.

A few exceptional psychiatrists like Pierre Deniker and Heinz Lehmann recognized right away that treatment with chlorpromazine was a qualitatively different therapy. That with the new drugs a new world was coming about. But psychiatrists in general were very slow... did not seem to be aware that the new drugs revolutionized psychiatry. So, it fell to pharmacologists, who came from the medical end, like Radouco-Thomas, to take the leading role in the founding of CINP. And the founding of CINP had to be encouraged strongly by

the industry. Ciba, Geigy, Sandoz and Roche were all involved. In Milan, Ciba seemed to be the most involved.

The figure who is hard to call in all of this is Rothlin; you've probably talked to more people about his role in this than anyone else, what do you make of it?

Rothlin is one of the controversial figures. Undoubtedly, he was not just a good scientist but also a very strong person. I have the notion that without someone like him bridging the gap between academia and industry, the CINP could not have been born at that point in time. To let him have his way was the price that had to be paid. Some of the founders would have liked to set the stage for the development of CINP on a broader base. Trabucchi would have preferred to open the doors as wide as possible. But Rothlin's position prevailed and the doors were closed, open only by invitation to a few. So neither Heinz Lehmann, nor Fritz Freyhan who played a most prominent role in the early history of American psychopharmacology, were invited to become founders of the CINP.

There seems to have been a serious clash of personalities between Herman Denber and himself.

Yes. There were clashes between Rothlin and some of the other founders as well. But, regardless of the difficulties they had with each other, the founding group represented a wide range of interests complementing each other in a very desirable way. Denber was a young psychiatrist working in a psychodynamically oriented setting in New York, who recognized the important implications for psychiatry that psychopathology can be induced experimentally. Radouco-Thomas was a young pharmacologist trained in traditional pharmacology who recognized that a new important field of pharmacology was developing. Bradley was one of the first of a new breed of neuropharmacologists… And Rothlin was the powerful former director of Sandoz who led the pharmacology laboratories of his company into the new age. It was very important to have someone of Rothlin's stature to bridge with industry because psychiatry was so slow to join in.

For me, a graduate from medical school in 1954 and then working in a junior position with patients in a large psychiatric hospital in Budapest, it was quite obvious that there was a major change. But my enthusiasm was not necessarily shared. Even towards the end of the 1950's, I found that some of my supervisors at McGill firmly believed that all that drugs like chlorpromazine can do is to render patients accessible to psychotherapy. Only gradually did they begin to change their tune by allowing for the remote possibility that the two treatments combined might be better than either one alone. And it was not before the late 1960's, that some of the best-known American psychiatrists teaching at some of the best-known universities of North America were ready to accept that neuroleptics work in their own right and, in fact, work better in the treatment of schizophrenia than any other treatment so far. The same story was repeated with the antidepressants. Even at respectable universities such as Vanderbilt - the university with which I have been affiliated for the past 17 years - the idea keeps lingering on that in depression, treatment with an antidepressant and psychotherapy combined is better than either of them alone.

It is clear that even people like Roland Kuhn, with the training he had, had great problems trying to come to grips with what had happened when there was a drug which helped people who were depressed.

But he did come to grips with it rather promptly in spite of being a psychotherapist. And while his peers had difficulties even to accept the fact, he was able to recognize it. It is fascinating that some people are able to overcome their beliefs. And this is, for me, the most important thing in the case of Kuhn. His recognition of the antidepressant effect of imipramine was a key discovery, and the simple fact that he was able, in spite of his training, to accept that a chemical can affect something as intimately "psychological" as depression, was instrumental in bringing psychiatry into the modern world. Because, if you really want to reduce things to basics, the discoveries which opened the path for the development of modern psychiatry are the discoveries of the effects of chlorpromazine, lithium, imipramine, and meprobamate. And of these four discoveries of the psychopharmacological revolution, one was his.

With all fairness to the vast array of drugs which followed, the best any of these drugs have done is to substitute one side effect for another, while creating by their rapidly growing number a tremendous turmoil for physicians, and by their steadily increasing cost a serious financial burden for patients. Because even with the impressive progress made in brain research, psychiatry has never really been able to resolve how to go beyond just using chlorpromazine in schizophrenia and imipramine in depression.

Could I ask you about that? In 1987 you wrote an article, which, by virtue of both its title and its content, was very different to anything that had been written before, or since - "The Prolegomenon to the Clinical Prerequisite." This has been one of the few efforts to go beyond just the simple giving of drugs to construct a rational basis for therapeutics. So there are two questions, first of all why were you interested to do that kind of thing but also why has the field been so slow to do it?

Well, I know why I had been interested, but I can speculate only, why the field has been so slow. I had become interested because I was determined to go beyond just using chlorpromazine in schizophrenia and imipramine in depression. And since, in my own evaluation, one of the most important contributions of psychopharmacology was that it focused attention on the biologic heterogeneity of populations within the traditional nosologic categories, I thought that replacement of biologically heterogeneous diagnostic concepts by homogeneous ones, at least in terms of pharmacotherapeutic responsiveness, would open the possibility for a more discriminate use of psychotropics.

I waited for a long time, though, before addressing the issue and only after many years of clinical investigations with newer and newer molecules did I acknowledge that none of the new drugs was better in overall therapeutic efficacy. So by the late 1960s, I was certain that a decision must be reached about whether there is a particular population which responds to a particular drug. And if there is such a population to find a way to identify it.

Regarding your second question, I really don't know why the field was so slow to follow suit. Understandably the splitting of the broadest possible population for which therapeutic effectiveness could be demonstrated was contrary to the interest of the pharmaceutical

industry because it narrowed the market for their drugs. And undoubtedly the field was busy with developing a complex methodology for the detection of therapeutic efficacy and with the testing of the clinical activity of newer and newer psychotropics. But probably the single most important factor was that its attention was distracted from the seemingly trivial clinical problem of heterogeneity of a diagnostic population by the newer and newer and more and more sophisticated theories about the action mechanism of psychotropics. The issue of identifying the treatment responsive population if any should have been dealt with immediately after the introduction of chlorpromazine and imipramine.

How do we do it?

We have no generally accepted way. For some time, I thought that for identifying the treatment responsive population one would need to find a way to link the action mechanism of psychotropics with the pathomechanism of mental disease. And since both, mental disorders and the action mechanism of drugs, can be described to some extent in terms of conditional reflex variables, I went ahead and developed a conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects. It was of sufficient merit to win the McNeil Award of the Canadian Psychiatric Association in the late 1960s. But before long I realized that what I was trying to do was far too complicated, impractical and might even be somewhat far-fetched. Therefore, after documenting what was done, I decided to move on and leave conditioning to those interested in personality and behavior.

By that time I had the belief that mental illness starts beyond what can be learned and was very much involved with psychopharmacology. First, I had been engaged in research in which we induced psychopathology with drugs, and later on in research in which we controlled psychopathology with drugs; and since it was possible to do it in both ways, I felt that finally we could meaningfully talk about mental illness because what we were talking about was no longer just a matter of belief, but was accessible and demonstrable experimentally. And it seemed to be that psychopharmacology had also provided convenient biochemical measures which link the action mechanism of the drug with the clinical state or even the pathomechanism of the illness. There were new hopes... and great disappointments when attempts to identify treatment responsive populations by biochemical measures yielded inconsistent findings.

At this point I realized that it is unrealistic to expect empirically derived objective measurements to replace traditional psychiatric concepts in the foreseeable future. With this in mind I turned to regression analysis to see whether the treatment responsiveness could be identified on the basis of symptoms, the elementary units of mental illness. But by doing this in a number of different studies, we found that the psychopathologic symptom profile of the ideal patient, who would have responded to the same treatment, was different from one study to another.

I don’t know whether our findings would have been different if the set of psychopathologic symptoms included in the linear regression equations were not restricted to behavioral rating scale variables. I was ready to explore this by employing the symptoms listed in the AMDP, but by the time I was ready to proceed Frank Fish reported that by dividing schizophrenia on the basis of Karl Leonhard’s criteria he found that unsystematic schizophrenia responds

significantly better to neuroleptics than systematic schizophrenia. To pursue this line of research further, I developed a guide to Leonhard's classification of chronic schizophrenia, and later a polydiagnostic evaluation with the capability of diagnosing the same patient by diagnostic formulations derived by different methods. It is referred to as the Composite Diagnostic Evaluation System, or in brief, the CODE System. The prototype is the Composite Diagnostic Evaluation of Depressive Disorders or CODE-DD, which includes 25 conceptually different formulations relevant to the classification of depressive illness. If the treatment responsive population to imipramine or to any of the other antidepressants can be identified on the basis of currently recognized nosologic end-points of depressive illness, it should be possible to identify it by employing CODE-DD.

You've been fairly unique in this regard. More recently there are other people who have been working on systems like OPCRIT and things like that, but they are doing it for slightly different reasons. Why do you think the field has been so lacking in interest in this exercise?

I might have been unique when I started, but I don't think that I am unique any longer. There is a considerable interest these days in the CODE System, just as much as in the OPCRIT. CODE-DD has been translated into Italian, French, Polish, Estonian and several other languages. And there is ongoing research with the CODE System in Hungary under the direction of Peter Gaszner, who was Vice President of ECNP and in Argentina under the direction of Ronaldo Ucha Udabe, who wrote one of the first texts in psychopharmacology with the late Edmondo Fisher. In fact, the Japanese have developed an even more comprehensive instrument referred to as COALA, which stands for Comprehensive Assessment List for Affective Disorders.

But I agree with you that for a long time there was little interest in psychopathology and nosology, although I would argue that this lack of interest was not restricted to the field of psychopharmacology. When psychopharmacology came about psychodynamics was the mainstream of psychiatry in the U.S., and a social orientation was dominant in psychiatry in the U.K., and neither psychodynamically-oriented psychiatrists nor social psychiatrists had much appreciation for traditional psychopathology and nosology. Both were actually more interested in the patient and how the patient deals with the disease and adapts to society than in the disease itself. Even in Germany interest, in traditional psychopathology and nosology was minimal because it was not found to be of much use clinically. And after the introduction of the new psychotropics, people like me were so taken by psychopharmacology that we believed that we need not be bothered with psychopathology or nosology. We would have preferred to replace rather than retain the old psychopathologic and nosologic concepts, and were disappointed that none of the biologic measures was shown to be anything more than epiphenomena of the behavioral state present with the illness.

There has been a tradition in the U.K., with people like Eysenck that has been concerned to develop on these lines...

Eysenck's attempt to render the biologic basis of personality accessible to pharmacologic manipulation was far ahead of his time. Whether one agrees with his theory is an entirely different story. His dimensional concepts confound the abnormal with the pathological, perceiving the pathological on a continuum with the normal... presuming that psychology and

psychiatry are one field in which the same language is spoken and the same laws prevail. Nevertheless, his work stimulated a great deal of interest and even today, he has followers all around the world.

During the 1960s, I was very interested in his work. But today I believe that mental illness is based on a pathologic process which produces detectable pathologic changes which become manifest in distinctive psychopathologic symptom patterns. And depending on the nature of the detectable pathologic change, there seems to be two major classes of mental disease: one with structural changes which are directly detectable by the method of pathologic anatomy, and one with functional changes in the processing of impulses, which have become indirectly detectable by the method of psychopharmacology. Not every psychiatrist, of course, would agree and some would even argue that the group without directly detectable structural changes does not fulfill Morgagni's criteria of disease. But is it not really just semantics whether it does or does not fulfill Morgagni's criteria? Regardless, psychotropic drugs have rendered the biologic substrate of these disorders accessible to pharmacological manipulation in a predictable way. And even if our residents are still taught that psychotropic drugs can only suppress symptoms without having an effect on the disease, the fact remains that responsiveness of a particular symptom to a particular drug depends on the illness in which the symptom occurs.

The field is so big now that there's no one individual or even a group of individuals who can stand back and try to put things together again. At the same time, the industry is both producing new drugs and producing entities that their drugs treat. Does the field have the capacity to analyze itself?

The field has grown tremendously, but I don't think that it is so big that it would not be possible to put it together again if the vested interests, which keep it fragmented, would permit this. The field is increasingly controlled by the industry... but the industry is not necessarily evil. Without industry the medicalization of psychiatry would be far from where it is today, and neither the diagnosis nor the treatment of mental illness would be sufficiently advanced that psychiatry could participate in an integrated health care system with the other branches of medicine. But the medicalization of psychiatry is far from being complete. Although one of the last major areas of resistance, the area of neuroses, was overcome during the last decade, the medicalization of the different disorders subsumed under the category of neuroses is still under way. We are, of course, paying an enormous price for this by using newer and newer drugs, which are more and more expensive, yet not even proven that they are better than old psychotropics. We are using these drugs also in wider and wider populations with more and more extended indications... And we might be treating artificially created entities which, even if they can be reliably identified, one wonders to what extent fulfill criteria of disease.

But while industry, to expand its market, is rapidly progressing with the medicalization of mental illness, it is leaving behind a disorganized profession of psychiatry, struggling to find its identity with steadily decreasing financial resources. In spite of this, I believe that the field has the capacity to analyze itself because we have all the necessary prerequisites for such an analysis. After all, we do have therapeutically effective psychotropic drugs to practice psychiatry as a medical discipline. And we also have the necessary computer technologies, which would allow us to offer a reliable and accountable clinical service, to

establish data bases, and to process and analyze the collected data with a continuous validation of diagnostic and therapeutic knowledge.

I am fully aware, of course, that even if we have the capacity, we do not have the capability to utilize our capacity within the traditional structural organization. Psychiatrists today are consumers or solicitors of the goods used in the treatment, diagnosis and assessment of the mentally ill. And associations, collegiums and societies are increasingly becoming brokers between the pharmaceutical industry and the profession. But a multinational corporation in psychiatry based on the model of multinational business organizations with a network of diagnostic and treatment centers, operating with the same computerized system and feeding into the same central data bank would have the capability. Such a corporation if it remains restricted to illness could provide a worldwide service with a sufficiently reduced expense that treatment would become available and accessible to everyone who needs it. I am keenly aware that attending to the illness without taking full care of the patient does not suffice. But, regardless of what I do or don't believe in, helping patients reintegrate with society is a social obligation that neither depends upon nor requires medical training, a privilege dependent on how much the community can afford it.

There is a particularly tricky group of people that I would be keen to hear your response on: what about personality disorders?

I have difficulties with the concept of personality disorders. Some are exaggerations of personality traits while others might just as well be the result of a pathologic process — in the same way as anxiety disorders are slowly being seen this way. What we refer to as anxiety disorders today were labelled for long as neuroses and perceived as abnormal personalities under stress. Even in the ICD-9, neuroses and personality disorders were still lumped together.The DSM-III was the first classification which separated them. Now I would think that some personality disorders are abnormalities in the statistical sense, while others are clinical syndromes, similar to the neuroses, which have nothing to do with development.

But I must admit that I have problems even with the concept of personality. I really don't like it. If people have so much difficulty coming to any kind of agreement about what a concept means, as in the case of personality, there must be something wrong with the concept. The only reason to have concepts is to be able to communicate, and if we have problems using a concept in communicating, we might just as well throw out such a concept. And if the dismissed concept leaves a void one should replace it with one which corresponds more with the real world. Eysenck went just as far as one can go in defining personality in a scientific way, but his concept of psychopathy has no roots in reality.

Well, he had hoped that the constructs he was using would be drug sensitive. He did predict that certain drugs were going to shift people along a dimensional spectrum but that didn't work out once imipramine appeared.

Whether it did or didn't, I don't know. Theoretically, it should have insofar as at least stimulants, sedatives, and alcohol are concerned. I would be more inclined to think that the reason why no one is talking about the relationship between Eysenck's dimensions of personality and drugs is because it leads to a dead end.

Let me bring you back. You and Hanns Hippius appeared to pick up this history issue more than anyone else. Why were you interested in the history?

With the rapid growth of the field, the CINP grew into a major, politically powerful organization and has undergone several drastic changes in its leadership. Since the time of its inception CINP was a President's organization, and during their short, two-year tenure each President was given a chance to leave his imprint. The history committee was really Ole Rafaelsen's creation about 10 years ago at the San Juan congress. Hanns Hippius and I became the first members... and a few months later Ole died unexpectedly.

Hanns and I continued with the activities planned, including the reconstruction of CINP's poorly kept records. We began reviewing history through the CINP congresses which we have been having every two years. And while working on Thirty Years we became aware that people who had been around when CINP was formed were aging, and felt that if we really wanted to find out not just what happened, but also how it influenced the course of events which led to what we have at present, we were getting close to our last chance. We thought that the best way of finding out was to ask each of the founders to give a brief account of their perception of the field in the mid-1950's and their perception of the field in the early 1990s. Psychopharmacology in Perspective, the collection of these manuscripts, was ready by the time of the Nice Congress in 1992. Soon after we began preparing the first booklet of a systematic review of the history of CINP, covering the period from the 1955 Paris Colloquium on Chlorpromazine, sponsored by Rhone-Poulenc, through the Milan Symposium, to the time of the inaugural meeting of CINP in the fall of 1957.

We are planning to continue our systematic review. There is, of course, a close relationship between the program of CINP congresses and the history of neuropsychopharmacology. And when looking at the program of the congresses, we could see a steadily widening gap between preclinical and clinical research... and an impasse in pharmacotherapeutic progress.

Whether feedback from psychiatry could have broken the deadlock is difficult to say. Personally, I would think that we would be far ahead in the pharmacotherapy of mental illness if Fish's findings had not been ignored and the differential responsiveness to neuroleptics between the systematic and unsystematic schizophrenias verified. I would also think that we could have cut short a lot of meaningless experimentation if it would have been clarified whether reserpine-induced psychopathology is dysphoria, a pathologic emotion, or dysthymia, a pathologic mood, and whether the anticholinergic-induced psychopathology is delirium, a clouded state of consciousness, or dementia, a disintegration of personality.

I know that it sounds like I keep saying revive good old psychopathology and nosology and all our problems in neuropsychopharmacology would be solved. But this is definitely not my position. All I am trying to say is that we should carefully examine whether psychopathology and nosology, the two basic disciplines of psychiatry, could provide biologically meaningful concepts before dismissing 100 years of psychiatric tradition. On the other hand, if none of the concepts of psychopathology and nosology turn out to be useful, which is unlikely but not impossible, I think that we would be justified in rebuilding the discipline that was called psychiatry from new, entirely different elements. The term psychiatry, with its link to the animal spirit, psyche, soul has become anachronistic anyway with the introduction of psychotropic drugs.

Since the 1960s there has been a growing tension between clinical psychopharmacology and neuropharmacology... and there has been also a growing tension within CINP. The organization was in place and held regular congresses every other year, alternating between one open and one closed meeting. And although each congress in its own right, was a success, the different disciplines remained isolated, and the people, instead of becoming one big family became polarized into political factions and national representations. Rothlin continued as president for a second term, but Trabucchi, who was considered by many to be the real founding father of CINP, quietly withdrew after the successful first congress he organized in Rome. And the revolution was killing its own children... during the second CINP congress in Basel, two of the original founders, Denber and Radouco-Thomas, were pushed aside. The same happened to Phil Bradley during the Copenhagen congress. Of the original founders, only Pierre Deniker was to become President. And the tension which pervaded the business meeting in Basel continued for years.

By the early '80s, it became evident that keeping the channels of communication open could not prevent significant differences in drug preference. Transcultural differences certainly cannot explain why maprotiline a selective norepinephrine re-uptake inhibitor is the most extensively employed antidepressant in France, whereas fluoxetine, a selective serotonin re-uptake inhibitor is in the United States. Nor can it explain why clozapine, a great success in Germany, is virtually not used by the Italians. It is telling that in countries which are less prosperous and even in prosperous countries among the poor imipramine remains the most frequently prescribed drug in the treatment of depression and chlorpromazine in the treatment of schizophrenia.

The history of modern pharmacotherapy in psychiatry is certainly not a straight forward story. It is rather disturbing that D2 receptor blockade, which, as believed for a long time is an essential prerequisite for therapeutic effects in schizophrenia, now appears to be a curse... that D2 receptor blockade is out and D4 receptor blockade is in without the slightest evidence that D4 blockers are more efficacious than haloperidol or chlorpromazine.

Even the chronology of development is somewhat confounding. For me, the psychopharmacologic revolution began with the introduction of chlorpromazine, but the muscle relaxant mephenesin, the predecessor of meprobamate, the first propanediol tranquilizer, and the antituberculotic isoniazid, the predecessor of iproniazid, the first monoamine oxidase inhibitor antidepressant had already been around in the early 1950s. One should probably start with lithium which, in the ultimate analysis, appears to be the most important contribution insofar as pharmacotherapy in psychiatry is concerned. And the first publication on lithium was in print already in the late 1940s.

There was considerable delay between Cade's early report on lithium in the late 1940s and Schou's demonstration of its therapeutic efficacy in the mid-1950s, and an even longer delay between Schou's report and the spread of lithium therapy in psychiatry. In fact, it took place only well after the introduction of the first benzodiazepines in the early 1960s. And the spread of the benzodiazepines, backed by Roche's multinational organization, was much faster than the spread of lithium, backed by Mogens Schou, a professor of psychiatry. But in spite of all the support the benzodiazepines received, the shift from the propanediols to the benzodiazepines in the control of anxiety took significantly longer in Europe than in the

United States. And even today, however effective and safe the benzodiazepines are, the use of propanediols in Eastern Europe and in the developing world continues.

I have no doubt that the introduction of the benzodiazepines was a major contribution. But even if the benzodiazepines are so close to the natural anxiolytic that mother nature created a benzodiazepine receptor in the brain, within the framework of the psychopharmacologic revolution the breakthrough drug in the treatment of anxiety was meprobamate. Frank Berger's contribution cannot be sufficiently emphasized. By recognizing the relationship between muscle relaxant and anxioytic effects, Berger revived the James-Lange theory of emotions, and rendered anxiety accessible to scientific scrutiny. I am not surprised that of the two meetings in psychopharmacology prior to the Milan Symposium, one, the Paris meeting in 1955, dealt with chlorpromazine, whereas the other, the New York meeting in 1956, dealt with meprobamate.

Silvio Garattini would also say that drugs like meprobamate looked as important to them in the 1950s as chlorpromazine and...

The relative importance of these two drugs depends on the framework of psychiatry one operates in. Within the European framework, the importance of chlorpromazine is overwhelmingly greater. But the European concept is a very narrow concept which grew out from the psychoses. On the other hand within the American framework, in which psychiatry included from the very beginning alcoholism, psychopathy and neuroses, the importance of meprobamate is comparable to chlorpromazine.

One also hears very little these days about reserpine. It is almost forgotten that during the mid-1950s it looked just as important as chlorpromazine. Some of these drugs provided important bridges. Just as the propanediols provided a bridge between the barbiturates and the benzodiazepines, reserpine provided the bridge between neuropharmacology and psychopharmacology, between therapeutic effects and brain monoamines, between transmission of impulses at the synaptic cleft and processing of experience... It was the recognition of the importance of serotonin release in the action mechanism of reserpine in the mid 1950s that opened up the possibility of employing the pharmacologic approach in the study of the brain and in the exploration of the relationship between biochemical mechanisms and mental functions. It was the introduction of the pharmacologic approach which turned the pharmacotherapeutic rebellion into a psychopharmacologic revolution.

What about Brodie's role in all of this?

He played the most significant role. He trained most of those who created modern neuropharmacology. It was a new way of thinking, a new way of looking at things that people picked up while working for him. Julius Axelrod, who as you know was awarded the Nobel Prize started out as a technician in Brodie's laboratory, Arvid Carlsson, who was first to figure out how chlorpromazine and haloperidol works, spent some time with him in Bethesda and one could go on and on with the listing of the names. It is rather unfortunate that some of them, especially in North America, imposed themselves as authorities in psychiatry and by doing so have created insurmountable difficulties for a healthy and desirable interaction between the two disciplines. Another person who is undervalued is

Nate Kline. He did some of the early clinical work with reserpine, picked out the monoamine oxidase inhibitors and had the guts to stand up for lithium's importance.

The other thing that he seems to have done that gets played down is his work in Congress that provided the funds to create the Psychopharmacology Service Center.

Yes, his testimony before a subcommittee of the US Congress in the late '50s played an important role in it. And there are a great many other things he did. He generated the funds necessary to open a psychiatric institute in Haiti, to sponsor the annual Denghausen meetings and one could go on and on. He was a great man, regardless of how one looks at it. I don't think he got the recognition he deserved. In a certain way there are similarities with Brodie, but of course there are important differences. Kline did not train up a school. Working with Brodie stimulated people to develop the methodology which created a new science. Now, I cannot say that the same applies to Nate, but he was certainly quick in recognizing the importance of psychopharmacology. And he did it in an era when you virtually could not get into academic psychiatry in America without being psychoanalyzed... when psychoanalysis was the mainstream of psychiatry, distracting attention from the possibility that the administration of a drug might correct something wrong going on in the brain. But even if Kline did not train a school, he pioneered a new way of thinking in psychiatry. It was this new way of thinking that made it possible to recognize the importance of the monoamine oxidase enzymes, and later on other genetically determined enzymes... and to develop the link between psychiatry and molecular genetics.

Is it totally impossible 10 years from now that we might re-write the history in terms of a lesser focus on chlorpromazine because the implications on genetic...

Probably not rewrite, but sort of round it up... and give proper recognition also to the chain of events triggered by the introduction of reserpine and the monoamine oxidase inhibitors. And instead of dismissing the neurobiologic approach to complement it with a molecular genetic approach.

Why did you leave Hungary?

I was on vacation, travelling around in the Balkan countries when the Hungarian revolution began. I flew home from Belgrade when the Russian troops moved out from the city and left before the borders were shut, after the Russian tanks rolled in. I had no clear cut plans. The reason I left was simply that I wanted to see the world outside the iron curtain and was interested to learn. I left sometime in mid-November and for a period of two months was permanently on the move. But by mid-January 1957 I was in Canada, a fellow at the prestigious Montreal Neurological Institute. Whether I got my fellowship entirely on merit it is difficult to know. As a medical student I won first prize for a work I had done in collaboration with a fellow student on post-traumatic epilepsy. And Penfield apparently was or was made aware of this work. It was certainly a good start for a 27 year old who just arrived to the new world. But then I felt that I was really more interested in psychiatry and decided that I should complete my training.

I picked the place Heinz Lehmann was at because I had heard about his work on chlorpromazine. I went there on the 1st of July 1958 and within a couple of months I had

been involved with him in research on phencyclidine. I also began with my work on conditioning. In those years we still had to write a thesis to get our diploma in psychiatry at McGill. And the title of my dissertation was conditioning and psychiatry. I received my diploma with distinction in 1960 and my thesis was published as a monograph in 1964 with a forward by Horsley Gantt, at the time one of the last living pupils of Pavlov.

After spending a year with Heinz Lehmann at Verdun I was ready to start working with Gerald Sarwer-Foner at the Veterans Administration Hospital but the departmental chairman, Ewen Cameron was looking for someone with the background I had in conditioning and psychopharmacology and I was asked whether I would be interested in working with him. I was, and after substituting for the chief resident at the Allan briefly I became Cameron's researcher for the rest of the year. And even after I had received my diploma I continued with Cameron as the junior member of his research team.

What was Cameron like?

He was an independent, goal directed, well organized man with exceptional administrative skills. He had studied with Henderson and worked with Eugen Bleuler and Meyer in his formative years but the Cameron I knew was definitely his own man. Strong, energetic and decisive with courage to pursue whatever he believed in. They called him Chief... and he called us "Docs" and the nurses "Lassies." He was the Chief, there was just no doubt about this.

In Cameron's time, the Allan was a truly eclectic place with facilities such as day hospital and specialty clinics, which were very much avant garde those days and with one of the largest and most respected training programs with residents from all around the world. All of this was of Cameron's making. What most impressed me was that Cameron ran the largest clinical service with the most difficult patients. Every day he walked around and talked to each patient and every other day we had rounds with him when we sat around a table. I was marginally involved because I was doing the research but still participated with my research patients.

I really think that what happened later was very unfortunate and uncalled for in his case. I cannot help but wonder why it happened in such an underhanded way and after so many years since everything Cameron did was done in the open and with the knowledge of his peers. He kept the cleanest and most precise records I had ever seen with all the information given on each patient to the smallest details. He dictated his notes in front of his team in his characteristic Scottish burr and whatever he dictated was typed in the record by the next day.

Where did all the controversy come from? What did it all mean?

It is somewhat difficult to remember after so many years but over the past thirty years Cameron has been vilified by the press. The difficulties began when it came to light that one of the sources of his funding, however small, was the CIA. The project that started the controversy was part of Cameron's long term research program based on a mixture of psychodynamic principles and learning theory, designed for patients refractory to the traditional approaches to therapy. For Cameron, as for other dedicated researchers in the field of the time, it was never clear where treatment ended and research started. This was

certainly the case for "psychic driving", a form of psychotherapy, he developed in the early 1950s. By the time I arrived to the Allan he used drugs, sleep, and sensory isolation to loosen, and depatterning to selectively erase pathologic patterns. And this is what created the problem. When Cameron left, his practices were scrutinized... but while all this took place the precarious balance at the Allan Memorial Institute shifted from eclectic to psychodynamic and in the years after the control of a small group of psychoanalysts was strengthened. It was a very closed shop, a fraternity of psychoanalysts.

I could be wrong but this is how I saw it. Cameron had been critical of psychoanalytic theory, rejected what psychoanalysis stood for. Now I am not trying to say that the Cameron affair was created by the psychoanalysts. But I do believe that Cameron's advocacy that learning might be more important in a broader sense than in the very narrow psychodynamic conceptual framework, contributed to it. It had been convenient for the psychoanalytic group to go along with what was happening and to sit back and listen to the never ending critical appraisals of Cameron's work by different standards year after year. What is somewhat surprising is that no one ever pointed out that while Cameron's team was depatterning a patient on one bed, another team on another bed of the sleep room was busy doing anaclitic therapy - one of those therapies based on psychoanalytic theory in which adults are treated as babies.

After all Cameron's idea to erase everything one had learned, get rid of the pathologic patterns, create a tabula rasa and try to rebuild things from scratch, program in new behavior, was not as way out as some people have perceived it. And even if many people had forgotten it conveniently, Cameron had only introduced the term depatterning for a treatment which was in use, but referred to as regressive ECT by others. As you know, there were all kinds of treatments in those days - apomorphine induced vomiting and atropine induced toxic psychosis were considered to be therapeutic. Insulin coma, and even prolonged insulin coma therapy was still used in the treatment of schizophrenia.

Cameron was of course familiar with all the different types of treatments and to combine pharmacotherapy with psychotherapy was very much in keeping with his general approach. He adopted the concept of psychic defences from psychodynamics but treated psychic defences as if they would have a biologic substrate. But being Cameron he was impatient, looking for short cuts, trying to speed up the therapeutic process and the idea of using drugs to facilitate psychotherapy had been around for a long time. There had been psycholytic therapy, which aimed to activate unconscious, repressed memories, and psychedelic therapy, which aimed to elicit profound cosmic - mystic experiences by the administration of LSD and psilocybin - in fact this had a great many followers for many years. Abram Hoffer, a member of the pioneering team formulating the adrenochrome hypothesis in the early 1950s used psychomimetics in the treatment of alcoholics. He, later, became well known around the world for promoting megavitamin therapy and orthomolecular psychiatry with the double Nobel laureate Linus Pauling. You know it is interesting that the two Canadian founding members of CINP were Abram Hoffer, who now lives somewhere around Victoria, and Ewen Cameron. Both of them have received excessive attention by the press over the years.

What one reads about Cameron is mainly about ethical issues. It is of course easy to agree that it is wrong to expose patients to treatment without proven efficacy, treatment which is in development, without their knowledge. But the real question is where to draw the line.

Because, if one takes it literally none of the psychotherapies had data in support of their efficacy those days. I would question whether such data exist even today. And psychic driving, Cameron's brand of psychotherapy was not sufficiently different from the rest that it would have qualified as a different kind of treatment. I spent lots of time with Cameron's patients, or at least with those assigned to me and explained just as much about their treatment to them as I was able to comprehend myself and able to get across. And in those times, we had neither ethics committees, nor consent forms. How much attention Cameron paid to these kind of issues, which today would be dealt with by institutional review boards and ethics committees I don't know. But I do know that he felt comfortable about how things were and fully responsible for what he was doing.

Since Cameron left McGill almost 30 years have passed and during the years my frustration with him has gone... I was terribly frustrated with my work at the Allan - mainly about trivial matters, like keeping my gadgets in working order. The difficulties interfering with my activities were there day after day and influenced my attitude towards and judgment about the research but even then the rationale of the treatment, which was at the center of the research, seemed to me at least as sound as the rationale of most other treatments those days and Cameron's speculations were more down to earth than some of the speculations I was exposed to in the seminars I had to attend during my training.

I am now able to look at the research I was engaged with on his team without any emotional coloring and I feel that whatever was done should have been done better, in a more sophisticated way. He should have been more careful of not confounding matters by tackling too many issues together, trying to get an answer to too many questions simultaneously. There were many questions there with important theoretical implications for psychiatry - like whether the pathologic pattern could be erased by physical means. Because if pathologic patterns could not be erased by depatterning, the most drastic means that could wipe out all that was acquired after birth, it would be very unlikely that these patterns were learned and if that was the case Cameron's findings would shatter one of the basic premises on which psychodynamics was based.

Another question with important theoretical implications was the one which dealt with the nature of the disorganization induced by sensory isolation or drugs. Because if the nature of the disorganization depends on the disease and not on the person afflicted with the disease, it would imply that the disease process is independent of personality development. But Cameron was not just bluntly entering the psychological-mental sanctuary by physical means, he was also trying to render accessible to scrutiny the detectable changes, if any, displayed during therapy, by the recording of everything for which a gadget was available. The money from the CIA was spent primarily on the development and employment of objective measures.This was something he had been interested in since the early '30s, when he wrote his text on Objective and Experimental Psychiatry.

I don't know whether he was aware of how sensitive an area he touched in his research. Nor do I know whether he was ready to conceptualize his own findings in the way I was doing. He never acknowledged that the answers to certain questions were already there in the notes he dictated with great regularity on his patients, in the files he was so proud of. One of the patients, whose file I am referring to, was a very severe obsessive compulsive he depatterned. She was confused and disoriented for days, but in spite of her organic state her compulsive

rituals persisted unchanged. Another schizophrenic patient remained unperturbed by prolonged sensory deprivation. She was actually better after she came out of sensory deprivation than when she entered. Such patients opened my eyes to see that some of the things I had been taught might not have been as true as I was made to believe. Whether those cases carried the same message to Cameron, it is difficult to know. He spoke little and even when he did I frequently felt that he said things tongue in cheek. By the time I could have asked him, he had passed away. Cameron died while mountain climbing... he died as he lived.

I joined Vanderbilt in 1976, and we left Montreal and moved to Nashville. Then last fall McGill's department of psychiatry had its 50th birthday. I was invited to the anniversary celebrations and, I assume with consideration of my monograph on Psychopharmacology for the Aged, I was assigned to a symposium on psychogeriatrics. When I went back, after being away for almost 20 years, I was struck by what I saw. The department seemed to be frozen in the state as it was in the mid '70s. It was on my tongue to say that you may argue endlessly about the relationship between mind and body but get rid of the double standards between the biologic and the psychodynamic and get on with treating patients. I left at the end of the meeting contemplating, that even if it had been right to criticize Cameron about some of the research he did, the outcome of his departure was devastating. It shifted the department into a psychodynamic mode at a time when the rest of the world was shifting in the opposite way. The department which in Cameron's time was the heart of Canadian psychiatry was struggling to adapt to the new world. I just cannot help to think that there was something else there and not just the funding from the CIA.

It was all very strange because around 1960/62, Cameron was one of the three or four big names in the world.

He was one of the Nuremberg psychiatrists and one of the psychiatrists who examined Rudolph Hess. He had been President of the American Psychiatric Association and the founding President of the World Psychiatric Association. Cameron was a hard working and creative man and this was his greatest strength. He was free of prejudices and binding beliefs and had the necessary drive to pick up and explore the possible usefulness in psychiatry of whatever new thing he picked up from the other disciplines. Most people work within someone else's framework, but Cameron had the imagination to build his own. He had arrived in Montreal, from Albany, in the early 1940s and was facing a society strongly controlled by the Catholic church. But he walked through without paying any attention to this and without ever bending his head. The clergy had no place in the psychiatric hospital insofar as Cameron was concerned. And he succeeded on his own to create the leading department of psychiatry in Canada, a department which was at that time one of the best in the world. No one in those years would have denied that Cameron was a great man. When Ellenberger arrived...

Cameron brought Ellenberger there?

Yes, he brought him there in the late 1950s or early 1960s. He was an eclectic and his department clearly reflected this. Regardless of what people say, he cared about his patients and he had an open mind. He was interested in everything new and tried to introduce it in his Institute. Hyden had hardly presented his theory that RNA is the molecular substrate of

memory when Cameron picked it up and was ready to start with a clinical trial employing RNA as substitution therapy in elderly patients with memory impairment. He was ready to build a bridge between molecular biology and clinical psychiatry. And when existential analysis emerged, Cameron without delay hired Henri Ellenberger but he really did not know how to deal with him.

Why not?

Cameron was a pragmatic and Ellenberger was a man of books. He was expected to see patients to generate his livelihood. I assume that the time required for practice was too much of a distraction for him. He was obviously working already on the Discovery of Unconscious, which became a classic by the '80s. Ellenberger was completely lost in the big machinery of the Allan and found refuge at the University of Montreal, where he became professor outside the medical field. His story reminds me of the story of Karl Jaspers who exchanged psychiatry for philosophy.

Was there anyone else he brought in like that?

There was Kral, one of the pioneers of psychogeriatrics, best known for separating benign from malignant forgetfulness. He collaborated with us in a project trying to predict therapeutic responsiveness to psychotropics by employing pharmacological load tests. He brought in Eric Wittkower, a leading psychoanalyst, who was involved with research in psychosomatics and cross-cultural psychiatry. One of the first people he brought in was Robert Cleghorn, who succeeded him at the Allan. It was actually Cleghorn's team, which commissioned the work which found no memory impairment in the depatterned patients by employing the Wechsler Memory Scale. I have not seen the report but I understand that in spite of the findings Cleghorn concluded that patients might still have difficulties with remembering because there are memory problems which are not detectable by the Wechsler Memory Scale.

Why is getting funds from the CIA such a potent stick to beat people with?

Because it can be implied that CIA funded studies were used for the development of brainwashing techniques. But of course the stick was not necessarily used. There were many distinguished scientists who got funds from the CIA. I don't really know who they were, I read about Harris Isbell, who was director of the addiction research centre in Lexington, Jolyon West, who was chairman of the department of psychiary in Los Angeles and Leo Hollister, one of the most prominent clinical psychopharmacologists of the United States. But there were many well known psychologists too. I read that Hans Eysenck, Carl Rogers and Fred Skinner received funds from the CIA.

But who really knows... And, you know, it was never completely clear whether Cameron knew that the source of the money he received for four years or so from the Society for the Investigation of Human Ecology was the CIA. I certainly did not. But even if he had known, he would not have cared. Funds from the CIA were just as good for him as funds from anywhere else. But as you say it has been used as a stick to beat him with.

How much do you think it links up with the clash of paradigms with the analysts on one side and the biological psychiatrists on the other? Someone like Frank Ayd would say that the biological people were seen as being in league with the devil, treating people in this inhuman way - so in a sense maybe the CIA links were just the icing on the cake.

This is exactly how I see it. The CIA link helped to blow out of proportion the criticism of Cameron's work and to make biological psychiatrists look as if they were treating their patients inhumanly. You should keep in mind that the Cameron affair took place before we began with our struggle to separate facts from beliefs and hypotheses from speculations in psychiatry. Just around the time when the different approaches in psychiatry were turned into paradigms and became politicized. The two most influential paradigms were the social and the psychodynamic, one the mirror image of the other.

I felt somewhat lost those days, because paradigms were meaningless words to me. I just couldn't see why it was so important to choose whether the social creates the psychologic - my indoctrination in Hungary - or the psychologic the social - my indoctrination at McGill. Neither seemed to me to have much relevance to psychiatry but I could see that paradigms are created by social forces and that psychologizing can distract from social problems - that is that it's the social structure which has fostered psychologizing in the US and sociologizing in the UK and that there are vested interests which have sustained the dominance of these approaches.

Absolutely. In England psychopharmacology happened outside of Oxford and Cambridge. It did not happen in the major centers.

It was the same in the United States and Canada. It was not at the Allan Memorial Institute, the primary teaching center, and not even at the psychiatric units of the Montreal General or the Jewish General Hospitals, but at the Verdun Protestant Hospital, a kind of State Hospital, which served the poor in the English speaking community of the city. And even at the Verdun, an ambitious Executive Director gave Dr Lehmann a hard time during the late '50s. Fortunately after he had been psychoanalysed, he moved away from Montreal to higher positions. But, as late as the early '70s, another ambitious Executive Director succeeded in preventing the implementation of a program which would have led to a rational use of psychotropics within the framework of a specially designed service structure in the hospital. Everything was in place to go ahead, but he interfered to prevent the shift in the balance between two paradigms, the psychopharmacologic and the social. I presented a brief outline of the proposed program at the CINP Congress in Copenhagen. There was great interest, but nothing else.

In the majority of the teaching centers of Canada and the United States the psychodynamic approach remained dominant during the 1970s. I assume the same applies to the social approach in the UK. But, you know, in spite of the brutal clashes between their prominent representatives, the social and psychodynamic paradigms are quite close. Both confound the disease with how the person with the disease is interacting with the outside world. And for the drug companies it was more convenient to deal with a profession split by different approaches, entangled in paradigms fighting each other about the acceptance of psychotropic drugs, than to deal with a unified profession, ready to accept that in mental illness, pharmacotherapy is the only rational treatment. A unified profession would not have been

happy to stop half-way in developing a psychotropic drug. After establishing efficacy, it would have insisted on identifying the treatment responsive population. We would not have ended up with nearly 500 semi-finished psychotropics, but only a few with well defined therapeutic indications.

So, in a sense the industry don't want a biological psychiatry that knows what it's doing.

Right. They encouraged the interaction between psychiatry and neuropharmacology in a number of different ways, including the founding of organizations like the CINP, but did not pay any attention to how the different groups within psychiatry interacted with each other. The pharmaceutical industry played everything according to the rules, but never did anything beyond what was absolutely necessary to do. In spite of all their conservativism, by focusing on money and by clearly identifying their goals, the industry has been instrumental in triggering and fueling the ongoing transformation of psychiatry into a medical discipline. This is happening because the industry has rendered pharmacotherapy accessible in the treatment of mental illness. The transformation began without the help and even in spite of the resistance of the academicians. This is why in the course of the transformation academic psychiatry has found itself floating in the air. The teaching of the treatment of mental illness has slipped out of their hands. I wonder for how long will it be possible to preserve and teach a psychiatric theory, which has nothing to do with the effective treatment of mental illness at the clinic.

In my opinion, the most important single contribution of the pharmaceutical industry was the development and introduction of a new model of operation in the form of the multinational corporation. And even if multinational corporations today exclusively serve limited business interests, they provided the basis, the foundation for a new world. But while instrumental in the creation of a new world, multinationals act on the basis of short term planning. The pharmaceutical industry has rarely gone beyond the generation of the minimal amount of information necessary for the registration of their drugs. And when they went beyond it was to support marketing. I know that the companies are criticized for this, but it is not the industry it is the profession who should be blamed.

We don't act as a profession?

You are perfectly correct and it is not the task of the industry to pull us together. Why should they do that? After all it would be against their own interest. But if the industry were faced with a different profession, a profession with an identity, I'm convinced that it would act differently.

They would collaborate with psychiatry and provide the necessary support - not generously, just as much as absolutely necessary. But they would no longer treat the profession with handouts, the opinion leaders of the profession as puppets and their collaborators from the profession as "call girls". Did you read Arthur Koestler's little book with that title? It is about scientists who become part of the international jet set and fly from conferences to congresses. You might find it amusing. I met Koestler sometime during the I970s in San Juan, while attending an ACNP meeting. He was invited by Nate Kline to participate in a panel.

A psychiatry which acted as a profession with a clearly defined identity could have stopped the invasion of neuropharmacology, channeling away the little money university departments of psychiatry have for teaching. The invasion of neuropharmacologists and the enormous confusion and shifting of priorities, created by their mere presence in departments, is becoming a more serious problem than the invasion of anthropologists and other social scientists had been during the psychodynamic era when the psychoanalysts dominated the field. And, you know, neuropharmacologists in the psychiatry departments have the titles of professor of psychiatry without ever having a formal training in the field, however unbelievable that may seem. What is even worse is that many of the psychiatrists, because of the shifted priorities in the departments spend their time in neuropharmacologic research instead of doing their clinical work. Can you imagine in some departments this is even encouraged?

I might be giving you the impression that I have no appreciation for neuropharmacology. It is really not so. I have great interest in it. And I am obviously very much interested how the brain created the mind and how the brain works. But this doesn't prevent me from recognizing that research in these areas is far beyond what psychiatry deals with. I would go even further. In the same way as I'm opposed to support research in neuropharmacology from the budget allocated for psychiatry or the budget of mental health, I am opposed also to the funding of brain research from federal, state, provincial or what have you grants allocated for health and welfare. Such grants are from the taxpayer's pocket and there are many socially more pressing priorities than the neurosciences. I realize that I probably belong to the small minority who believes that all the money from the budgets of health and welfare should be spent on taking care of sick people directly and not by investing in highly sophisticated research.

I think it would be more appropriate if neuroscientists would be in Institutes like the Mario Negri, or have their own multinational corporation and we psychiatrists should also have ours... I really think that if we psychiatrists could come together and organize ourselves in a multinational corporation we could do so much more for everyone including ourselves. And we would not be at the mercy of businessmen or politicians.

To open up progress, there is a need for a change and for me a multinational corporation of psychiatry appears to be the rational next step. I have considered a number of different alternatives but none of them seemed to offer greater advantages for patients, psychiatrists, industry and even for the society we live in. In such a corporation, psychiatry could offer the least expensive and most accountable, accessible service to patients. We have all the necessary technology to provide the backbone of a multinational corporation of psychiatry. We have suitable programs to develop the necessary software for the implementation of the same standards in diagnostic and treatment services everywhere around the world. We have the sophisticated communication systems which would allow for the delivery of centralized education programs and we have the computer capabilities to store, process and analyze the collected data in any manner we wish. We could provide the necessary unbiased information for education to universities, feedback for planning to the companies and the statistics for the organization of mental health service to whoever is responsible for it.

Talking about tensions between psychiatry and neuroscience prompts me to ask you about your Tennessee experience. When you went there it appears to have been something of a

hot bed of psychopharmacology between Fridolin Sulser and Oakley Ray. Is there any reason why this should have been the case?

While Allan Bass was chairman, the department of pharmacology of Vanderbilt became one of the tops in the United States. With the help of Frank Luton, the first qualified psychiatrist in the State, a disciple of Adolf Meyer, Bass succeeded in persuading the State of Tennessee to collaborate with Vanderbilt in founding a new kind of facility for research in neuropsychopharmacology. The idea was to have basic scientists and researchers work closely together in it. One of the buildings at the Middle Tennessee Mental Health Institute, the State Hospital serving the area, was dedicated to house the new facility and the Tennessee Neuropsychiatric Institute was opened with substantial NIMH support in the late 1960s. Bass first recruited Jim Dingell, a young pharmacologist who was studying the metabolism of imipramine, and then Fridolin Sulser, a medical doctor with industrial experience who had spent some time with Bernard Brodie at NIH. John Davis, the first clinical director of TNI, got on board somewhat later. Davis, who became well known for his book with Donald Klein on the Diagnosis and Treatment of Psychiatric Disorders, had David Janowsky working with him, who developed during his short stay at the TNI the cholinergic hypothesis of affective disorders.

Then it just happened that around the same time the Veterans Administration Hospital in Nashville, which was closely affiliated with Vanderbilt, recruited Oakley Ray, a psychologist with a background in brain research. A clear thinker and excellent speaker, Oakley became one of the most popular teachers at the University, and gained an international reputation with his timely text on Drugs,Society and Human Behavior. So by the time of my arrival to the TNI, a couple of years after the exodus of John Davis and his team, Tennessee was a well known center of neuropsychopharmacology. Of course, it helped Tennessee's reputation that in 1971 Earl Sutherland from Vanderbilt won the Nobel Prize for his discovery of cyclic AMP.

Fridolin Sulser became one of the biggest names on the international circuit with his beta receptor down regulation hypothesis.

Sulser was already well known by the time of my arrival at the TNI. He had the reputation of a person difficult to deal with but he directed the preclinical division of TNI over many years smoothly and efficiently. He is a man with many talents - an accomplished researcher, a skilled politician, a good fund raiser and a persuasive speaker. Fridolin was always enthusiastic about the ongoing research in his laboratory and has never given up his dream to direct a research institute dedicated to neuropharmacology or molecular biology. He shifted the focus from presynaptic to postsynaptic mechanisms in the action of psychotropics... his description of postsynaptic beta receptor down regulation during treatment with antidepressants had a great impact on neuropharmacologic research.

After my arrival in Nashville, there were difficulties between Sulser and I, which unfortunately were perceived as a clash between personalities. This distracted attention from the essence what was going on. The real issue, even if never spelled out clearly, was my position that neuropharmacology and psychopharmacology are two distinct disciplines, which must interact with each other with mutual respect but without either of the two dominating the other. For me, it was obvious that neuropharmacology, which is focused on drugs and

deals with the detection of their action and the biological substrate involved in their action, is distinct from psychopharmacology, which is focused on illness and deals with the detection of which psychopathologic symptoms and the identification of which illnesses are affected by psychotropic drugs. But what was obvious to me was not obvious at all to Fridolin. He just could not accept that for psychopharmacology one needs a different training, background and maybe even a different kind of thinking. He just could not see where neuropharmacology ends and psychopharmacology begins. In retrospect I can see that this was probably not just a blindfold... and that I probably touched one of the unspoken taboos. Because if my position had prevailed, it would have endangered the funding of neuropharmacologic research in many centers in the United States. And you know this whole issue is still not passe. Neuropharmacology is still channeling away funds from mental health and psychiatry. I hope that psychiatry will be able to put an end to this before being asked to put an end to it by the community.

Fridolin has his neurobiology laboratory these days at Vanderbilt Medical Center in the department of psychiatry. Beta receptor down regulation, a definite step in the chain of events in the brain after the administration of certain psychotropic drugs, did not provide the royal road to the understanding of the pathomechanism of depression but it was picked up by the pharmaceutical industry and turned into the pivotal test in the screening for potential "antidepressants." The problem with this is that it has led to us being provided with "newer and newer" antidepressants" of which one can't clearly be distinguished from the other. But of course this is far beyond Fridolin's control. It is not his fault... it is psychiatry that is to blame.

Why have the analysts here and the social psychiatrists in the UK and the purist basic scientists that work within the university framework looked down so much on any of the clinicians or basic scientists who work for the industry? It isn't as strong here as it is over in the UK, where until recently if you worked within the industry you were persona non-grata. But in some respects one of the best places for people to work from recently has been within the industry.

I thought that kind of discrimination is over. It was one of the many ways to keep psychopharmacology out but it didn't succeed and we now have a steadily growing migration from academy to the industry. There are distinct advantages to working in the research departments of the drug companies. One is that your managers will provide for your support and ascertain that your research is done under optimal conditions. I don't know how it is in the UK but this is in sharp contrast to doing research at the universities in the US, where your departmental chairman and his growing entourage, will expect you to provide support for their expenses and all you can expect in return is to be administered - or in everyday language to be bossed around and bugged endlessly to write applications for research grants. It's insane to spend months writing a grant application, which by the time its approved, if its approved, is already out of date.

And these days you have to write five applications for one that's approved.

And since everyone is busy writing new grant applications, no one is paying attention to the need for a fundamental revision of psychiatric theory and education. But the pressure to prepare grant applications can't explain the absurdity that, at a time when it is generally

acknowledged that mental diseases are brain diseases, some experts in the field at some of the universities persist on keeping psychodynamics as the focal point of residency training. Nor can it explain the incredible truth that even 40 years after the introduction of chlorpromazine, some departments still refuse to accept that there was a psychopharmacologic revolution in psychiatry in the late 1950s.

There is another problem, of course, which is that by now psychopharmacology, or more precisely the pharmacotherapy of mental illness with psychotropics, is an internal part of undergraduate and postgraduate education in psychiatry but in spite of all the advances in communication technology, education in psychiatry, including education in psychopharmacology, differs from department to department and from one country to another. There is no good reason to teach pharmacotherapy differently at different universities within the same country. There is a simple, practical reason for some differences between countries because each country has its own drug regulatory agency and, however strange it is, has somewhat different psychotropic drugs available or the same drug, just across a border, may be available for different indications and in a different formulation. It's aggravating enough to have you present your passport and visa when passing the border from one country to another but to...

But we wouldn't have a World Cup without nations.

In a way, that's all they are good for. Tribalism in the era of multinationals... and each tribe, each university with a distinct psychiatric education and training. But seriously, mental illness is the same everywhere in the world. There is just no good reason to teach a different psychiatry in Budapest, Montreal and Nashville and if businessmen can form multinational pharmaceutical corporations which develop and market psychotropic drugs across countries, psychiatrists should be able to form multinational educational corporations which develop and disseminate educational material on how to use these drugs optimally in mental illness around the world.

Well, the argument against that would be, I guess, an ecological argument, that we've got to keep a diversity of species.

Actually I do believe in diversity, even if I recognize that mental illness restricts diversity and squeezes the diverse into stereotypes. I'm not talking about a "brave new world" in psychiatric education. We should be listening to diversity of opinions, while communicating facts which are separated from fantasies, and theories which are separated from speculations.

Is psychopharmacology a subversive science? Compared to physics, which is theory driven, which builds large machines to demonstrate particles which physicists predict are going to be there, in psychopharmacology new drugs or machines, like PET scans, produce observations which we didn't expect were going to be there and this forces us to go back and tear up our theories rather than add to them. It's almost the opposite to physics in one sense and from that point of view, you wouldn't expect to find psychopharmacology in Oxford, Cambridge or the Maudsley in the UK or Yale or Harvard here, which like their science classical. They like their theory first and deductions from a hypothesis and they give grants when you've got that kind of grant proposal.

I never thought of psychopharmacologic research in those terms. I understand of course what you are talking about but personally I think its wrong to label psychopharmacology a subversive science, because it appears driven exclusively by external forces to the extent that the introduction of every new drug or instrument disintegrates the old universe and opens up a new one. While undoubtedly this is the impression one gets about psychopharmacology through its most visibly promoted proponents, to define psychopharmacology as what psychopharmacologists do is begging the question.

The replacement of the cholinergic hypothesis with the catecholamine hypothesis and the catecholamine hypothesis with the indoleamine hypothesis of depression in rapid succession was undoubtedly in the interest of the drug firms. It's one of the common strategies of the pharmaceutical industry to attribute clinical relevance to pharmacological actions with psychotropics. By talking about catecholamine and indoleamine hypotheses of depression, we have undoubtedly given credibility to the marketing of antidepressants which are selective monoamine re-uptake inhibitors. What's overlooked is the simple fact that all these hypotheses are actually speculations, because no one has ever identified either in terms of psychopathologic symptoms, or in terms of nosologic forms a distinctive treatment responsive population to any of the monoamine selective antidepressants.

We can't really say that theories have been rapidly replacing each other, because the clinical data necessary for formulating those theories have just never been there. On the other hand we have all the necessary means and orientation points for the formulation of a parsimonious psychiatric theory of mental illness, which, if proven correct in a classical way through the testing of a series of hypotheses, would bring together psychiatric theory and practice separated since the introduction of psychotropic drugs. It would also provide clinically meaningful end-points for genetic, biochemical, physiological or pharmacological research in psychiatry. At this point the priority is to find our way to move ahead and break the deadlock in psychopharmacologic progress.

Let me get this clear, because it seems of central importance. What you are saying is when people don't respond to drugs, the industry use this as an excuse for saying we need to develop better drugs of the type we already have, and neuroscientists use it as an argument for more neuroscientific research, whereas in actual fact what should happen is more psychopathology.

Yes, in my opinion only proper psychiatric feedback can break the deadlock in pharmacotherapeutic progress. Proper psychiatric research would have identified the place of the SSRIs in the treatment of mental illness without the introduction of the ill-defined concept of serotonin spectrum disorders. Because regardless how they are promoted the fact remains that the SSRIs are therapeutically effective only in an undefined population within any of the diagnostic groups of the alleged spectrum and in none of the diagnostic groups of the alleged spectrum is therapeutic responsiveness restricted to SSRIs. I can understand why the drug industry is trying to do everything to render such a concept acceptable, but how the profession can go along with it is above my head.

I'm even more puzzled about why the profession considers it more important to learn about the action mechanism of psychotropics than about their clinical applications. We should know it by now that the study of the action mechanism of psychotropics can't provide a royal

road to the understanding of the underlying pathophysiology of nosologic concepts, because on the basis of our current knowledge none of the psychotropics we have is either selectively efficacious in a distinct psychiatric illness and/or equally effective during its different developmental stages. Neuropharmacologic research by furthering the knowledge about the action of psychotropics can lead only to the development of drugs with similar pharmacologic profiles and clinical effects to the ones we already have. I wonder why it took decades to figure out that increased affinity to D2 receptors doesn't improve the overall therapeutic efficacy of drugs in the treatment of schizophrenia and greater selectiveness to NE or 5HT2 receptors doesn't improve the overall therapeutic efficacy of drugs in the treatment of depression.

I don't have a crystal ball to foresee the future, but for one or another reason I have the notion that we will see more action in terms of new drug development through the manipulation of postsynaptic events and especially through the manipulation of postsynaptic receptor sites. After all it's the postsynaptic receptor which is responsible for the propagation of the electrical activity induced by the neurotransmitter released into the synaptic cleft,and it's the state of the postsynaptic receptor which,however remotely and confusingly,has some kind of relationship to the clinical state. And one should not forget that it was only after the introduction of radioactive isotope binding techniques in the late 70s that research in this area began.

So, binding technologies did make a difference?

In a way they did. They undoubtedly stimulated research to develop drugs which selectively bind to one or another receptor type or subtype. It is impressive how fast neuropharmacologists are moving in identifying newer and newer receptor types and even more impressive how fast they decipher their functional significance, which is not a simple task, because the same receptor, can be linked to the inhibition of emesis in the area postrema, to the modulation of sensory input in the substantia gelatinosa and to the regulation of anxiety in the limbic area. But when working in this fascinating area of research on the clinical side one should always keep in mind the Antaeus legend, because in the world of receptors one can get easily carried away and lose touch with Mother Earth .

Antaeus?

Antaeus was the son of Earth, a giant, who couldn't be killed while he was touching Mother Earth. According to the legend, Hercules picked him up, and when he lost touch with Mother Earth, killed him.

A few years ago I was following with great interest the work, which suggested that in obsessive compulsive disorder there is a hypersensitivity of postsynaptic 5HT2 receptors with downregulation of this hypersensitivity in the course of successful treatment with a SSRI. I thought that we finally have a clinical syndrome, which is clearly linked to a particular biologic substrate and which clearly responds to a particular group of psychotropic drugs. Unfortunately neither of my expectations were fulfilled. Hypersensitivity of postsynaptic 5HT-2 receptors turned out to be non-specific for obsessive compulsive disorder. It was found to be present also in panic disorder. And in terms of selection of treatment, hypersensitivity of the postsynaptic 5HT-2 receptors had no relevance whatsoever. In fact

panic disorder was found to respond just as well if not better to treatment with alprazolam,a short acting benzodiazepine, or imipramine, than to treatment with an SSRI.

There is an obvious problem in having some isolated findings here and some other isolated findings there and it 's an even bigger problem, that on the basis of such isolated findings one may decide about treatment which is not the optimal for the condition or in the best interest of the patient. The point I'm trying to make is that centrally coordinated clinical research in psychopharmacology is becoming an absolute necessity. And I just can't see the feasibility of centrally coordinated research in clinical psychopharmacology without a multinational professional corporation in psychiatry. At this point this would even be in the interest of the multinational pharmaceutical industry.

During the past decades the wealth of some of the multinationals has outgrown the wealth of some countries and at present we are seeing a rapid concentration of power in the hands of less and less companies. There are also some indications that multinationals are preparing to shift the focus of their operations from isolated products, with a product for each different medical discipline, to lines of products, with each line including a set of products for a particular discipline such as psychiatry, with different multinationals representing different lines across the world.

Of course all this is mere speculation based on very limited factual information but I have no doubt that with modern communication technology the present country and product based operations are becoming counterproductive and unmanageable. And since I would envisage worldwide development for the different lines of products, multinational pharmaceutical corporations will have to shift their alliance from government to profession with a choice to deal with independent multinational professional corporations in the different medical disciplines, or set up their own multinational clinical divisions in the different areas. Both options have advantages and disadvantages. In the meantime, companies will have to continue to operate in their present mode, working with national regulatory agencies in the best way they can to ascertain the protection of their investment.

Do you think regulation has been industry friendly? There's a good argument that can be made that we wouldn't have had the modern multinational corporation without regulation which forces smaller companies off the market.

Whether regulation is industry friendly - personally I would think it is - depends on how you look at it. The drug companies would certainly not say that the national regulatory agencies are particularly friendly to them and I don't think that those working in the agencies would say that they are particularly friendly or unfriendly to the companies. But then looking at it from a very different angle, the regulatory agencies in countries like the US and Canada have been as you were saying friendly to the big companies by setting the minimal standards at a level that the cost involved to get the necessary information and to prepare a submission was sufficiently high that only the big companies could afford it.

Is there a risk that the FDA-industry complex could lose contact with people on the street? This comes up in criticisms of Prozac, by patients groups pointing at the complex of the corporations and the FDA...

I like your term FDA-industry complex. Undoubtedly Prozac is a rather controversial drug but its problems are really not the kind of problems that, operating within the frame of reference of the agreement between the company and the government, the FDA could do anything about. In so far as I'm concerned, Prozac can't make a person dangerous to others who has no potential to become dangerous, although it might make someone who is potentially dangerous become dangerous but, of course, there might be several other drugs which have a similar potential.

Let me tell you my story with Prozac, for which I might be on some kind of blacklist with its maker. When it was released as an antidepressant in the U.S., I was on the pharmacy committee of Vanderbilt and on the basis of the information I had and with careful consideration of an excellent review from a Fellow from clinical pharmacology, I concluded that the drug was just not a sufficiently potent antidepressant that it should be put on the formulary of the medical center. In some way I was even surprised that Paul Leber, whom I very much respect, let it through just because the drug was clean on the toxicity screen even if the proof of efficacy with the required 5% level of probability was present only in a somewhat less seriously depressed population than usual.

My position after having some clinical experience with Prozac has not changed much in so far as Prozac as an antidepressant is concerned. But I must add that I wish that Prozac had developed clinically in a different way - even for the indication of depression because it is one of the more interesting psychotropic drugs. I'm glad that later on other indications, such as obsessive-compulsive disorder and bulimia surfaced. But then probably the most important is that the SSRIs are forcing us to face the issue of whether the use of psychotropics should be restricted to the treatment of disease or extended to the modification of behavior, or even to render life more pleasurable.

I agree the SSRIs can't treat anyone who is depressed any more successfully than the older compounds but what they can do much more successfully is they can influence sexual behavior - they can treat premature ejaculation, for instance. And the industry have even been out and done surveys to show that 1/3 of males have premature ejaculation problems, so there is a great deal of distress there that could be alleviated but they won't do it - at the moment anyway. They feel the consensus isn't there for that kind of social engineering at the moment.

It's one of those strange situations where business interest tones down a potential indication instead of drumming it up. But since the potential for influencing sexual behavior is there I hope that it will not take too long that industry will bring out people from the closet with premature ejaculation as it did bring people out with agoraphobia. This is another area where, in my opinion, a multinational professional corporation could help the pharmaceutical industry a lot. Since we have the capability to do social engineering to some extent it's really just a question for how long it would take to open up for it, which might differ from country to country.

Well, there's always this curious transcultural thing. If you look at what the best selling antidepressants are in any one country, they vary widely.

I'm glad that you are bringing this up because even if there are transcultural differences which have developed through differences in diet or through inbreeding, they are skin deep and the only thing which might be influenced by them is the propensity for certain side effects. I understand that in some way it was in the interest of the drug companies to keep the possibility of transcultural differences alive but have never understood why the idea that mental patients are different from the rest of people, in this regard, had so many proponents among psychiatrists.

Some time ago one could hear it said that patients need different neuroleptic dosages in different countries. But when in the early '80s, we conducted a study which dealt with the distribution of the different forms of schizophrenia in the hospitalized population in different countries and collected information on the dosages of neuroleptics used, we learned that the dosages used between two Japanese centers, one in the North and one in the South of Japan were greater than the difference between the dosages used between either of those centers and the center from the United States. But the differences in the use of psychotropics between countries are steadily decreasing. And even if a drug is put on the market with indications which don't correspond beyond a certain point with clinical reality, there is a process which brings it closer to it, however slowly.

Dialectically?

In a way. Actually we have the necessary technology these days to develop drugs uniformly for everywhere with all the steps in the decision making process regarding diagnosis and assessment of change captured but we are not doing it. In the same way, as in sports where we let the referee have the final say even if he is clearly wrong as shown on a video-recording, we keep in drug development a certain subjectivity. I understand of course that most people would think that's right but personally I'm unable to comprehend, even in sports, if the referee was wrong why we stick to the wrong decision when we are in a position to correct it.

It introduces the arbitrary human element, I suppose which can have its own justification.

Looking back to those early years of the 1950s, I'm always amazed how fast things moved ahead with the development of chlorpromazine. In less than a year after its synthesis, Laborit made his fundamental observations which led to the administration of the drug for the first time to psychiatric patients at Val de Grace. Undoubtedly, the observations of Delay and Deniker were the turning point in the development of the drug but Rhone-Poulenc moved just as fast as it could, not just with the drug, but also with the development of a series of analogues.

Could you say that the companies recognized the new drugs even quicker than the professionals? They were instantly off trying to find analogues and were prepared to put money in it.

Undoubtedly! Geigy started virtually without delay with the development of imipramine, on the basis of the structural similarity between the phenothiazine and iminodibenzyl nucleus. And by 1958, Lundbeck had the first thioxanthenes. Ciba got busy with the Rauwolfia

alkaloids, Roche with the hydrazine type of MAOIs and Carter Wallace with the propanediols...

While the profession was 10 years later still asking whether this was important.

Disappointing but true. It was only after the publication of the results of the Veterans Administration Collaborative Studies in 1960, that the profession finally accepted in the United States that something important is happening in the treatment of schizophrenia. And it was only after the publication of Klerman and Cole's report in 1965 that they were ready to accept that depression might be influenced pharmacologically.

But this is part of why I was saying to you that psychopharmacology is subversive. It wasn't the recognised scientists in Oxford and Harvard who discovered all this - it was people in companies - who put their money on it.

Although I don't see psychopharmacology as a subversive science, I've the feeling that our positions are quite close. First of all, I agree with you that modern psychopharmacology was created by the drug companies and that people from the drug companies have played an important role in moving psychopharmacology ahead during the past 40 years.The difference between our positions is, that I believe that psychopharmacology at a certain point entered a stage of development in which it had become counterproductive for the drug companies to move things further, because of their business interests. And it was at that point that psychiatrists, dedicated to psychopharmacologic research took it over and became the moving force.

Look at the psychopharmacology of schizophrenia. Psychopharmacology focusses attention on the biologic heterogeneity of schizophrenia but this is obviously contrary to the interest of the drug firms. In trying to prevent the falling apart of the neuroleptic market, industry is lavishly supporting and propagating neuropharmacologic research on receptor changes in schizophrenic brains or linkages through the D4 receptor to genetics. This kind of research is based on the assumption that schizophrenia, a concept, is one disease, whereas psychopharmacologic research should be trying to disentangle the biologic heterogeneity of schizophrenia found in clinical investigations. There is no support from industry for this kind of work and no appreciation for the need in American universities.

In a steadily increasing number of departments, the chairs are filled by psychiatrists, whom I refer to in Milovan Djilas' term as the "new class" within psychiatry. And this "new class" of psychiatrists by conveniently confounding neuropharmacology with psychopharmacology go along, on the basis of pragmatic considerations, with industry and neuropharmacology, perpetuating the deadlock in pharmacotherapy. Psychiatrists of the "new class" are ambitious, goal directed, keenly aware of the transformation psychiatry is in and they know how to pull the strings. There is a definitely laudable intention to integrate psychiatry with the rest of medicine, to replace subjective assessments by objective measures and supplement the information obtained by interview with findings derived by sophisticated instruments - indeed their determination to bring to psychiatry whatever modern technology can offer, regardless of need and price, outweighs common sense. By focusing on MRI and PET, they distract attention from the overdue re-evaluation of psychopathology and nosology. It's

pathetic but without ill will they are successfully destroying the little bit of psychiatry left in the departments after the lengthy domination by psychoanalysts.

If you visit one of the avant garde departments of the "new class," you will be overwhelmed by information on ongoing research in collaboration with neuroradiologists, biochemists and other sophisticated instrumentalists. Eventually, though, you will realize that no one is engaged in psychiatric research to generate the "clinical prerequisite" that could render the findings, with the sophisticated instrumentation, meaningful and interpretable.

In spite of all the difficulties psychopharmacology is moving ahead and, even if not without resistance, it is dragging psychiatry into the modern world. I was lucky in a way, because I had just graduated when psychopharmacology was starting in 1954 and people like Mogen Shou and Max Hamilton were just a little bit older than me - sufficiently older so that I could learn from them, while I still could get to know them, because I too was involved what they were doing. I have been all my professional life in Academia. I'm 65 now and the time is here to move along and try to find a way to put into practice what psychopharmacology can offer and what I have learned over the past 40 years. I have thought about writing a history of psychiatry. The title would be "They Used to Call it Psychiatry".

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