A PSYCHOPHARMACOLOGY THAT NEARLY WAS
OLDRICH VINAR

You began doing medicine in the early 50s?

I began my university studies in 1945 and I finished in 1949. There was a great shortage of doctors at the time in the former Czechoslovakia, because the Germans who had occupied the country from 1939 closed the Universities. To cope with this shortage one could do a medical degree in 4 rather than 5 or 6 years. I began my studies in Brno in Moravia which was liberated by the Red Army some 3 months before Prague. So I had one semester done already in the spring of 1945 and when my parents moved to Prague, I could finish my studies there with students of the Charles University who began to study before the War. These students were moved through especially quickly. It turned out though, that the advantage of graduating so early led to a duty to serve in the military service for two years. My colleagues who had not studied so quickly and graduated much later, served only 6 months because the legal conditions for the military service for doctors changed in between.

Nevertheless, I was not sorry for this long military service. It was comparable to being sent to a medical practice somewhere in a mountain village. I had to work as a general practitioner not only for the military personnel but also for the civilians in places where the civilian doctor was far away. The military service was just an intermission in my career as a psychiatrist.

After graduating, you couldn't choose where you went. I always wanted to do neurology, so when I got a letter from the Ministry of Health saying that I should begin to work in the Hospital for Brain Disorders in Kosmonosy I was quite happy. I thought that it would be a hospital for patients with neurological disorders. When I got there I found it was a psychiatric hospital with 1200 patients. At that time, even the word psychiatry because of "psych" was felt by the Communist government as something which belonged to idealistic philosophy.

What was it like there at that time?

As I said there were about 1000 to 1200 patients in the Hospital and only one psychiatrist – the Director - who was a native Bulgarian. The first thing he told me when I came was that I would be on duty the next day. Then, we went to the wards to make the rounds. The patients were all shouting and screaming. He warned me never to go there without being accompanied by nurses. It was a shock for me to see such aggressive patients and patients in catatonic stupor – I still have a vivid recollection of a patient standing in a corner on one leg. I was told that he had been doing it already for months. I saw patients in bizarre clothes and in bizarre positions, some naked and making obscene signs. Many patients just sat at large heavy tables starring at the wood and leaving their nasal secretions drop on it. The patients came to the Director and to me asking for an immediate discharge menacing or begging, arguing that they were not mad and that it was due to a mistake or due to the activity of their enemies that they had been sent to this "prison". Many patients mumbled and/or communicated aloud with their voices. Often they tried to grip my hand and to hold it as long as they could. Often the nurses had to liberate me.

What was available for treatment at the time - ECT, hydrotherapy?

ECT was used. Hydrotherapy was not used. Insulin coma treatment was introduced after I came to the Hospital. I believed then that it was effective in schizophrenia. Later, I realised that the more important mechanism of its action was probably social and psychotherapeutic in some sense and not a biological one.

I learned that during the War, in the Kosmonosy Hospital, there had been a number of "special treatments" (Sonderbehandlung) for patients with a serious condition - oligophrenia or schizophrenia. I found some records of this. Some of the patients had been deliberately injected with tuberculosis and killed by the German doctors according to some protocols. Others had been sterilised. Unfortunately when I realised the importance of these records and went back some years later to find them notes, they were gone. Apparently some officials had come and removed them.

Apparently there were a number of things that happened around Europe at this time. For instance in Vinatier hospital in Lyon they were saying to me that while there was no order to kill any patients it was clear that food, which was short, should not be given to some patients. Did you come across anything like this?
This I didn't see. You must remember I wasn't there during the war, myself. The Director told me a story about a patient who was sent there by the court. He apparently had been a miller and had been accused of saving up food for the resistance. For such a crime there was a death penalty. But when interrogated by the Gestapo all he would say was "I shall bring you two sacks of flour". He repeated this so often, whatever they asked him, that even the Gestapo decided he was mad and they sent him to the hospital.

He repeated this phrase in the hospital whenever he was asked anything but there were no other signs of psychiatric disease. So it was clear to the Director that this was no psychiatric disease. He tried several times to get something else out of the man but he couldn't - "You can tell me the truth, I know you're not mad". When the War was over and the Russians came, he said to the man that he could tell him now what was really the case but still "the patient" said "I will bring you two sacks of flour". Nothing else. This was puzzling but the Director discharged him. The next day he came back with a wagon with two sacks of flour in it. It helped the hospital a lot. This was the kind of story you got from this period. It has stayed with me.

Coming back to my work in the hospital, I was not only a psychiatrist for the patients. I was also their general practitioner. There were no other specialists available. I had to do dentistry and obstetrics - as well as the psychiatric care. At this time, you must remember, psychiatric patients couldn't be sent to a general hospital. Because of this training and my experience during the military service, I still feel that I understand the medical problems of psychiatric patients in a way that some other psychiatrists who have not had this kind of training do not. Also, I think that I understand well the problems of the general practitioners.

After the War as I understand it there were only a few Czech psychiatrists left.
Yes. There were only 40 in the whole country, which had had 15 million people before the War. Many of the psychiatrists in the pre-war Czechoslovakia were

politically left-minded intellectuals or Jewish, some of them both Jewish and Communists. If they did not succeed in escaping abroad, they perished in the concentration camps. Those who emigrated, did not come back.

This must have left a huge vacuum, with very few senior figures left.
There were about 4 professors. In the main, those who were left all belonged to a German organic tradition in psychiatry - interested in histology and other such aspects of the organic approach. One of the most influential professors was Myslivecek. For me, another figure was important - an assistant professor of psychiatry at the Charles University, Dr Taussig. I never actually met him. But before the war, he began to write a textbook, which really was a series of his lecture notes. These notes were published after the war as several entries in a medical Encyclopedia. When anyone asked me who my teachers were, I used to say this Bulgarian Director of the hospital, Dr Danov and Dr Taussig who was sent to Auschwitz in 1942.

Given such grim conditions in the hospitals around this time, did you stay psychiatry?
Well there was a certain opportunity, even during the communist regime, to follow our interests. Already during my studies, I spent summer vacations working in the Neurological Department, where Professor Henner was the Director. There was also a possibility to state a preference after my studies for what I wanted to do, and so I wrote a letter in 1949 saying that I would like to do neurological work in this Clinic. In 1956, I got a reply saying that now there was a vacancy. But by 1956 I had seen the first effects of chlorpromazine and I was no longer interested to move to neurology which seemed to me to be a static branch of medicine compared to psychiatry.

When did you get the first batch of chlorpromazine or when did you produce your own phenothiazine first?
We heard and read about chlorpromazine early in 1953. One of the advantages of Kosmonosy was that the Director had good contacts with clinicians working in Germany and elsewhere and because of its German tradition, the library of the hospital was quite good. We got our first batch of chlorpromazine in 1955 but we had already known earlier about Laborit and artificial hibernation. Because we couldn't get chlorpromazine, due to my close contacts with some pharmacologists in Prague we could get an antihistaminic called Theadryl - moxastine teoclate. We tried this out on psychotic patients and the effects were quite good. Many patients got better. We used this during the 50s and even early 60s because the supply of drugs was poor. Sometimes we could get phenothiazines and other times we couldn't get them. Whenever we were in short supply of phenothiazines, we shifted the patients to moxastine and it helped.

Was this a phenothiazine antihistamine?
No it wasn't. Just an antihistaminic.

Now this is interesting. You're clear it was having some useful effects.
Yes. We published on this (1). The effects were antipsychotic even though it was not a phenothiazine and there were no clear extrapyramidal side effects - it was rather like a sedative neuroleptic comparable to chlorprothixene or

levomepromazine. At the time we could introduce phenothiazines - these “Capitalist drugs” to the Czech Republic under the mask of drugs that helped with sleep treatment according to the Pavlovian doctrine which was the official medical ideology. There were attempts to induce sleep by conditioning, but usually we had to use barbiturate hypnotics. Moxastine could replace hypnotics – at least in part.

But did these drugs continue to do some good after the sedative action had faded away?
Yes, they did, at least in the majority of the patients. With the rise of the dopamine theory of schizophrenia, histamine fell in oblivion. Only recently, the role of histamine pathology in schizophrania has been emphasized again – for instance by J.C.Schwartz.

I learned soon that to respond to treatment was not always for the best. One patient I remember was a lady, suffering from schizophrenia, who had command hallucinations, which ordered her to kill her two children. She did. Later she responded to our moxastin and a psychotherapeutic approach and got some insight. Afterwards she told me Doctor you should never have cured me. Now I am a killer of my children. Before that I thought I was saving them from the Devil. This has stayed with me as a reminder of how our interventions may produce complex outcomes.

Another patient I remember had auditory hallucinations and a delusion that around his house there was a black beast, the size of a cow, which had bloody red eyes which were like flames, which was stalking him. He heard persecutory voices around his house denouncing him. Fortunately, the Director also saw this man and he too was persuaded that this man had a florid schizophrenia. After about 10 days the police came to the hospital and ordered the man to be discharged immediately. These “delusions and hallucinations” it seems were all true facts. This man had been organising a co-operative of a Soviet kind among the farmers in his village, which meant the loss of their private property. This was in the time when the communists took over and the farmers tried to defend their houses and fields. They had some kind of radio-equipment installed in the cellar of the man’s house and broadcasted commentaries about the situation in the village in which they were saying that such and such a person might have to be killed because they organised a communist co-operative. There really was a machine, like the cow he was describing. This brought it home to me that even fantastic and bizarre hallucinations and delusions might be true and I have been very cautious about this ever since.

I also remember a young girl of about 17 who became hebephrenic. One of the really odd things is that we don’t see this kind of hebephrenic presentation so often anymore - they used to be about 15 - 20% of schizophrenic presentations in the early fifties. Anyway this girl had hebephrenia with all the classic signs. I read a paper by Canadian psychiatrists, the Sackler brothers (2), on the possibility to treat schizophrenia with testosterone. I still remember the mixture - we should give 100mg of testosterone and 3mg of estrogen daily. After about 6 weeks, the patient was no better but after about 2 months she improved so much that she could be considered clinically recovered. But when we began the treatment she was a young and attractive girl and her weight was 55 kg and afterwards it was 72 kg and she was much less attractive. This was before we had chlorpromazine. I’m sure the

treatment was good for her but this introduced me to the idea that weighing the benefits against what the patient has to pay in terms of adverse-effects is more important than we thought at that time.

This also motivated me to get interested in endocrinology. There was an influential book by Manfred Bleuler at this time on endocrine treatments, covering thyroid hormones, steroid hormones, insulin and the sexual hormones.

Was there any thinking about what was wrong with the patients from an endocrine point of view?
Not really. The approach was that the patient had a mental disease and in a sense we changed the mental disease by giving them an endocrine one instead. Thyroxine treatment in periodic catatonia was an example.

Did chlorpromazine and the phenothiazines make a big difference to all this?
Yes, a dramatic difference. Within a short time, the whole atmosphere changed. Afterwards it was considered as a joke but the greatest benefit, in the first instance, was for the nurses in the sense that the work in the mental hospitals became comparable to work in any other hospital. The joke was an answer to the question whom did the neuroleptics really help and the answer was first of all the pharmaceutical industry, second the nurses, then the doctors and the patient was only the fourth or the last beneficiary.

One of the interesting things about chlorpromazine tablets at the start were that they were considered dangerous to touch. There were many allergic dermatologic reactions to it among the staff. Some nurses had to transfer to other jobs than psychiatry because of the severity of their allergic reactions. In some places, for instance in the Soviet Union, they had a special room in the hospital where they administered chlorpromazine, using gloves. The interesting thing about this is that there really were some very severe dermatoses and they were quite frequent, but of course you don't see this at all now.

This seems to have been a common and world-wide phenomenon and not just a rare Czech one. Did this happen both patients and nursing staff or was it mainly nursing staff?
It was mainly staff. There were other complications in patients. There was pigmentation, including pigmentation of the eyes and photosensitivity. Some patients, even now, like this photosensitivity effect in order to get a sunburn.

How do you explain this? Was it some hysterical reaction or was it something Rhône-Poulenc were putting in the pills at the time.
I don't know. I once asked our pharmacists about this and they said there was no change in the constitution of the pills. I think it had more to do with the reactivity of both the patients and the staff and a change in the frequency of certain kinds of allergies in the population. You find from time to time that certain allergies appear and others disappear.

We used to see jaundice in 3 – 5 % of patients treated with phenothiazines but now you don't see it at all. The other thing for me is tardive dyskinesia. Usually if it

appears, this is supposed to appear after two years of maintenance treatment. Up till the mid-60s, I had many patients on chronic treatment for 5 or 6 years or more but it was nearly non-existent or very rare. Since the mid-1960s it seems commoner. So it seems that there can be changes in the reactivity of the patients.

So the psychiatric syndromes are changing and both acute and chronic reactions to the pills are changing with some things vanishing and others emerging – its all very strange isn't it?

The ideas also appear and disappear and re-emerge. The only research that I could do in the 1950s was work that was consistent with Pavlovian theory. So we spent a lot of time elaborating conditioned reflexes not only in laboratory animals, but also in patients. I was not satisfied with Pavlovian philosophy so I tried to do experiments to test some aspects of this. This led me to develop a way to examine conditioned reflexes in patients. There was a method introduced by Ivanov-Smolenski, which was called a verbal-motor method (3). I had no equipment to do it as they did it in the Soviet Union, except sphygmomanometers which measure blood pressure. I would inflate the cuff halfway and I could measure on the sphygmomanometer how much the patient was responding to a stimulus when the task for them was to press the cuff and raise the column of mercury, while elaborating a conditioned reflex. They would have a light, which flashed, or a buzzer as the conditioned stimulus and a command to press the bulb afterwards as a model of an unconditioned stimulus. Schizophrenic patients could elaborate these reflexes quite readily. They pressed the bulb already as a response to the light or buzzer and did not wait for the verbal command. The reinforcement was to be told "Well done". Part of the trouble was that the control healthy persons didn't elaborate "conditioned reflexes" to the light or the buzzer so well as the schizophrenics. I explained this in Pavlovian terms – that the patient got much more reinforcement out of a "well done" than the controls because they were dependent on the doctor (4,5).

When such a model of a conditioned reflex had been elaborated the light or the buzzer was changed for the word. Instead of switching on the light I said, "light". The healthy controls were now much more likely to press the bulb or ask whether they had to press the bulb – usually asking whether the switch was wrong. The majority of the schizophrenic patients, who responded to the light or to the buzzer by pressing the bulb, did not respond to the word. They just ignored it.

This was in 1959. I remembered all this recently when I read the work of Timothy Crow. In Pavlovian terms there are hierarchies of stimuli. First order stimuli are things like lights or buzzers while words are second order stimuli. First order stimuli belong to the first signalling system. Second order stimuli belong to the second signalling system. In the schizophrenic patients when I spoke the word "light" instead of turning the light on, there was no response. The healthy controls in contrast responded by pressing the cuff or asked, "is there something wrong with the light – have I to press the bulb?" When you read people like Crow now, they are reporting essentially similar findings. The Pavlovian "disorder of the cooperation of the two signalling systems" is quite comparable with Crow's "disorder of the reversibility in the transition between the signifier and signified as of the element of indexicality".

The thinking was if we knew how to provoke some of the features of schizophrenia we might be better able to treat it. I think, simple though it was this was a very good model in some respects. We considered LSD-induced states to be a good model. When control subjects took LSD they were liable to have similar difficulties as the patients suffering from schizophrenia. They responded well to the light and buzzer but not to the spoken words “light” or “buzzer” When they took chlorpromazine their responses to words improved and the symptoms of their experimental psychosis disappeared (6,7,8).

Another interesting difference between schizophrenic patients and healthy control was in the intensity of the pressor response. In healthy controls – usually without their conscious knowledge – the response was higher when the intensity of the stimulus e.g. buzzer or light was higher. There was quite a good positive correlation. In some of the schizophrenic patients, there was no correlation between the strength of the stimulus and the strength of the response. In other patients, especially those who were hallucinating there might be a “paradoxical phase” according to Pavlov, where they responded most vigorously to the mildest stimuli. So this shows you something of what we could do under very primitive methodological conditions.

Later, we tried to induce changes in the mental state by delayed auditory feedback and compared patients with healthy controls under the influence of LSD (9) and the effects of neuroleptics in these conditions (10). Again, there were some similarities between schizophrenia and LSD-alteration.

It makes you wonder how much we have moved forward at all.
Yes I was thinking this yesterday when in your lecture you mentioned that isoniazid had been shown to be an antidepressant. We were very close to the pharmacologists. We used hydrazides on their advice and found some of them to be antidepressants. I can even now remember some of the names of depressed patients who improved. We used isoniazid but we also used cyanazide, which as far as I know was not a monoamine oxidase inhibitor, and this result was published in our Journal of Physiology (11). This was at some time in the late 50s.

We were able to keep up with all these developments because there was at the time an active Czech pharmacological school, where Professor Votava and Benešová were very active. Professor Nahunek, a psychiatrist in co-operation with them, developed a theory, that the neuroleptic drugs, which did not cause extrapyramidal symptoms, could be useful in depression and so we looked at levomepromazine and thioridazine and sometimes also we would use chlorpromazine. According to a broader theory of that school, anticholinergic action should be connected with antidepressant and anxiolytic effects.

You’ve mentioned one or two key people but what about Miroslav Protiva because he seemed to be the genius behind producing a whole range of Czech versions of the Western drugs. When did you meet him?
He was in the Institute for Pharmacy and Biochemistry but even before I met him, I had close contacts with a number of people from his Department. One of them was a pharmacist, a very modest person, but with bright original ideas, Bedrich Hoch. At that time, the people of the Institute for Pharmacy and Biochemistry came to our

wards to see some of our patients. We also went to their Institute to see the rats and rabbits and the effects of the drugs on them. When Bedrich Hoch came to our wards, saw that we were having great difficulties with anxious patients. At that time these conditions were called anxiety neuroses. He suggested that it was well known that when people were tired from physical work that they were much less anxious. And what happens when you are tired from physical work or training? Well, lactic acid builds up in the muscles. This is produced by physical work. So he suggested that we try lactic acid injections in these patients. He came along and we tried to treat some patients in this way. Not many because of course what we found was these injections made some of the patients much worse. They provoked panic anxiety. When Donald Klein came out with his Panic Disorder theory a few years later, I realised that we had had the same phenomenon in our hands at the time and had missed it.

But to come back to Miroslav Protiva. He was one of the best synthetic chemists I have ever known. I think that he was on a comparable level as Paul Janssen. They were of course friends. He discovered several series of seven membered ring compounds, among which one of the best known was dosulepin (Prothiaden), called dothiepin in England. It was quite easy at that time for us to test out these compounds because there were no strict regulations by the State or ethics committees. After the chemists made the compounds, one of the pharmacologists, usually Professor Votava would try it out on himself.

What can you tell me about Zdenek Votava?
He was a pharmacologist who was interested in CNS compounds. One of his close colleagues was Olga Benesova. Votava had been a pupil of Professor Helena Raskova, a lady who had been a leading Czech pharmacologist for decades and held important positions in the international pharmacological organizations such as IUPHAR. She helped many Czech and Slovak pharmacologists to get grants and to work in the USA and elsewhere in the world. Professor Raskova helped Czechoslovak psychopharmacology and me a lot. She thought that I was - at that time - a rare psychiatrist who did not just swim with the tide of the current psychological theories and was seriously interested in the biology of the mental disorders. So she provided a sort of pharmacological basis which provided a strong support for the Czechoslovak psychopharmacology forum.

Votava had an interest in conditioned reflexes and knew well how to elaborate them. His method was to investigate both the pharmacological properties of the drugs and also their behavioral effects by means of conditioned reflexes. This was a quick and simple way to look for predictions of clinically useful effects. If there was no toxicity but there was a clear effect on the conditioned reflex tests there might be something in the drug. Or if it reversed the effect of ptosis in mice for instance after reserpine, he would try it as an antidepressant. If it inhibited conditioned emotional responses, it could be tried as an antipsychotic.

Votava and Protiva were based at the Institute of Pharmacy and Biochemistry, which was financed by the Czechoslovak Pharmaceutical Industry - SPOFA. There were quite good conditions there and they had groups of other chemists and pharmacologists working with them. In about 3 to 4 months a drug which was

synthesised by Protiva would have been tested pharmacologically by Votava and it was then assessed in patients. I had a clinical ward in the Institute of Psychiatry where I did a great deal of the testing. Professor Raskova was at this time chairman of the Pharmacological Board of the Ministry of Health. When there was some evidence that according to the animal tests the newly synthetized drug was not toxic, I could get very soon the permission from the Ministry to use the drug in patients. Professor Raskova would agree saying to me “Oldrich, as far as I can judge this might help the patients, so it is your responsibility now”.

I understand you and Votava used to have this drug often yourselves first, one of the things you commented on was that you sometimes knew there was a new drug around when you saw Professor Votava lying on the corridor.
I had the feeling that physically I was stronger than Votava and also that I knew something more about the real impact of side effects than he did, so I felt I should take a role in this testing. I was perhaps more cautious when choosing the dose. The pharmacologists did some calculations beforehand as to the right dose but sometimes they got it wrong. So, it became well known in the Institute for Pharmacy and Biochemistry that Protiva had synthetised a new drug when Votava was found in an orthostatic collapse in the corridor of the Institute. Very often as well, when the pharmacologists made estimates of the right dose for patients, I would feel nothing, which left me with the impression that we can’t necessarily judge the impact on patients from the effects on healthy volunteers. You cannot expect that someone who is not anxious is going to have the same response to an anxiolytic as someone who is. Or that someone who has not got a headache will have the same response to an anti-headache pill as someone who has. But this idea, that because I am not ill I will not feel the effects, probably also led me to be a volunteer for tests of psychotropic drugs in an LSD induced state.

For about 6 years, as part of this human psychopharmacology, we experimented with the hallucinogens and other drugs. Many of us had LSD and other drugs in combinations with chlorpromazine or reserpine. Then, we found that volunteers had very bad reactions to the combination of LSD and reserpine. They suffered after-effects for some time afterwards, which could be interpreted as a worsening and not an amelioration of the LSD-alteration (12). Because reserpine was considered as an efficacious antipsychotic at that time, I felt that LSD could be not a good model of schizophrenia and abandoned the idea that we would test new psychotropic drugs on this model in humans.

Did this work with LSD at the time have any influence on Stan Grof who later emigrated to the USA and used LSD a lot in holotherapy as he later called it – aimed at remembering birth events and past lives?
Stan worked with me but not for very long, perhaps a year. His brother Paul worked with me for much longer. It was because of his experiences with us that Stan got the idea that working with LSD was the best way to do psychotherapy and he later developed his ideas in this area. If the reactions can be controlled well there is something to be said for this approach and also I still think that experience with LSD could be helpful for nurses and doctors to get some experience of these things. LSD in fact could give you some insights on the psychological management of mental disorders

Czechoslovakia was a small country, so you had to try and keep in touch with colleagues who were more interested in psychotherapeutic approaches. I was asked several times to come and talk to the society for psychotherapy in Czechoslovakia. The Chairman of this society was Ferdinand Knobloch who lives in Vancouver, now. Essentially, I always tried to combine the therapeutic effects of drugs with psychotherapeutic approaches. This is now of course a very common practice. But even now, you meet doctors who do not wish to spoil the psychotherapeutic approach with drugs. Speaking to them, I usually argue that in certain cases of diabetes, which are not very severe, you can manage these by "behavioural" means alone. It is only when it gets more severe that you need to administer insulin. In the case of mental disorders, there is a good case for starting with psychotherapeutic approaches and only if you are not successful to proceed to using drugs. This gets tricky if you have a case where you have some feelings that the case you are seeing might at some point in the future develop into a full-blown schizophrenia. In such cases the use of a low dose of medication from early on seems like a good idea – this is in contrast to the diabetic model.

In the mid- to late 1950s while people like Protiva were producing the drugs, you began to get interested in clinical trials and rating scales. How did this develop?

We had some old psychiatrists in Czechoslovakia who were quite hostile to this approach of reducing syndromes and clinical signs and symptoms to numbers and this influenced me at the start. When I read the first papers trying to use statistical methods in these clinical situations, I also thought this was impossible. Everybody is a different individual and every situation is individual. You cannot compare them using figures in this way.

But I was lucky. Very early in the psychopharmacological period, I had to travel to a meeting in Bratislava. I went by plane and on board I was sitting between two wine experts and I was able to listen to their discussions. They were going to a meeting comparing wines and they were discussing some aspects of their work. They were talking about the wines in terms of their being long or short, light or heavy, full or not. They were comparing on them very many different dimensions. It struck me that their problems were the same as mine. If this could be done for something like wine, why not in the clinic? I asked them what was the reliability of their ratings, their inter-rater reliability. They told me that it was perfect, they almost never make a mistake. So that made me a convert and I went on to elaborate rating scales.

At that time, the BPRS had just been produced from the Lorr rating scale. I tried to develop our own psychotic rating scale together with Stan Grof and another colleague Joseph Vana. We elaborated a rating scale called FKP. This was for all psychoses. But one thing about it was that I considered that ten of the items could be rated in a bipolar way. For example, mood can be rated as something more which was positive or less which was negative, the continuum being from depression to mania.

In the case of depression, I got to see the Hamilton rating scale. I thought it was good but that there could be some modifications of it. There are a number of items

on the Hamilton scale such as early morning awakening and diurnal variation of mood that are designed to pick up certain forms of depression rather than to rate the severity of the depression per se. We modified it so that we left out these items. Then we had an FKD-scale for depression and an FKP-scale for psychosis. We began using the FKD-scale in 1962 although it was only published in English in 1966 (13,14). We also had a side-effects scale VP and DVP (15). I had it when I visited the NIMH and the Biometric Laboratory of the George Washington University on a grant in 1969, where I met William Guy, the man who devised the Clinical Global Impression Scale. He incorporated my Side Effects Scale as TES –Treatment Emergent Scale in the ECDEU manual of rating scales.

One of the interesting aspects of all this is that we really do not measure side effects at all properly. Perhaps this is because of the nature of clinical trials we do in the West. But up till recently, we have been relying on spontaneous reports rather than trying to collect data systematically. As a result we really do not know the proper incidence of any side effects or even the full range of side effects.

Yes, I made some methodological work on this. I compared the results when you ask the patient systematically about every item on the rating scale or just ask them if they had any side effects. The difference was tremendous. When we systematically investigated side effects, there were over three-times as many side effects picked up. But on the other hand, there might also be some bias in asking systematically about side effects that you will suggest things or record things that really are not causing any problem.

When you read the chapter by Paul Grof in Tom Ban's book, you find that he says that by the early 1960s your department had almost gone biological psychiatry and clinical trials mad almost. Everyone who entered the clinic was being randomised to something or other and no-one ever knew what any patient was actually getting.

I don't think we went really mad about this. Paul is right that it was not always easy for doctors who did the ratings to speak to patients, when they did not know what drug the patient was getting. The medication was discussed openly only when the patient was discharged. Otherwise, I still think that the conditions of the "continuous controlled trial" were more natural and better accepted by the patients than the usual way when you have the majority of patients in your ward treated openly and some – who fulfill the criteria of being assigned to a trial – treated under double blind conditions. It creates a difficult social situation in the ward. If all patients – without exception – are treated under controlled conditions, the difficulty of dealing differently with a part of patients does not exist.

One of the first studies we ran was to compare dosulepin (Prothiaden) with imipramine and we found that there was not a statistically significant difference between them. I suggested in fact that we should drop dosulepin on the basis that it was not superior to imipramine and if we had imipramine surely that was all we needed. Fortunately, Professor Eugene Vencovsky, a well known figure in clinical psychopharmacology in Czechoslovakia, published a report about six patients treated under open conditions and recommended that dothiepin should be produced and our industry followed his advice.

But you have to remember the reliability of the rating scales we were using at this time still had not been fully established. Someone I had the great honour to have been in a friendly contact with at this time was Kurt Freund. He was in the very strict German research tradition. At that time, the reliability of our rating scales was not yet tested and as a result the publication of results of several of our trials was postponed because Dr Freund did not recommend it.

Under his influence, I decided to do something more than just to test the reliability.of the scales, which I should tell you about. I wished to weight the items. The Hamilton scales and other scales are checklist scales, where all the items are given equal weight. Normally you don't know whether the difference between a score of 5 and 3 on one item is the same as the difference between a 3 and 1. So we did a study with all Czech psychiatrists, asking them to estimate the distance between different scores and also what was the weight of each item for the severity of the psychosis or the severity of the depression. We began to use the weighted scores when rating the symptomatology in our patients (16).

But you weren't just using rating scales, you had all of the clinicians doing randomised control trials.
This was very easy at that time. I used my connections with the Institute of Pharmacy and Biochemistry, with Protiva and Votava, to get a supply of drugs which otherwise would have been expensive for the clinicians to get. In addition, Western and other drugs were not always available, so this was a way to ensure a supply. The clinicians who co-operated in the multicenter trials I organized could be sure of getting the drugs.

Where did your ideas about doing randomised controlled trials come from – why not just go on clinical impressions?
Once I went to Yugoslavia on holidays and the only book I brought with me was a book on multivariate statistics by Donald Mainland. It really was easily readable. It explained very clearly all about the silly and stupid errors clinicians can make when they get an impression whether something works or not. It explained in a way that almost made you laugh so that my wife at one point wondered if it was some sort of humorous novel I was reading. After reading this I was convinced that we must stick to work that was methodologically controlled, that involved randomisation, if we wished to get scientifically acceptable result.

When did you begin the first trial then?
It was in 1959. But because of Kurt Freund and his concern for methodological rigour I was not allowed to publish the data. But my wife who is also a psychiatrist had participated in the trial and she published the results. This was my cover. Actually, she actually did much more than act as my cover. She has seen the patients assigned to the trial and when I came home and talked about many of these issues, she pointed out mistakes and made very significant suggestions.

After a few years you had got to the point where you were doing an awful lot of clinical trials?

Yes and we got to the point of running multiclinical trials, along the lines of the Veterans' Adminstration Projects and the NIMH Projects in the United States. Several hundred patients were treated under these conditions. Generally, however, we didn't use placebo as a control. We just had placebo washouts.

Having had the experience with these large trials, I introduced the continuous controlled trial (17) in the Research Institute, with conditions which were even more strict. When the patients came to the Centre, from the beginning of their stay they got placebo unless there was a risk of seriously aggressive behaviour for instance in which case they might go immediately on active treatment. At some point then in the next three weeks, the patients on placebo would be switched to active treatment, unless of course they had already responded to placebo. I still have a sample of about 36 patients, who in spite of the fact they were diagnosed as having schizophrenia have not received neuroleptics because they improved sufficiently on placebo during the first 6 weeks of hospitalization. This small group came from a larger group of over 600 patients (18).

How did all of this clinical trial work fit in with the fact that the Czechs and Slovaks had probably the first national Psychopharmacology Association, before either the Americans or the Germans, as I understand it.
It was in 1959, we formed our group. I think we are the oldest group in the world to organize regular annual meetings. It happened partly by chance. One of my good friends, Jaromír Rubeš, a psychiatrist, became a Director of a spa in Moravia, Jesenik (Grafenberg). He invited the members of the research commission of the Ministry of Health to spend a week there, reviewing any progress in the previous year. He offered us a week in the beginning of January when the spa would otherwise have been empty. When he invited us, I suggested that he also invite others who were interested in psychopharmacology because he had enough rooms to accommodate all of us and we could discuss the results openly. This was how the annual meetings started. The first one was in 1959 and they have been running ever since.

I had a problem. I became the President of the Society and I remained the President for 35 years. I couldn't get rid of the job. I tried hard to stand down but my friends warned me against it because under the Communist system if somebody resigns everybody assumed you had been politically pushed out which meant that you would be fired also from your job, or that you had done something really very wrong. Nobody would understand that it was your free decision. So it was only when we got our freedom that I could change the rules and introduce an obligatory system of Presidency Elect, could give up the office of the President and remain just on the Council.

From the beginning, I insisted that our meetings had to have pharmacologists, physiologists and psychologists as well as psychiatrists and also chemists like Protiva. I was also against the idea of having separate sessions for pharmacologists and separate sessions for clinicians for instance.

This is what you see in the West a lot now and it's a problem because its harder and harder now to find people who can see the larger picture.

I can tell you it was quite difficult even for us to resist this. I had to veto some of the decisions of the organising committee. If you separate the sessions, I said I would have nothing to do with it. I really think that this interdisciplinary focus helped us very much.

One of the problems always was to get results out of the clinicians. You give them the drugs and train them on the rating scales. By the way, I am not impressed with the inter-rater training Western companies do now. They have a video of a patient and get clinicians to rate aspects of the psychopathology and they compare the results. This is a nonsense because in clinical practice you speak to the patient and can ask questions to be able to understand his symptoms and only then you do the rating. Really rating the patient from a video tape is just a test of whether people understand English.

It isn't only a test of whether they understand the English language but it tests whether people can adopt a very Anglo-Saxon set of concepts which underpin most of the current scales. This is a very different worldview that the Middle European view and also very different to the Southern European view. If you go to Spain or the South of France, they talk about impulsivity in a way that they clearly understand but which your average English speaking psychiatrist has great difficulty with. The Anglo-Saxons don't have emotions or impulses, they only have thoughts!
This also applies to the gestures and facial expressions of the patients. These vary hugely across Europe so that again rating a so-called standard patient on a video is a nonsense. They don't all have the English poker-face.

Yes it's hard at times to see how the English could work out that someone has a negative syndrome.
Anyway in 1961, I introduced another sort of continuous control trial to the research ward. The patient, or their relative, when they came to the Institute had to sign that they agreed to be treated with drugs where they wouldn't know what the drugs were and that they might even be placebo. So they were being asked for a general consent for their whole stay in the Institute. One of the motivations why they agreed to this was that they knew whatever the circumstances, they would get the best of care that was available. Everybody knew that there were difficulties in getting hold of Western drugs at times, for example.

Research then didn't have a bad name in the Czech Republic did it, given that only a few years before in the Second World War research had a very bad name? Were they happy that your motives were good, that you weren't some kind of Nazis?
There were no problems that I remember.

This is interesting. There are huge variations worldwide on this issue of how prepared people are to trust doctors. The Japanese it seems are not keen to volunteer in this way and neither for instance are the Dutch. The Americans largely recruit to trials by paying patients which has its own problems.
I think right up to the present day, there is no distrust of this kind in the Czech and Slovak Republics. There is no worry about exploitation. It seems that some

journalists may be trying to generate it. But until now, people trust doctors, maybe more than they should. I am an editor of a journal Remedia populi (Medicaments for people), aimed at educating patients to become partners in the therapeutic process and not to just accept a paternalistic approach. The intellectuals understand it but many people in the street are not interested. This is an advantage for research maybe. One of my criticisms of current informed consent forms is that what we do is often not fair. The main thing is whether the patient trusts the doctor rather than whether they have been informed about every single detail of what a medication may do. You can have 10 pages of side effects but at the end when the patients read it, they will very often turn to you and say "Doctor should I sign this?" If I say Yes, he signs. It's just a game for legal purposes it seems to me. It is myself who remains fully responsible – even for the "decision" of the patient to sign.

This system of the continuous controlled trial worked for almost 12 years. It allowed us to really compare drugs, which were introduced during these years with drugs, which had been introduced several years earlier. I made checks of the reliability of the ratings across the years. For example, we used clopenthixol in 1964 (19) and I introduced it again in 1967 and compared the ratings we got earlier and the ratings and outcomes were the comparable. We had some priorities, e.g. we tested high doses of diazepam in psychoses already in 1966 (20). We really had a marvellous databank but then my political troubles started.

This story reminds me of the saying that good deeds have to be punished. In 1970, the CINP meeting was held in Prague. Now I organised the CINP meeting in Prague, so I got an invitation and support from the organising committee in Paris to attend the 1974 meeting. This was standard practice. I prepared a paper on our rating scales and the issue of weighted scores for the Paris meeting.

Now, I also got an invitation to the meeting from a colleague who was a friend of mine – we were both members of the same sports club. It was like a rotary group. You had something like this even under the Communist system, although we had to pretend it was just about sport. Anyway, in 1974 this man was the only representative of the Western pharmaceutical industry in Czechoslovakia. He worked for Sandoz. After 1948 all the offices of Western companies had been liquidated but his post escaped because he was called a Scientific Research Officer, so it did not seem to be a commercial venture. Anyway, he said he would invite me to Paris and that Sandoz would pay for me. I told him that I already had an invitation but that the Director of the Institute I knew would be very pleased to get an invitation. So he invited the Director. He had a good time in Paris, stayed in good hotels, was brought out to meals. He may even have got some pocket money. It turned out that this made him afraid of having been spied by some Czech Communist agents on what he was doing while he was in Paris. He feared that the hospitality given to him could lead to a suspicion that he had too close contacts with the Western industry and that his position of Director would be threatened. Having come home he was interviewed by the police about his trip. This was "normal" at that time. Only recently, when the files of the Communist police were opened, I could read that during this interview, to cover himself, he said that they had better watch out for Vinar who is clearly very powerful if he could arrange his trip. And this marked an end of my career in the Institute of Psychiatry.

Anyway, the Ministry of Health did not agree with my trip to Paris and I was stopped from going to the CINP meeting. My post-graduate student read my paper on the rating scales (16). I don't know whether it was understood or not because his English at that time was poorer than mine. We had 2000 or 3000 patients rated with these scales, not only in Prague in the Research Institute but also in other centres in Brno, Bratislava and in other University departments and in many psychiatric hospitals. We had begun in the 1970s to put the quantified data on punch cards. Anyway, after Paris, when there was no favourable response to the report, I realised that our scales had no chance of being accepted internationally. Therefore, I advised the colleagues that there was no point in using our rating scales "for export" anymore because there was no chance that people in the West would appreciate what we were doing or adopt our methods. Since then, they have been used only in trials where the results have been published in Czech or Slovak journals. Especially after the importance of the distinction between the positive and negative symptoms of schizophrenia, I am sorry not to have been more assertive in introducing the FKP scale. It describes two areas of psychopathology. There are ten items describing symptoms which form a bipolar continuum, where we used a plus score and a minus score to express positive and negative items and there are also 8 monopolar items describing symptoms which are present or absent. Our positive and negative items overlap with the positive and negative symptoms of PANSS to a great extent.

The rating scales and all the data from our continuous controlled trials were separate from the usual documentation on the patient. When the patient was discharged we took the research data and we had just begun to put the data on punch cards as I explained when dramatically the Director advised me that I change my position and my role to the University Clinic. I had to leave that day. From that day on, he didn't communicate with me at all. I called him by phone but I couldn't get through to him. I sent him several letters but he answered none of them. I waited at the end of the day for him to leave work at the Institute and met him on a path in the park of the hospital and tried to speak to him but he wouldn't stop. It was clear that there were some problems but what?

On the day I was thrown out, I had to abandon the Institute in 24 hours, so I couldn't collect any of the data, even if I had been allowed to take out this kind of luggage. It remained there. Seven years later I was able to get in to the building again but the files were all gone. We had just begun to work on the data when I was thrown out. For instance, I was unhappy with the idea of looking at the effect of the drugs on overall outcomes and we had begun to correlate the effects of different drugs on different symptoms. We had data on a range of neuroleptics and we also had data on hallucinations for example and the effects of different neuroleptics on hallucinations. We might have been able to decide if one or other neuroleptic was better for hallucinations. We also had early data on efficacy of different neuroleptics on different receptors and we were able to show for example that there was a negative correlation between activity on dopamine receptors and some of the negative symptoms (21,22,23). When I spoke to Professor Carlsson about this first, he said to me that this was a nonsense, there must be some mistake. But of course, this is now thought of as the orthodox view. I am trying to do the same thing again for some of the newer antipsychotics, but unfortunately not with my own clinical data

obtained in very well defined conditions.

What a disaster!
Yes especially now. One of my old ideas was that histamine was more important than people thought. Maybe Eugen Bleuler was right I thought – his accessory symptoms which overlap with the positive symptoms of schizophrenia were just some sort of defence against the underlying disintegrative process. In this case histamine is something which in somatic medicine had a role in defence against antigens. On this basis, the accessory or positive - symptoms could be viewed as some sort of allergic symptoms and antihistaminics might be useful in their treatment. This is a very primitive idea but we had a chance to look at it and in our correlations, the affinity for histamine receptors of the various drugs really did have several very high correlations with a number of features of the mental state – such as critical insight (21). We had got to the stage of publishing this in English but only in one of our own journals. I hadn't got all our data fully analysed so that it could be sent to a Western journal when everything got interrupted.

So up to 1970 Czech psychopharmacology is marching in step with Western psychopharmacology. You're producing just as good drugs, maybe doing better clinical trials, you have the first national psychopharmacology association but after the mid-1970s things change in perhaps both good and bad ways. In the mid-1970s in the West, we have a significant increase in technical capacities that do not become available as readily in the East – radiolabelled receptor work for instance. The other thing is a marked commercial development. Psychiatry in the West was not very commercialised until the mid-1970s, it did not differ so much from Czech psychiatry, but after that things change in a way that did not affect you. Now in the West, nobody thinks there's any problem having Prozac for instance. The only worry for many of the women here in Paris will be whether the green and cream capsule colour codes with the outfit they have on. In Prague, I am sure until quite recently, people were probably much more reluctant to seek help or to take pills for milder nervous conditions. I can see that this could be both good and bad. Any thoughts?
In the mid-1970s, in the discovery of new psychotropic drugs the emphasis shifted from behavioural pharmacology, which was very cheap to biochemical psychopharmacology where you really need very expensive equipment. This opened up a technical divide of 4 or 5 years between what was happening in the West and in the East. But this was not always because Communist Czechoslovakia was so poor but because of the "planning process" – the bureaucracy. You had to ask for things in triplicate and it went through all sorts of committees and when it was finally approved the equipment you had asked for might be already old-fashioned. It was a tragedy. You could have bought for the same amount of money or even cheaper, something which was much better. But no - you had to get what you asked for three years previously. So we lost out.

Also after this period, you found that a greater number of the drugs which had been introduced in the West, neuroleptics or antidepressants, were not bought in sufficient amount for us. In part this was because the drugs we were producing ourselves were not marketed in a way that made money that would have allowed us to buy

other medicines. One of the few exceptions was dothiepin – Prothiaden, which was sold worldwide. The other drugs did not make money. Some of us travelled through Hungary, the Soviet Union and the rest of the Eastern block. I went not only to Russia, but also to Baku and Yerevan as well as to Estonia, where I lectured about our drugs. They always told me they would buy them but the orders never came. This brought developments to a stop. We had for example moxyphetin which according to the animal data was an excellent SSRI. We had it before fluvoxamine was introduced, but its development was stopped. So there were economical reasons why Protiva's continuing work got less and less support. From the mid-1970s, also there was less chance to export to the West or to get the drug into a clinical trial programme on maybe hundreds or thousands of patients, which was what you needed for the American market.

When the law was lifted on Western companies having a representation in Czechoslovakia, many of our psychiatrists got recruited in as labour workers to clinical trials by Western companies using instruments and methods, which I considered to have shortcomings. You couldn't raise doubts about the protocols because you found that they couldn't change even silly mistakes because it was a protocol for Western Europe and America as well as for us. But even so, these trials were much more attractive financially to our psychiatrists so they got involved and ironically therefore after we got our freedom it became harder and harder to do our own work. When I approached colleagues, they would now ask "what will you pay for it?"

What about the commercialisation that happens in the shape of National Campaigns to detect and treat depression. These campaigns are devised by psychiatrists but they get supported by pharmaceutical companies and in the West they couldn't happen without company support. Until recently you didn't have all this but now maybe its beginning.

I think that the risk of overprescription of antidepressants is not very high compared to other countries. There is still a considerable stigma to be treated with a psychotropic drug. I think this is very important particularly for people who are also somatically ill. I have been trying to educate cardiologists and other physicians in recent years to listen to the patient on these issues. I have emphasised for instance that pain might be a symptom of depression and indeed that an antidepressant has a direct analgesic effect, which can be discussed even without raising the mental aspects. In this area we are behind the West.

Things are changing though. This year you can read in the newspapers articles by psychiatrists persuading people that they need to get their social phobia treated. This has become fashionable. If they have problems with public speaking they should think about fluoxetine or sertraline. But on the other hand we have had good national statistics on the use of psychotropic drugs. What you find is that there is a much lower usage of antidepressants than e.g. in Scandinavia. It used to be only one third of the international average although now it has moved up to about one half of the international average. We also use less anxiolytics but there is a much higher utilisation of analgesics. We are higher than the national averages abroad. I suspect that many of the depressions masked as chronic pain in the Czech Republic are being treated with analgesics.

So you are suggesting that in a sense there is a natural level of drug taking and that the job is to make sure they are on the optimum treatment rather than on treatment.
Maybe yes. On the other hand, one of the positions that I was able to get when I was thrown out from the Institute was in a clinical department for the Czechoslovak pharmaceutical industry running clinical trials. These were large open trials but I could get some feedback from them. Nearly all the clinicians interested in clinical pharmacology and pharmacists during this time co-operated with me. After 1991, the majority of the employees of the Czechoslovak industry became employees of foreign firms. So, I can speak to them as to my former colleagues. Things have begun to change again. Some Western companies have approached me regarding studies facilitating the introduction of the drug to the Czech Republic. In this case, I have said that there is no point running double-blind trials because these will all have been done elsewhere and there is no point subjecting yet other patients to placebo if in a trial done abroad the difference was already proven as statistically significant. I recommend that they do large open trials in conditions of routine pracitice. I also ask them to use the clinical global impression scale (CGI) as the main outcome measure because I think this is all you need. I also insist that it should be allowed to combine the drug with other psychotropics, e.g. hypnotics to mimic the conditions of the routine practice. The aim is to get large samples, e.g. to be able to discover rare adverse effects.

I am sure you are absolutely right on this – excessive rating scales, placebos and even blinding aren't necessary if your aim is not to have a scientific evidence of efficacy. Randomisation is all you need and large numbers.
My most recent experience in this area was a study here in the Czech Republic where we had 600 patients looking at positive and negative symptoms. This was a large number for a small country. When it came to the ratings, I didn't define what positive and negative symptoms were. I just gave the clinicians a scale from 0 to 10, to estimate the impact of negative symptoms for this patient and the same for the positive symptoms. By chance it turned out that the Slovaks ran the exact same trial using the PANSS and a lot of other elaborate rating scales. We met together at a psychiatric meeting and they presented their results. They got a 17% decrease in negative symptoms and so did we using our simple estimate scales. The two groups could have exchanged slides. So I think using these simple methods we could do much larger trials and we could learn something different from these studies.

How much contact was there between the Poles, the Czechs and Hungarians?
Not so much. We had a number of Hungarian drugs. The reason for this was that Paul Janssen's father had been a representative of the Hungarian company Gideon Richter in Belgium. Because of this Janssen sold many licenses to Hungary, many butyrophenone neuroleptics, which the Hungarians could then export to all of Eastern Europe. Drugs with comparable effects were also synthesised by Protiva. Sometimes, he synthesised the Janssen drugs. He could always find a way around the patents to make our own versions of them. He used to have fun explaining to Paul Janssen how he made Janssen drugs by a different method.

So we had Hungarian drugs and our own versions of Western drugs and our drugs which you could not get anywhere else. Until today we have our own prochlorperazine and perphenazine and we also have our own neuroleptics oxyprothepine and oxyprothepine decanoate, which on a double-blind trial basis compared very well to fluphenazine decanoate. It was not significantly better on symptoms but it does produce significantly less side effects.

You've described a situation where during the 1960s Czech psychiatrists worked as a team but now you individually contract with Western companies to do studies and in a sense the industry has split you up, which means that it can dictate to the group of investigators in a way it couldn't before. The professional voice of psychiatrists has been lost.
This is true. I think the problem is even greater now in the East because the financial motivation is much stronger for our psychiatrists. So if an independent voice is going to emerge will it not have to be in the West now?

I can see what you are saying but I think we have been broken down completely – we just don't have the tradition of working together as a national group.
Still in our national meetings, we discuss this aspect very openly. People say to each other Jaroslav or whoever, you just support Wyeth or whichever company. From this point of view what the Americans do, which is to get a declaration of conflict of interest in the programme is I think very important. On the other hand at some of these Western meetings you see some of the big names hopping from one symposium to another saying that a NaSSA is the best thing ever in one and then later that day a SNRI or NARI is the best in another symposium.

Do you think that the kind of short term acute studies we have been running in the West have misled us. We seem to be having great difficulties proving that lithium, carbamazepine, valproate and other anticonvulsants work. Even the industry with their great resources cannot do it. It needs more than money it seems. It needs a different set of methods and motivations.
We published a paper on this (24). You have to use different methods if you want to judge the beginning of a relapse or recurrence in a person in remission than to evaluate the treatment response in an actually ill person. You cannot use the same methods throughout. This is where some of the scales for social adjustment may be particularly important. The classic symptom scales reflect only the endstage of a process that begins with impairments in social adjustment.

There is an interesting problem here. The other national group who have been able to work together in the way you guys did have been the Japanese and they were able to show that carbamazepine is prophylactic. But if you take valpromide, its now used in huge amounts in the US but based on clinical impression really. Clinicians just know it works but running the usual kind of clinical trial to show this seems not be possible. It seems that bipolar disorders and some personality disorders are the kinds of condition that really push up against the limits of Western clinical trial methods – at least as they have been understood up till this. It requires it seems almost the kind of datasets you had – data collected over years.

I can only agree with you. We still have patients who have been on lithium for decades. We tried to develop some methods along with Schou to look at the beginning of a relapse. We were often faced with the problem of the patient who wanted to stop treatment, who said "Doctor the only thing that makes me feel like a patient is the fact that I have to take a pill, can I not stop it?" Monitoring the effects of stopping in these circumstances led me to publish a paper on the possibility that mania could be a withdrawal syndrome of lithium (25). One of the things that triggered this thought of for me was a patient I had who went on lithium because he had had about 6 episodes of depression but he had never had an episode of mania – until she stopped the lithium I had put her on. She underwent a surgical operation. The surgeon advised an operation and that she should discontinue her lithium before the general anaesthesia. By the time she ended up in hospital she became manic and was trying to seduce the medical staff. This is something you particularly see with lithium. It's not obvious after valpromide, for instance, but even there I'm cautious. But I agree we need new methods to tackle these prophylactic questions.

Do we also need clinical groups who are really motivated to answer the question, who are not just motivated by money?
Well I agree we had this. I am sure there are still people who would do this kind of work without needing to be paid for it but the proper protocols for this kind of study have still not been worked out. We are doing something like this in post-traumatic stress disorder with citalopram at the moment. We had a natural disaster – a flood - in Moravia, a part of the Czech Republic and we are investigating whether citalopram makes a difference to the long term incidence of depression and/or panic anxiety disorder. This is not supported by the company except for the supplies of the drug and it is not being done in the form of a placebo controlled blind study but what we are doing is a systematic follow-up comparing the patients who got citalopram with those who did not.

Who else within Czech Psychopharmacology have been important?
Metysova and Benesova have been important. Olga Benesova has been a very experienced pharmacologist. She has done a lot of excellent work looking at the effects of drugs and comparing differences between the effects in young and old rats.

There is a new generation of psychiatrists doing research in clinical psychopharmacology - Václav Filip, Cyril Hoschl, Dagmar Seifertova Jaromir Svestka, Eva Ceskova, Jan Libiger, Roman Jirák and Ivan Tuma.

In the last years, I have been trying to involve other medical specialists to study the effects of psychotropic drugs in their patients. Speaking to one of our best internists, Professor Joseph Marek, he mentioned that psychopharmacology is just endocrinology of the brain.

Who was Alice Leeds – in Tom Ban's book she features in more photographs than any other person?
After the invasion of the Russians in 1968, I was invited to Belgrade, where Alice Leeds with the support of Jerry Levine, started a project of a WHO network of centres for the study of psychotropic drugs. There I met Michael Shepherd who had

a great influence, as well as Alec Coppen, Malcolm Lader. There, I met also Nenad Bohacek and his assistnat-professor Norman Sartorius from Zagreb. It was important to be able to meet up with people after the Russian occupation and make these kind of contacts.

Alice Leeds was doctor in Holland who escaped from the Germans and emigrated to the United States. She was very determined to get collaborative research going. She had a great energy and drive and it was possibly important at this time that she spoke English, German and other languages very well.

In the early days, in fact, we used to meet with the Germans, Austrians, Poles, Russsians and Hungarians quite often. One of the motivations for the Germans in this was that a meeting in Czechoslovakia provided an opportunity for both East and West Germans to meet which otherwise was very difficult for them. So we organised some symposia, for instance in Carslbad, where German was the first language. People like Bente, Hippius, Ackenheil and Matussek came along. Norman Sartorius used to come along as well.

Yugoslavia where Norman Sartorius was based was very important in all this. Yugoslavia was an extraordinary country. People from both East and West could go there easily. I was invited to many meetings there. Nenad Bohacek was the Chairman of the Yugoslavian Psychopharmacological Association and he invited me 5 years in a row to give a guest lecture. The fact of similarities between the Slav languages was helpful. I even got to the point of knowing how to discuss issues in Serbo-Croatian.

I had a surprising experience two years ago in Israel, where at a meeting in Beersheba, I gave my paper and then afterwards, I was asked from the floor if it would be possible for me to have the discussion in Russian. So many Russian speaking Jews had emigrated to Israel that many of their discussions were now in Russian. Because of my experiences trying to sell our drugs in Russia I was able to do this and we had the discussion in Russian. It's funny the way history turns isn't it? In many ways I prefer to look to the future, its only you who pulls me back to the past. But I am sure that as they say, if you do not know the history you are condemned to repeat it. On the other hand, you cannot trap people with the history.

I agree completely, you have to use history to show people ways to move forward not to stop them doing things. My worry is that when we forget history we also forget about other developmental paths that we may need again in the future.

Yes. I still have the feeling that there are many more surprises to come in the future. I expect great progress not only because of molecular biology, genetics and genomics but also due to a better integration of neurosciences with endocrinology and immunology. We have only one regulatory system and historically it is only due to different methods of study that there was a separation of neurophysiology, psychology, endocrinology and immunology. We have seen changes in immune state in anxiety and used levamisol to improve immune functions in pharmacoresistant depression and in those patients where the immune functions improved, the depression was alleviated. We should study the mechanisms of

binding neurotransmitters and drugs to receptors together with immunologists and allergologists. The problem of how to explain the origin of antibodies to antigens may shed light on the problem of how to explain the existence of binding sites to diazepam or imipramine. These drugs may not only act on immunity, they may act differently according to the current immune functioning of the patient.

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