THE PSYCHOPHARMACOLOGY OF LIFE AND DEATH
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Tell me how you started?

It was 50 years ago next February that I started working in this department. Originally, we were in a 100 year old building and we moved about 20 years ago to this new research tower in the Semmelweis University. In 49, when I passed my examination in pharmacology, I was invited by the professor of pharmacology, Professor Bela Issekutz, who was the leading pharmacologist in Hungary, whether I had an interest to come and work in his department. His department was a very famous department, so I was more than glad and happy to accept. I got my MD in 51 but in the last two years of this I was more in the department than in the university and I neglected my studies to the point were I was worried I might fail my MD.

That time, in 49, you have to realise that it was after the war and the communist take over which was in 1948. The lab was very poorly equipped and there was no money to buy anything. We couldn't travel outside the country and the only contact between scientists was personal contact. The Hungarian Physiological Society was the classic society for our work. It was 40 years old probably at that time. They had once a year a meeting and in this meeting all the research workers in the field met and discussed their problems. This was the only place to meet. Also because of the tendency to make socialism independent of capitalism, new journals were organised. The Acta Physiologica Hungarica was I think established in 1950. We tried to emphasize English because we could see English was becoming the working language but articles were also accepted in French, in German and in Russian of course. So you see there was a real isolation. It was not an ideal setting for research but still despite all of those problems it was probably the most beautiful years of my life. This was because the fantastic activity and enthusiasm there was in the department.

At the time, the Hungarian Academy of Sciences was well established. It had been newly reorganised because of political considerations but they got money and they gave money so even I, as a medical student, got some support from the academy. What I got was at that time almost the same amount as a young physician, an MD, got after qualifying. So they tried to encourage research work and young people came to the department. The old generation had been lost in the war or they left Hungary - this was the case for some of the best neuroscientists and leading personalities. Albert Szentgyörgyi who discovered Vitamin C had been working here, but also he left the country in 1950. We had a library and some of the Western journals came. If they came, they came late usually but we tried to keep us as much as possible with world developments. Essentially we worked very hard. I remember when I started working, I was usually in about 8 in the morning and I left the department about 10 pm or 11 pm. There was no technical assistance. Everything we made by ourselves. So it was mainly the spirit for work, this enthusiasm and the feeling of understanding things that drove us. This was the situation from 49 to 56 when the Revolution came.

At this time was pharmacology here part of physiology?

Yes that's a very good question. Just as everywhere else in Europe, pharmacology was part of physiology. There were no independent pharmacological societies at the time. We were part of the Hungarian Physiological Society. There was not even a pharmacological section in the Hungarian Physiological Society. Its interesting, a section of pharmacology (SEPHAR) in the International Union for Physiological Sciences (IUPS) was established in 1960 and its first Congress was in Stockholm in 1961. It was only in 1962, that an independent International Union for Pharmacological Sciences IUPHAR, was established. Börje Uvnäs, an excellent scientist, who organized the meeting in Stockholm became its first president. The second IUPHAR Congress, as a matter of fact was in Prague in 1963. Its president was Helena Raskova, the first general secretary of IUPHAR. At that time, in most of the European countries, we mostly depended on the German Societies, because German science had been before the war the leading science in pharmacology. It had had an influence on us all for decades and decades

From that point of view in Budapest was pharmacology viewed with respect the way German pharmacology was or was it more like in France where pharmacology seems not to have been viewed with as much respect?

It was like the German situation. Pharmacology was highly respected, though it was handled as a part of physiology. I was probably the one who changed its status. I tried, and I was successful fortunately, to establish the Hungarian Pharmacological Society of which Issekutz was the first president. I was the general secretary. He was absolutely against the idea, as were other big names in pharmacology in that period around 1960. They wanted to keep it together with physiology as it had been for all their life. It was a conservative mindset. They thought it wouldn't be to good to split thing. I was a young man so I had a quite different view. I wanted to have it independent and I had some support from the president of the Academy of Sciences. So we finally established the society and we were among the first 10 or 12 nations participating in IUPHAR. Later on I became a councillor for IUPHAR and a first vice-president.

So pharmacology became independent and began to make its own Congresses. We had congresses with international participation in Budapest in 1974, 1976, 1979 and 1985 and we had 6 symposia at each. We produced the proceedings of each in six volumes, published by the Publishing House of the Hungarian Academy of Sciences and from 1979 Pergamon Press joined editing the volumes. These meetings were supported by the Hungarian pharmaceutical industry. In the late 80s, the support which we got from the state - from the Academy, from the Ministry of Health - as well as from the pharmaceutical industry started to decrease, first slightly and then more and more subtantially. This was the forerunner of the big changes in our society. So I think that Pharmacology in Hungary which had a very well developed history and interacted with a good pharmaceutical industry lost out to some extent

Who were the pharmaceutical companies and what was their relation to the pharmacological departments in the university?
The pharmaceutical industry was established in the end of the last century. The big company was Chinoin. Later came Gedeon Richter and then Wander and so on. Chinoin is still the same but linked to Sanofi. Richter is the same but Wander is now EGIS, linked to Servier.

This department of pharmacology here was established as part of the medical faculty of the Pazmany Peter University, which was established in 1769. This medical faculty became in 1951 the independent University of Medicine in Budapest, from 1969 the Semmelweis University of Medicine. In 1872, the department of pharmacology became an independent department - this was only 23 years after Buchheim's first pharmacological department in Dorpat. So that was very early on. At that time of course, Hungary was a substantial power together with Austria and they had some influence and power, as well as being in the German sphere.

All in all I would say that we had a fairly well developed pharmaceutical industry. For example, Vitamin C was first produced here by Chinoin. Some of the first sulphonamides were also produced here as well as many other drugs. Pharmaceuticals were among our leading industrial achievements. When the so-called socialist countries worked together, Hungary's pharmaceutical industry was really the best of them. In Russia, the situation as always was that they were both very poor but they were also very rich, so some things were very highly developed. It was very curious.
I visited there often and in one institution you met people who were unbelievably poor and isolated so that they did not know what was happening elsewhere. But then you went to other Institutions linked to the Academy of Sciences and these people were incredibly informed. They had in their libraries the last issues of the journals and so on. It was very complicated.

Now in the 20s, Issekutz realised that pharmacologists had to work together with the industry. He was very interested in practical aspects of drug research and established close collaboration with the industry. He also realised in due time the importance of structure activity relationship studies in drug development and established in 1948, with the financial aid of the Hungarian Academy of Sciences, an excellent laboratory for synthetic chemistry. Though this laboratory moved later from our department to a newly established Research Institute of the Academy of Sciences, Issekutz's chair was in the 50s an ideal place to learn both the methodology of classical pharmacology and the essentials of drug development and also the way how to work together with the medicinal chemist. Those who worked in his laboratory became later the leading pharmacologists in the university departments and in the industry, and those who left the country after 1956 got sooner or later leading positions in the West.

When I took over the chair in pharmacology at 62, we had excellent contacts with the pharmacological industry where the most experienced medicinal chemists worked. So if, for example, I needed a good chemist it was reasonable to look for a partner in the industry. This is what happened with

deprenyl. Mészáros, the research director of Chinoin was a close friend of mine, we worked together from the early 60s and developed a new family of minor analgesics, the selected reference substance of this family, Probon, which I selected in 1964 for clinical trial, is still used in Hungary and in a couple of other countries. We met with Mészáros in those years in my laboratory almost weekly to talk about our work. When I needed to make some amphetamine derivatives a chemist who has experiences in the synthesis of phenylethylamines, he brought me together with Ecsery who worked in Chinoin in this field. So it started and I worked with Ecsery thereafter in harmony until his death

You mentioned the role of the chemist. I think this is important because they influence the pharmacologist it seems to think differently to the physiologist

There were two main lines of development. The one Issekutz followed was to offer support to industry, if it had a problem - whether to make me-too drugs with new patents or not. Everybody of course tried to make a me-too substance of something when it was known that it was working. If an MAOI was shown to do something, they tried to make another. So, they went to the university departments where the good scientists worked and they offered them support do the pharmacological work. The industry would then have a plan that gave them a patent while the scientist could publish. My case was different. I never accepted a project which was brought to me on the basis of if you do this we will pay for it. Sometimes I would agree as the Chairman of the deparment and some of my staff would do it. But my way was if I had a problem, I would look for the best pharmaceutical industrial research site to help with the chemical tool to solve the problem

When you began, the amphetamines had already been produced. What led you into the CNS area?

Yes. I started working in the early 50s. The years between 50 and 60 were the golden decade of psychopharmacology. I was a young worker when the new psychopharmacological drugs appeared. I often made the reports on these new developments for the group in the department on, for example, the phenothiazines or the MAOIs or the whole story of reserpine. I think I was the first in Hungary to work with reserpine and with tetrabenazine. I worked with the amphetamines in this context. So, the whole story with the catecholaminergic and serotoninergic systems was part of a psychopharmacology that I really got acquainted with in statu nascendi. These agents were experimental tools for me to get closer and closer to my problem, which I named the problem of ‘specific activation of the brain’. You can call it a drive. What is this drive?

Right let me ask you about this theory of drives and how did the amphetamines link in with it?

In 49, I started here and by 51/52, I had already found my problem. The problem was this. Take an animal, for example, that is hungry he forages in the surroundings actively. This is fantastic but when he eats and is satisfied he sleeps or rests. Or another example, the rabbit is feeding on cabbage and is very relaxed. An eagle comes. Now the relaxed rabbit has less than a

second to change from that relaxed state to the highest activity. To get running with all his power because his life is at stake. That's the problem. What happens in the brain and why is it that one animal can run so fast that it escapes but the eagle catches the other and eats him. Why is one animal a high performer, and the other a low performer. This activation and what underpins it was the problem I have worked on day and night for years. Drive is a very nice psychological term but what is the physiological basis of what happens in the brain with these drives.

I developed a useful theory, at least I think so because it led me to what I know now. This was the so-called Theory of Active Reflexes. This became a monograph. I was ready with the theory in 56/57 but I did not dare to make a monograph on the issue until 69. When I came out with it then, although we had some contacts as I explained, I was still very isolated from the rest of the psychopharmacology world. The book is not very well known still because it was published primarily in Hungary, although there was a joint edition of the Publishing House of the Hungarian Academy of Sciences and the Hafner Publishing Company in New York. But it contains most of what I learned in my life and what I know now is based on that theory about a specific activation mechanism. This is the mechanism that answers the question of what is the difference between the two rabbits. I came close to the answer as I see it in 1996 with two papers in Life Sciences. So almost 40 years work - it's a very long story. If everything had worked out all the time and if there hadn't been the cold war with two world independent of each other, we would have got there faster. I missed an opportunity when I was younger to go to the West, which may have been a mistake

You had some contacts with Daniel Bovet on this issue. How did you meet him and what was he like?
Daniel Bovet, one of the really great figures of pharmacology in our century, was a shy man, disposed to seclude himself. He was borne in 1907 in Switzerland, graduated in Geneva and worked later with Furneau in Paris. It was he who realised in 1936 that Prontosil, the first substance discovered by Domagk in 1935 to save mice from streptococci infection, was inactive *in vitro.* It is transformed in the organism into a highly active killer of the bacteria. This led to the development of the sulfonamide family. Bovet discovered the first antihistamine in 1937. He got the Nobel Prize in 1957. When I met him he was the leader of the Pharmacological Department in the Istitituto Superiore di Sanita in Rome. He lived probably in Rome because his wife and cowerker was the daughter of Nitti, a famous socialist politician,once member of the Italian Parlament.

I think we met somewhere in 57 probably and then he invited me in 58 to the first CINP meeting which was in Rome. He had to help me because, even though I was supported by the Academy of Sciences, I couldn't pay for all of that. It was the first time I had been alone in the West in my life. It was absolutely curious. At that time, I had published some work with Bertha my wife, on a method to differentiate between tranquillisers and drugs like the barbiturates. I think it was this that led to the meeting with Bovet who had heard about it. He had developed at the time his variety of the shuttle box

method which we are still using. He was very interested in our work because that was one of the first indications that we could differentiate with our method between tranquillisers and barbiturates, which was very important at that time.

That was what brought us together. I told him there was a very special situation of activation of the brain where some neurones end up on an enhanced activity level etc. This is the question of drive and how some group of neurones organises for example for the finding of food or the sexual partner. I met him at a meeting and we talked about it. We did not have the laboratory facilities to look at the EEG but he had a very good colleague, Longo, and he offered me to send my young talented, co-worker Kelemen, later a professor of authority in Hungarian pharmacology, to work with Longo on this EEG work.

I told them that I think that there is a low level activation which is not specific and a higher level and that we should be able to distinguish them. We found that we could distinguish on EEG between extinguishable conditioned reflexes and inextinguishable conditioned reflexes. We published on this in 1961. Even though Bovet was co-author in the papers, nobody reacted, despite there being both Hungarian and English versions to the publication.

The ‘specific activation’ of the brain, Drive, when you think about it is fantastic. Something brings the animal from a normal level of activity to a level 10 times or 50 times higher, almost instantly. I now know this is done through the catecholaminergic system but how is another story, the story of the catecholaminergic activity enhancer (CAE) mechanism which we may discuss later. I developed a method to distinguish between extinguishable Pavlovian reflexes and non-extinguishable reflexes based on ‘specific activation’. Clearly activation of this kind cannot be something that is extinguishable. Bovet realised the importance of this and we really demonstrated the difference

Were you not at odds with communist teaching at the time, talking about unextinguishable reflexes? Everything was supposed Pavlovian, wasn’t it?

Of course I was. Pavlov was of course one of the ever lived greatest physiologists. His pioneering contribution was the translation of ‘association’ into the language of physiology. He demonstrated that the physiological basis of this phenomenon, known for thousands of years, is the building of a new temporary connection, a ‘conditioned reflex’, in the brain. As the conditioned reflex is extinguishable, its analysis needed very special methods, the isolation of the animal from the outside world. After Pavlov’s death Soviet physiology made, because of ideological considerations, a doctrine of the theory of conditioned reflexes and their work became accordingly sterile. My problem was to find the physiological basis of the drive, the analysis of which needed to forget about the classical methods used by the Pavlovians. This was the rub.

You can’t imagine what happened. There was a Soviet so-called advisor, responsible for keeping research in Hungary in the field of ‘higher nervous activity’ in the proper line. I gave an important address on my theory which

was, of course, absolutely anti-Pavlovian. It was in a Hungarian Physiological Society meeting around 55. Makarichev was this man's name. I gave the paper in which I attacked the Pavlovians, showing that the Pavlovian approach is a very unnatural thing and that extinguishable reflexes are not important. What is important is the drive, the active unextinguishable reflexes. They always asked me why was I doing this and I would answer because the Pavlovian approach is wrong and because what I am saying is right even though it is harder to work with. I gave my paper. Makarichev had a Hungarian supporter of course, that was what it was like in those days. Issekutz, my boss, was a liberal man, but he was afraid of trouble for the department, even though he was a member of the Academy and a very good authority. Anyway, he asked me to come to his office. You know, Joseph, he said, you are probably right but this is new stuff. It's better not to give the paper. This is against Pavlovian ideas and Makarichev has asked about it and a professor of physiology, Lissák, is also against it. But he told me 'as a scientist, if you still decide to do it, I won't tell you not to do it because its wrong. I just give you the advice not to do it. You are a young man'. But it was not in my nature not to do it, so I told him I would take the risk and I did it.

I was a little lucky probably. The 56 Revolution came soon afterwards and Makarichev was called back to the Soviet Union. Maybe this was part of the reason why I escaped. But when I published the book in 1969, these ideas were still not happily accepted.

The central questions from my point of view are how can youth be defined, how long does it last and how is it terminated. Or using a more scientific sounding terminology, what is the essential difference between developmental and post-developmental longevity and what is the cause of the transition from one phase to the other. Why and how does natural death set in and why exactly does it do it the way it does. In other words, why and how is post-developmental longevity terminated? What is that central difference between the brains of high and low performing individuals? Why are high performing rats significantly longer lived than their low performing peers - this is the case. We found this in 88. I think I have the answers to some of these questions now but it took a long time and not many people still realise the essence of the problem

Where did Deprenyl begin to play a part in the story?
In all this, Deprenyl was an excellent experimental tool .When I developed it, I did not know it would be so useful. It was developed in the 60s. I was interested in amphetamines and the effect of reserpine as well as the effect of the MAO inhibitors. This was what I had in my mind when we finally set about making Deprenyl. This first Hungarian paper was published in 64 and the first English paper in 65. If you read the introduction to the 65 paper you'll see what was the aim. 'It is known since 1933 that β-phenylisopropylamine or amphetamine is a psychostimulant. Its effect is accompanied by an intense sympathetic activation and a slight decrease of the cerebral monoamine-oxidase activity. In recent years potent MAO inhibitors have been introduced into therapy, which do not provoke an acute excitation of the central nervous system but possess clinically useful psycho-energizing, antidepressant

effects. In the past few years we tried to find compounds possessing both the amphetamine like psychostimulant effect and the psycho-energetic effect characteristic of the potent MAO inhibitors'.

So I wanted had to have the two effects together in one molecule. The starting point of our investigations was the β-phenylalkylamines. We took into consideration that on the one hand benzylpropinylmethylamine-pargyline- was a potent MAO inhibitor but it did not cause any acute stimulation of the cerebral nervous system. On the other hand we knew that amphetamine is a strong psychostimulant but it hardly inhibits MAO at all. We screened about 30 compounds before I selected phenylisopropylmethylpropinylamine (E-250), which later became Deprenyl. This compound met our requirements.

So it only needed 30 compounds. Because of earlier work with rat behaviour, I had always the feeling that this psychostimulant effect of the amphetamines and the psycho-energizing effect of the MAOIs, could be somehow put together. You see the psychostimulant activity always looked like it was a very complicated phenomenon with parts that could be broken down. I always had the feeling that the hypermotility the amphetamines cause is only a part of the story but I couldn't say why. What we knew then was that amphetamines act by releasing catecholamines from the catecholaminergic neurones in the brain and in the periphery. When you give amphetamine intravenously, you immediately see a blood pressure increase because of release of noradrenaline from the peripheral noradrenergic nerves. But you don't see this when you give E-250. You don't even see it when you give it with amphetamine. So it does not release catecholamines and it blocks the release caused by amphetamine. This was a great discovery and I knew that I had to select this compound. But for practical reasons I also had to follow the MAO inhibitor story because all the world wanted MAO inhibitors then. Then the different forms of monoamine oxidase, MAO-A and MAO-B, were described by Johnston in 1968.

No-one seems to have known this man - did you know Johnston?
No. I think he died very early. I corresponded with him and one of his co-workers who continued with his work. Johnston developed clorgyline about 3 years after my compound was developed. Now he realised something very important which was that clorgyline inhibited only one form of the enzyme, leading him to call that MAO-A and that it was not blocking the other form which he called MAO-B. Now in 71, I discovered that my compound deprenyl was the complement of clorgyline. It blocks MAO-B. I reported this at the first MAO meeting in Cagliari organised in honour of Herman Blaschko, a great scientist whom I later got to know. At this meeting, I reported the MAO-B inhibiting effect but nobody cared. Nobody reacted

Why?
Oh this is natural. There is no stronger reflex among scientists than to reject the new which is not mine. I remember once when I was invited to Washington by Mimo Costa. Norton Neff, who worked in his laboratory, complained me that they are unable to inhibit properly the metabolism of phenylethylamine and asked my opinion. I reminded him that he participated

in the meeting in Cagliari where I introduced my new substance, deprenyl, which does the work. I supplied him with deprenyl and they soon described its high potency to inhibit phenylethylamine metabolism. With the passing of time more and more people began to use it, because it was an excellent experimental tool. The first paper on deprenyl was in 64/65. After that the number of papers between 66 and 82 was 372, that is 22 per year. Our first paper describing that deprenyl is the selective inhibitor of MAO-B was published in 72 and in 82 this paper became a 'citation classic'. Between 83 and 91 there were over 150 papers on deprenyl, per year rising to over 200 from 92 to 96 and over 300 last year.

But this discovery of the MAO-B inhibiting properties put into a shadow the other aspects of the specific activation problem I outlined above. If deprenyl was a specific MAO-B inhibitor, it was ideal because in 1963 Blackwell wrote his famous paper on the cheese effect. Deprenyl, however, was the first MAOI without a cheese effect. We showed that deprenyl not only did not potentiate the catecholamine releasing effect in response to tyramine but it inhibited it. This you might have thought would be valuable for human therapy. We knew of this benefit already in 66. Almost immediately after
I made deprenyl, in 64/65, I asked a good friend of mine Ervin Varga, who was that time assistant professor in the Psychiatric Department of our University and worked later in the US, to check on its antidepressant effect and to check whether it could be given to man along with tyramine without side effects. His investigations showed that it might be highly active in cases of depression and also that it could be given together with tyramine. But nobody cared. The paper of Varga and Tringer, published in Acta Medica Hungarica in English in 1967, remained unnoticed

Why?
Nobody cared. Some of them said you can't have an MAO inhibitor without a cheese effect. Finally I had a word with Merton Sandler, who was a fantastic friend, and I asked him to look at this. He did it and he found there was no cheese effect. I took care to keep my name off the paper demonstrating this but still nobody cared. Birkmayer in Vienna really used it first.

You know that in 60 Hornykiewicz discovered that in Parkinsonian patients, there was very low dopamine - 10% of the normal dopamine levels. He realised that a dopamine substitution therapy is needed and asked Walther Birkmayer, an expert in treating Parkinson's disease, to work on it. As dopamine does not penetrate into the brain, the precursor, levo-dopa, had to be given which is rapidly splitted in the brain to dopamine. Because levo-dopa causes many side effects, the idea was to make a sparing effect with MAO inhibitors but because MAOIs enormously potentiate the catecholamine releasing effect of levo-dopa, the scheme had to be abandoned. Birkmayer realised that deprenyl was probably the stuff he needed and gave it as an adjunct to levo-dopa. It was his coworker, Peter Riederer, who called his attention to deprenyl, and Riederer's good friend Moussa Youdim, who visited me in Budapest, brought deprenyl from me to Vienna.

By the mid-80s, however, I started to have doubts about the role of the inhibition of MAO-B in the beneficial effect of deprenyl. I made a lot of experiments and I found more and more that deprenyl is activating the dopaminergic machinery in the brain but that what it was doing could not be the consequence of MAO inhibition. I began to change the story. Many of my friends at that time said to me 'Joseph, finally everybody accepts your original view that the selective inhibiton of MAO-B is of crucial importance in the effect of deprenyl but now you are against it, why is this?' I had realised however that this is not the main importance of the compound. Deprenyl has a highly important activating effect in the brain, on the catecholaminergic neurones which had until then been completely concealed.

To show that this was so, I asked Ecseri to work with me on some structure activity relationships. He died in the course of this and the work was finished with some of his co-workers. I told him look now I needed to eliminate the MAO inhibitory property of deprenyl, maintaining the other action it has. This led us in 92 to PPAP a completely new and very important compound (Fig.1).

We started this work in early 89. I realised finally that we owe the loss of the catecholamine releasing property, so characteristic to deprenyl, to the bulky substitution attached to the nitrogen, so we put in bulky substitutions to amphetamine. The main aim was to eliminate MAO inhibition. The propargyl group in deprenyl was what was needed to produce covalent binding to the flavine in MAO-B and therefore inhibition of the enzyme. If you put a propyl group in instead, there is no binding and no inhibition. I also put a propyl group in instead of the methyl group to the α-carbon to make sure there was no methamphetamine derivative of this compound, as there is with deprenyl. Amphetamine derivatives, you see, are better than methamphetamine derivatives on this catecholamine activating effect. PPAP then was the substance we ended up with. This substance definitely activated the catecholamine system as amphetamine does but without being a catecholamine releaser as the amphetamines are and it also blocked the catecholamine releasing effect of tyramine because all these substances compete for the plasma amine transporter. Finally it was not an MAO-B inhibitor. My efforts in the 60s to persuade Chinoin, who owned the patent, to develop deprenyl as the first MAOI free of the cheese effect, remained unsuccessful. Now I hoped that the high international reputation of (-)deprenyl will be helpful to develop (-)PPAP for clinical trial. My attempt, however, to persuade Chinoin (later Chinoin-Sanofi) to finance it, was again unsuccessful.

The proof that PPAP acted like deprenyl was fantastic. But it posed another mystery. How was this substance doing what it seemed to be doing? I tried to understand this. What happens? How is the catecholaminergic neurone, let us say the nigrostriatal dopaminergic neurone, being turned on be either deprenyl or PPAP, which is a non MAO-inhibitor. How is it possible that the nigrostriatal neurone is activated but the substance is not stimulating the receptors, neither D1 or D2, it is not inhibiting the uptake system, it is not inhibiting MAO and its not releasing dopamine. These are the four mechanism we know of. Something else had to be happening. There was one clue.

Whatever this was doing had to also be done by the basic substance, the original brain component, phenylethylamine. What is phenylethylamine?

Well, in 96 I published the answer. The essence of the problem is simple. If you take the endogenous substance phenylethylamine, we know that it is an amine releaser. But it is not only a releaser; on the contrary it is only a releaser in a relatively high dose. In a low dose it does something else but this is in fact always masked by the other effect. If you take a brain stem and measure the amount of noradrenaline coming out at the resting level and then stimulate it and measure what comes out following stimulation, you find that when you stimulate, much more comes out. So there is an impulse propagation mediated release. Give a small amount of phenylethylamine and stimulate, what you find is there is an enhancement of the impulse propagation mediated release. So there is a hitherto unknown mechanism working here, a catecholaminergic activity enhancer, CAE, effect as I named it, which is capable of enhancing exocytosis. How does this work? Well we have to find that out.

Now in finding this, I also made a second discovery, I found that tryptamine the indole derivative of phenylethylamine has the same enhancing effect. So this mechanism applies to noradrenergic, serotoninergic and dopaminergic neurones. Deprenyl had an enhancing effect which is as potent as phenylethylamine and did this much more potently than methamphetamine. It was also an inhibitor of MAO-B. If you go back to phenylethylamine, it has a catecholamine enhancing effect, a releasing effect and it is a substrate for MAO-B.

PPAP, though is an enhancer only, although it is an amphetamine derivative. We were very excited by this and so it seemed to me were Sanofi whom we discussed this with while Pierre Simon was there. When he retired they lost their interest in PPAP. But when I discovered that tryptamine also had effects, I set my sights on a wider horizon. We should make the PPAP analogue of tryptamine. This should be an enhancer, not an MAO-inhibitor but above all should not even be an amphetamine derivative anymore. Because the Hungarian group of chemists I worked earlier have dispersed now, I found a good group in Japan I could work with, a small firm, the Fujimoto Pharmaceutical Company in Osaka.

The firm is owned by a wonderful man, Mr. Kunyoshi Fujimoto, whose father established the Company and it is still family owned. We have with Mr. Fujimoto the same obsession, collecting painting. Interestingly, we both collect, as one of our favourites, the paintings of Bela Czobel, the famous Hungarian painter, who died in 1976. Czobel exhibited in the now historical exhibition of the Salon des Independants in Paris in March 1906 where Matisse showed his epoch-making Le Bonheur de Vivre, 8 paintings together with Braque, Delaunay, Dufy, Marquet, Vlaminck, etc. and in the again historical exhibition of the Fauves in 1906 October in Paris, 6 paintings together with Matisse, Delaunay, Dufy, Marquet, Vlaminck, van Dongen, etc. Isn’t it symbolic that a Hungarian pharmacologist from Budapest and a

Japanese businessman from Nara, visit each other in their homes to admire the beautiful colors of the Czobel paintings they collected? As Keats said:

Beauty is truth, truth beauty, - that is all
Ye know on earth, and all ye need to know.

Good art and true science keep the noble human values alive, no matter how the struggle for power and money corrupts the world.

Now, Mr. Fujimoto gave me the chance to work with his group of chemists in Osaka and perform my planned structure activity relationship study aiming to find the proper, new patentable CAE substance. We reached our goal, and I selected (-)1-(benzofuran-2-yl)-2-propylaminopentane, [(-)BPAP] for further studies. This substance is a tryptamine derived CAE/SAE substance, has nothing to do anymore with the amphetamine structure and is about hundred times more potent than (-)deprenyl in antagonizing the effect of tetrabenazine in the shuttle box. The Fujimoto Company owns the patent and I am just writing the first publication. I hope to be successful this time and see in the not too distant future the effect of (-)BPAP in a DATATOP-like study.

To illustrate that the CAE effect and the catecholamine releasing property of an amphetamine derivative are unrelated to each other, let me mention a highly characteristic difference in these two actions which I observed from the beginning of my work with deprenyl. I selected in the late 60s (-)deprenyl as the reference compound and this enantiomer is used in the clinic. My main reason for this decision was that (+)deprenyl was more potent in inducing hypermotiliy than the (-)enantiomer. Now it is well known for decades that the (+) enantiomer of an amphetamine derivative is substantially more potent than the (-)enantiomer in inducing the release of catecholamines from their stores. Regarding the CAE effect of an amphetamine, however, the contrary is true. This is why we use (-)deprenyl, (-)PPAP and (-)BPAP for enhancing the impulse propagation mediated release of catecholamines in the brain

From a behavioural point of view, what does a CAE substance do?
Well, take a shuttle box. In the shuttle box, you can measure conditioned avoidance responses (CARs) and escape failures (EFs). The third condition you can measure is the inter-signal reaction. The animal jumps from one side to the other of the box when it gets an elecric shock and when the conditioning is done it has learnt to jump without the electric shock. If it then jumps in 5 seconds without a shock this is the conditioned avoidance response. If doesn't jump within 5 seconds to the electric shock, this is an escape failure. You train it for 5 days, 100 trials per day and you measure the CARs and EFs and the inter-signal reaction because this shows the general state of the activation of the animal.

When you give tetrabenazine, which lowers the pools of catecholamines, you find there is an almost complete inhibition of the ability to build up conditioned avoidance responses. So catecholamines are important for this learning. The number of escape failures rises to very high levels with tetrabenazine. Now, if you give deprenyl, though a high dose is needed, you see that in the presence of deprenyl, even if you give tetrabenazine, that the catecholamine system is still working. So the enhancement of exocytosis that deprenyl brings about

makes it possible for the neurone to respond to the stimulus and emit that minimum amount of the catecholamines needed to learn the response. (-)PPAP is about twice as potent as (-)deprenyl in antagonizing the effect of tetrabenazine in the shuttle box, while (-)BPAP is about 100 times more potent than (-)deprenyl in this test. Thus, we may now say that (-) deprenyl is a relatively weak CAE substance and we shall have much better chances to reach our aim by using (-)BPAP.

What does this mean? It means that we can change the activity of say a nigrostiatal dopaminergic neurone, we can enhance it without changing anything on the receptors, without changing the uptake system or anything to do with the neuronal metabolism or with the nonspecific release from the neurone. Everything remains physiological. Just the animal, by being given a very low amount of the stuff has a higher activity level. As I describe it in my papers, the catecholamine system works like an engine, the engine of the brain. The lower performing individual has an engine which has a lower capacity than the engine of the higher performing individual and what you are doing with these agents is you safely increase the activity of the engine. You raise it to a higher level and the more active the substances we get, the lower amounts of substance we will need to bring about this effect.We now then have the opportunity to keep our catecholaminergic machinery in the brain on a higher activity level without changing, as other pharmacological agents do, the surrounding physiological circumstances.

What is the importance of this? Well we have shown recently with my co-worker Ildikó Miklya that you have a higher activity level of the catecholaminergic and serotoninergic machinery between weaning and sexual maturity. This is a new finding. When you measure the release of dopamine, for example, or the other amines, in rats you see a change at 3 weeks. Why? Well this is the time of weaning. What is weaning? This is the time when the animal becomes independent of the mother and has to find its own food. At this point in time, there is an increase in the activity of that system and this is a physiological enhancement of the system, a mechanism that works on a higher activity level, which lasts until sexual maturity is complete. After that the system is coming back to the preweaning level and thereafter it is subject to a very slow decline. This is the post-developmental phase of life.

You can see then that I can offer you an answer to some of the early questions. What is the difference between the developmental and postdevelopmental phase of life? My answer is that in the developmental phase of life, mammals have a significantly higher activity level in their engine - in their catecholaminergic machinery - and this is the reason why small boys spend so much time running around the place - 100 times more than the adult. The aging phase then, at least from the brain point of view, is the slow but continuous decline of the catecholaminergic machineries. As regards this enhancement mechanism, I'm sure we shall find lots of other ligands, which have effects on these mechanisms.

Now lets look at the nigrostriatal dopaminergic neurones. This is well known to undergo a slow continuous decline. We lose, according to health

professionals, at least 13-15 % of our striatal dopamine in each decade after the age of 45. Our levels go down and down. We have a 100 % dopamine at the age of 45 and we lose 15 % per decade after than. At 30 % of the normal levels, we reach a critical level where we develop the symptoms that was described in 1817 by James Parkinson. When you look at that and you take the average lifespan, you see that everybody will reach that level at the age 105 but 99.9 % of the population will not reach that parkinsonian level at a normal aging rate. But 0.1 % reach that level and they precipitate the symptoms of the disease, usually between 55 and 75, sometimes earlier sometimes later. Why?

I am not sure that they must have any special cause because there are big individual differences in a population in any performance. For example, a 70 year old man can perform sexually like a 40 year old and vice versa. So, it may be that we just have in that group, those in the normal population which show the highest aging rate and they live long enough for this to show. It seems today that we have more Parkinsons patients than they had earlier but maybe they just died earlier before. I am not sure. If you look back at when the MPTP story was at its height, everyone thought that we shall find either an endogenous or exogenous MPTP but nobody has. I think this is because they are looking for something that doesn't exist. It will be interesting to see.

But to come back to low and high performers. In the early 80s, I studied with my co-worker Dalló, as a dopamine dependent function, male sexual behavour in the rat. If you have a higher dopaminergic striatal activity, you have higher sexual function and vice versa. We found that when you give a small amount of deprenyl, this function goes to a higher activity level. You can also postpone the aging related decline in sexual function that you find in both the rat and in man. So you have both an individual variation in this function and a decline in function that goes in parallel with the decline in the nigrostriatal system deterioration. From this, we got the idea to make an experiment. We took 1600 males of the same strain and the same age and made 4 consecutive weekly tests to see how they behaved as regards mounting, intromission and ejaculation. We selected out 94 who on each of the weekly mating tests did nothing. And we also selected 99 who in each of the 4 consecutive tests had at least one ejaculation. We divided both groups in two, one of which got saline and the other deprenyl for the rest of their life. We measured mating weekly and in the shuttle box we measured three monthly their learning ability. We also looked at how long they lived. What we found was a huge difference between the two groups. During the first 36-week period of the experiment the high performers produced 80 times more intromissions than the low performers. When treated with deprenyl, there was a 40 fold increase in the activity of the low performers. They didn't reach high performer level but they significantly improved. The high performers also improved but not as much. And while both high and low performers on deprenyl showed an age related decline, neither declined to saline treated levels. Now if you looked at the age of death, the saline treated low performers had an average death at 134 weeks, but the deprenyl treated low performers lived for 152 weeks on average. The saline treated high

performers lived 151 weeks and their deprenyl treated peers lived 185 weeks on average.

So my hunch is that nature has given the high performing animals a good catecholaminergic engine and because evertyhing is lower, this is why the low performing animals die earlier than their high performing peers. When you look at the high perfoming ones, they were wonderful but even they showed the decline and giving them deprenyl made a difference. So you can correct what nature has given. This didn't just apply to sexual performance, it also applied to learning. The low performers are slow learners. So it is not just sexuality, it is a question of a low level of activity in the catecholamine system.

Does this apply to man? I think the following conclusion is reasonable. We have a catecholaminergic machinery which declines. If we keep it on a higher activity level, we decrease declining performance. I published an experiment relevant to this in 1982. Rats like man, if they live to a certain age, completely lose the ability to ejaculate. Reaching that endpoint depends only on survival. Rats reach that endpoint at the end of their second year of age. This gives you an exactly measurable endpoint. If you take 45 rats on saline and 45 on deprenyl and measure when it happens, you find the loss of the ability to ejaculate is shifted in time by the deprenyl. If this is due to an age related decline of the striatal system, you don't need to measure the whole thing, you just need to measure a small part of it to see the rate of decline.

This is what the DATATOP study did in the States. They studied altogether 400 patients with placebo, 400 with deprenyl. They were never treated with anything else. They were de novo Parkinsonians freshly diagnosed. So they still had some reactive nigrostriatal dopaminergic neurons in their brain. They had an exact starting point - diagnosis - because diagnosis means they have the 30 % level of dopamine. Their endpoint was also excellent. They measured levo-dopa need. This is very measurable. They knew from 10s of 1000s of data before that, after diagnosis, in about a year the further deterioration of the neurones should lead to levo-dopa need. The first paper was published independently from the main study by Tetrud and Langston. They realised that they had 25 on placebo and 26 on deprenyl. They did not know who got which but realised that as time was passing, they had much fewer people needing levo-dopa than would have been expected. So they wrote to the FDA - gentlemen it looks like something dramatic is happening. It would not be ethical to continue the original study for 5 years, so let us break the code. They found that the average time until levo-dopa was needed was 312 days for patients in the placebo group and 549 days for patients in the deprenyl group. What they published was exactly what we found with our rats on deprenyl. This is remarkable. What I say is this they selected the 0.1 % of the human population which has the worst engine. But even in the worst, they were able to show that a daily regular 10 mg dose of deprenyl slowed the rate of decline. This was wonderful but then you know there was the study done in England by Lees, published in 95, showing mortality was increased with deprenyl

What do you make of that?

Well a range of commentators (Dobbs et al., 1996, Knoll, 1996, Olanow et al., 1996) pointed uniformly to the substantial overdosing of levo-dopa as the cause of the observed deaths with deprenyl as an adjuvant in this trial. According to Dobbs et al., the 'idiosyncratic prescribing' of deprenyl in combination with levo-dopa in the Parkinsons Disease Research Group of the United Kingdom (PDRG-UK) study led to the misconclusion of the authors. Let me tell you what happened. They of course gave deprenyl to those Parkinsonian patients who needed levo-dopa and combined deprenyl with levo-dopa. This means that you have two effects. First you have the enhancement effect which is a beneficial effect. The worse the condition of the patient, the lower the possibility for this beneficial effect. Now what they did was to overdose with levo-dopa because deprenyl is levo-dopa sparing. In this case, you have to be very careful. Deprenyl, as we know from many studies, is absolutely safe. But if you potentiate levo-dopa by a MAO inhibitor, then you will have serious side effects from levo-dopa if you do not decrease by at least 20 % and up to 50 % of the levo-dopa dose. This is what happened, and this is why their finding was in striking contra-distinction with all other experiences published in different countries. By that time multicenter trials had been performed in the US by the Parkinson Study Group (1989), in France by Allain (1991) and in Finland by Myttyla (1992) none of which found the side effect described in the PGRD-UK study. Birkmayer even found an increased life expectancy resulting from the addition of deprenyl to levo-dopa treatment in Parkinsons disease.

One of the things that happened in the UK because of the Lees paper was that an awful lot of Parkinsons patient had their deprenyl halted and one of the obvious that happened, which I saw was that an awful lot of patients became more depressed. What do you make of that?
Of course because deprenyl has antidepressant effect. As I mentioned it before deprenyl's antidepressant effect was published by Ervin Varga in 1967. The first study done with deprenyl was done measuring its antidepressant effect

Well is it an antidepressant because of the MAO-B effect or because of the enhancing effects
Both maybe, but this was never carefully analysed. The rapid onset of the antidepressant effect of deprenyl speaks in favor for an important role of the CAE mechanism in this effect of the drug. This was so conspicuous in the first clinical study in 1967 that Varga and Tringer referred to it even in the title of their paper. I think it was a mistake that the clinicians never took advantage of the peculiar antidepressant effect of deprenyl. Maybe this drug had been the best for safely countering the mild forms of depression. Although the original findings of Varga were later corroborated by Mann and others, deprenyl was nowhere registered as an antidepressant. Unfortunately PPAP was never analysed for an antidepressant effect in man because it was never developed for clinical studies. Now the real answer to your question may become clear if we are successful with the new compound. But why shouldn't a compound which is increasing the catecholaminergic system activity safely be useful in depression? I don't need to tell you that mild depression is probably more important than severe depression because hundreds of thousands of people

have mild depression. This may be because of their life circumstances or because they have a poorer engine or for many other reasons. I believe that the higher the level of the catecholaminergic system is maintained at the better and the slower are the changes to get to the stage of mild depression.

I think that in the future, it will be realised that humans need, probably starting immediately after sexual maturity, to use a very small dose of an enhancer, to keep the engine of their brain on the higher activity level. This will work for decades. It will improve the quality of life in the latter decades, hopefully shifting the time of natural death, probably decreasing the precipitation of depression, maybe eliminating the precipitation of Parkinson's disease and possibly reducing or delaying the onset of Alzheimer's disease.May I mention here that the results of the first multi-center trial conducted with deprenyl in Alzheimer disease was published in 1997 with the conclusion that the drug slows the progression of the disease.

To start using a CAE substance in due time as a prophylactic agent this is what I'm fighting for. I know the difficulties. The whole registration process works against it. No bureaucrat working in regulation has any poblem if a drug is not given and for this reason 1000s suffer. But if the drug is very active and even then some patients have a definite problem from it, then this might be a very serious problem for the bureaucrat who is responsible for approving it and they behave accordingly. This is a serious problem to breakthrough. I don't know how to do it, maybe the mass media

But unless this compound is one that was available over the counter and not so expensive then you are into politics. If the wealthy can afford it and the poor cannot
Yes but here you need it to be generic. If the competition is big enough then it brings down the price. Or alternatively, if it is accepted that this is needed for everybody, sometime in the future it may be put in the water like iodine. This looks strange now but once it looked very strange to think that I could go by plane from Budapest to New York within a couple of hours.

People can adjust
Yes, if it is accepted that everybody needs help to fight against the physiological slowing down of the system, then its another story. Here you have this beautiful data from the DATATOP study, which is so beautifully in agreement with all my studies, but still if you ask the best clinicians whether they think MAOIs or neuroprotection are needed, they have no view

Three or four years ago there was a big fuss about neuroprotection. Deprenyl was acting by reducing apoptosis. It was doing this because it was enhancing superoxide dismutase (SOD) activity. Was all this neuroprotection story wrong?
I showed in 1988 that SOD activity was enhanced in rats treated with deprenyl. My finding that the scavanger function of the nigrostriatal dopaminergic neuron is enhanced in deprenyl-treated rats was corroborated. But I also showed in 1989 that (-)deprenyl exerts this effect in the catecholaminergic neurons only and this selectivity too was found by others.

Thus, we may say that because deprenyl treatment is enhancing the activity of the nigrostriatal dopaminergic neuron, the scavanger function of the neurons is enhanced as a corollary of the CAE effect of the drug. My data suggests that the enhancement of catecholaminergic activation not only works in the brain it also works in some peripheral systems. So I don't think that we really need to search for some absolutely unknown system when we have the sympathetic system there and we know that deprenyl for instance acts highly specifically on this. It is now fashionable to talk about the 'neuroprotective', 'trophic-like neurorescue', 'apoptosis reducing', etc. effect of (-)deprenyl. These are excellent slogans to get grants and funding, so why not using them. In my view deprenyl, like its parent compound phenylethylamine, is just an enhancer of the sympathetic regulation and is changing thereby hundreds of exactly measurable cell functions.

Let me give you another insight on this. Neuromelanin is, you know, the morphological sign of the fight of the neurone for existence. 80 % of dopamine is localised in the striatum and dopamine is the only transmitter which produces toxic metabolites, hundreds of them, quinones and others. So you produce a lot of toxins and the neurone have to survive.This is why the nigrosriatal dopaminergic neuron is the most endangered neuron in the brain and this is the reason why this nucleus was called substantia nigra because it is stained black by the industrial waste as it were. You don't see it in a 5 yr old boy dying but in a 50 yr old you see it. What I did was that I looked for a partner to develop a method to measure neuromelanin in rats. Then we gave 18 months deprenyl to the rats and this fantastically inhibited the accumulation of neuromelanin. The age related change in neuromelanin wasn't found. I think the reason for this is that if you keep the system at a higher activity, this is the same as keeping it younger, and everything about the system shows this. I believe the most important thing is to keep this basic system of brain activation working properly

And the serotonin system
Yes of course it is also of tremendous importance. In many instances it works like a brake on the catecholamine system.The fact that β-phenylethylamine and tryptamine are both CAE/SAE substances shows that a common mechanism regulates exocytosis in the catecholaminergic and serotoninergic neurons in the brain. We are really at the very beginning to understand the physiological significance of this common mechanism

Did you ever meet Hess - the man who called the catecholamine system the work system of the brain - the ergotrophic system -and the serotonin system, the trophotrophic system?
No I didn't. Of course, I know his work well. I think that the catecholaminergic system in the brain is really tremendously important for life, it has a basic importance for activation. The dopamine component of the catecholamine system is very important because this is the most rapidly aging part of the system. There is little doubt than in the post-developmental phase of life the quality of our life is primarily dependent on the basic activity of this engine and the rate of decline in its capacity. There is no escape from this conclusion and I am sure that it will be accepted in due course, whether or not I am alive to

see it. With regard to the serotoninergic system. I hope that (-)BPAP will be a helpful experimental tool to better understand the relation of this system to the catecholaminergic brain machinery and to find out its share in the brain regulation of the quality and duration of life in the mammalian organism

Let me go back to the start. There has always been a problem with the amphetamines. Why?
It stems from their releasing properties. Though it was carefully analysed, there are no papers published of any dependency problem with deprenyl. It has nothing of the amphetamine side effects. The specific effect of the amphetamines stems from the fact that you release and you continuously maintain in the brain very high levels of noradrenaline, dopamine and at even higher doses serotonin and in so doing you create a non physiological situation in the brain which finally leads to dramatic consequences. If you get rid of the releasing property, you go down a safe line of development. In ways therefore that really important work was in the early 60s, when I showed that deprenyl is not a releaser - it is even an inhibitor of release. There is no safer chemical in pharmacology today. I have been teaching pharmacology for 50 years and what I have to teach for all other compounds is that with them we are stimulating receptors directly, inhibiting uptake directly, or inhibiting metabolism or that we release amines in ways that are not normal. We need to find out how to influence things physiologically. We should be changing things in the way the neurone itself changes things according to need. From this point of view shifting low performers to the better performing level is just shifting things within the physiological range. Stimulating artificially initiates a lot compensatory mechanisms which come into play then

What would the difference between PPAP and a noradrenergic reuptake inhibitor be?
If you block uptake inhibition, you change a very important regulatory process and therefore you trigger off a lot of other compensatory function. In contrast, if a low performing rat has the same machinery as a high performing animal just lower, then you just change that for the better. That’s something quite different.

Right but its also not just medicine, it’s politics
Well we shall see how it works and we shall find the endogenous ligands. This mechanism is fantastic. It’s basic to how the brain regulates its own activity. I described it as the specific activation mechanism. This is in fact the most important question of all. How can a brain be rapidly activated? This is the life or death question. I think that we have to seriously reconsider what is the reason for the differences in performance. How is it possible to make from a low performer, a high performer?

If you face that question, you can ask the final question about life span. In man, the technical lifespan is 120 years. With the new compound, I expect that for both rats and man that we shall be able to shift the time of natural deaths significantly. Then the question will be not what is the mean technical lifespan but what is the upper limit. For nature, there is no difference between 120 years and 240 years. Most of the bodily systems which die at death are

not worn out. They would almost all be completely able to go on for much longer if need be. Nature controls activity and life span through activity. But if we find the mechanism by which this is done, then it is up to us to change it. Don't forget that man finally conquered levitation and landed on the moon. There was a restriction in space but we overcame that all the way from the dugout to the space-rocket

Fine but is this medicine? Medicine has been about treating disease but what you seem to be talking about is an enhancement technology
Of course. But look at Parkinson's disease in my approach. I believe the healthy system has to be supported in order to avoid the precipitation of Parkinson's disease. Of course this is certainly true for the definitely age related diseases like Parkinsons and Alzheimers. Other diseases may be another story. But in age related diseases, I believe if we fight against unavoidable physiological decline and find a way to slow that, as a corollary we will fight against age related diseases. These won't be precipitated in the normal lifetime. In my view, the main problem is the inborn difference between individuals, which can probably be changed.

Does the nitric oxide story fit in here? Viagra is very much in the news restoring sexual performance. Nitric oxide is in the brain - it probably links into the catecholaminergic systems somewhere
Its very hard to answer this question now. We thought calcium fluxes might be more important. But nitric oxide provides a very important system. Its another endogenous very short lived system. How, this activation locally in the catecholamine system is related at all to the CAE can only be answered when we know more about where it acts and where my new compound works. It is reasonable to assume that the endogenous ligands and (-)BPAP act via highly specific CAE/SAE receptors in the brain. We started experiments with labelled phenylethylamine and tyramine and we need also labelled versions of my compound to find this out. When we find that then we shall need to find out what are the endogenous ligands to these receptors - are phenylethylamine, tryptamine and tyramine which have these effects the only endogenous ligands or as I suspect are there other ligands too. I suspect there are other ligands which are probably a thousand times more active than phenylethylamine, tyramine or tryptamine because those amines have this effect but relatively high amounts are needed to exert the effect. But there is no doubt that what we are working with here is something very basic.

Nitric oxide perhaps is important in one other respect. Up to only a few years ago, no-one knew anything like this existed. So even if its not involved, it acts as a reminder that there may be lots of things in there that we don't know about yet
Yes. Anyone who thinks that they know what's really going on in the brain is making a big mistake. They only want to hear about things that fit in with what they know already. This is even true for the catecholamine system

You have made it very clear how important this question of life and death is but why has no one else been chasing this the way you have

Don’t forget, my basic problem was to understand what is drive or as I formulated it, the ‘specific activation of the brain’. I was lucky that deprenyl finally helped me to answer this question by leading me to the discovery of the catecholaminergic activity enhancement mechanism. Now we may say, that ‘specific activation’ means primarily the enhanced exocytosis in the catecholaminergic neurons in the brain, i.e. the brain engine works because of the physiological need on a higher activity level. To the question, why this effect of phenylethylamine and the amphetamines remained undetected. Because the catecholamine releasing effect of these substances masked their CAE effect. Deprenyl, the first CAE substance which was devoid of the releasing effect, was the tool which revealed it. But it’s taken me close to 50 years to understand what’s going on, so clearly no-one else was likely to see it very quickly either.

I was unable for a long time to see it. I saw and I wrote on it, without really seeing it. I even made annotations ‘forget about the MAO-B action’. But I still didn’t see it. You have to remember that it was a fantastic effect of the amphetamines this releasing effect. If you look at that effect, you couldn’t easily imagine that something else was going on behind it. I thought that there might be something else but why or how to show it and then it happened. Tryptamine convinced me. It has a CAE effect also, and now (-)BPAP, the tryptamine derived CAE/SAE substance, is much more potent than the amphetamine derived substances, deprenyl or PPAP. This is I think convincing evidence that the CAE/SAE mechanism is a common mechanism which regulates the catecholaminergic and serotoninergic neuron in the brain. It seems obvious that this is a basic mechanism, of the nature of which we have to learn a lot in the future. So David, I hope that (-)BPAP will serve as an excellent experimental tool for this purpose.

It is remarkable that we can elicit with very low doses of (-)BPAP an enhancement of the impulse propagation mediated release of dopamine, noradrenaline and serotonin in the brain. For example: if we take out the raphe of a rat treated 30 min earlier with a subcutaneous dose of only 0,0001 mg/kg (-)BPAP, the amount of serotonin released from the tissue will increase from the normal value, 0,391 to 1,040 nmoles/g tissue; and the amount of dopamine released from the substantia nigra will increase from 6,8 to 14,8 nmoles/g tissue. Having isolated the effect, we now know it can be stimulated with very small amounts of amphetamine or phenylethylamine and also deprenyl. Up till this we have been using 10 mgs of deprenyl. Why: Because at the end of 1965 when I asked my good friend Varga to make the first antidepressant experiment, I calculated the dose from the MAOI perspective. This dose was taken over by Birkmayer and then everybody was going on with it. Regarding the CAE effect, only a tenth or a fiftieth is enough. So I think we overdose the de novo Parkinsonian. If we shall have the opportunity to make a Datatop-like study, with (-)BPAP, I would recommend only a daily dose of 0,01 mg from this substance. Time will be needed to understand the CAE/SAE mechanism. Time will be needed to accept. I only published on this effect in 96. Time is needed for the response. But don’t forget, I published in 1965 on deprenyl and it was 17 years later that one of our deprenyl publications became a citation classic.

That's not so unusal. If I had been a professor in Harvard, things might have moved quicker. I have sometimes had basic important papers turned down by Nature and Science, which were later published by others. The reason - because I'm not English or American and neither of them were interested in Budapest. Neither the English nor the Americans like to think that anyone other than they can come up with anything important and they have the power. But I'm not complaining. I'm a member of a number of Academies of Science and have a number of Honorary Doctorates. I got a couple of prizes. In 1985, on the occasion of my 60th birthday, the Publishing House of the Hungarian Academy of Sciences published a Festschrift with 49 papers written by excellent authors and edited by three of my best pupils, K.Kelemen, K. Magyar and E.S. Vizi. I don't believe, however, that honours are so important because so many get them without any merit and so many others with merit don't get them. A lot of these things depend on your friendships etc. I think that's not important. Its good, its very pleasant if the world accepts in due time and they give you recognition and money but in the end only time can reveal the truth - whether I'm right or they are. Time!

We've mentioned Bovet but who else did you meet in your career whom you thought was important or who impressed you?
Well there have been so many people I have met at organized meetings, on lecture tours and elsewhere that it seems wrong to pick out a few but I will mention a few people whom I met when I was younger. I remember for example that once I spent an afternoon with Erspamer in his study in Rome. I knew of course very well his papers which deeply impressed me. The discoverer of serotonin never repeated himself, he always dug out something new and important. We started to talk about his research than he asked me about my work but soon we just talked about research itself, its meaning for us, its role in our life, etc. I left him with the feeling that we have so much in common in our basic attitude towards research.

I had the same feeling when I met Bacqu. Once I had the opportunity to spend by invitation a few days in Liege. Bacqu, one of the pioneers in catecholamine research, was my host. I admired his work and based on the spirit of his papers I was excited in advance to meet him. We spent a few days together and this meeting still lives freshly in my memory. It was an excursion in the past of catecholamine research with a special guide, an important participant of the story. Another dedicated scientist, also one of the pioneers in catecholamine research who told me gripping stories regarding the early history of the catecholamines, was Herman Blaschko, one of the most charming and fascinating men I ever met in my life.

As a young man I had an unforgettable meeting with Bernard Brodie in 1961. It was the 1st Congress of IUPHAR in Stockholm. The leaders of the national Pharmacological Societies were invited to a reception in the US Embassy. The reception had of course a fixed time interval. I met here Brodie and we started to talk about reserpine because I published that time a paper with some new aspects regarding the action of this drug in the rat. Later on I realized that my working hypothesis presented in this paper was wrong. Time

passed, the reception ended, he did not allow me to leave. We talked at least two more hours in the Embassy. He was so famous that he could allow himself to behave like that. I was astonished that an epoch making scientist spends with me, an almost unknown young worker, hours just talking about reserpine. Looking back to the 60s we may really say that time proved the high importance of Brodie's pioneering work in drug metabolism and the high significance of his contribution to our knowledge about the catecholaminergic and serotoninergic systems in the brain. He deserved for sure the Nobel prize for which he was repeatedly, but unsuccessfully, submitted.

Because of the cold war period we had much closer contact with the scientists in the Soviet Union than with the West. I developed special personal contact with many Russian pharmacologists. I should mention Anichkov, Zakusov and Mashkovski from the elder generation and Kharkevich, Rayevsky, Lapin from my generation. Anichkov was a remarkable scientist, who as a young man worked in Berlin with Paul Trendelenburg, one of the heroes in pharmacology. He was the co-author of the famous paper of Trendelenburg in 1929 which first described the effect of oubain on the heart-lung preparation. The two leading pharmacologists of the Soviet Union in the 60s, Anichkov and Zakusov, illustrated the joke - there are three categories of leaders in the Soviet Union, the ones who were in jail, the ones who are in jail, and the ones who will be in jail. Anichkov and Zakusov were in the camps for several years before I met them. Though I was repeatedly invited in their homes and spent unforgettable nights with them and their pupils, nobody ever mentioned the camps, even in the most relaxed hours, after huge quantities of vodka. Everybody always remained silent. In the 60s and 70s Anichkov and Zakusov got the highest official awards in their country and represented passionately the ideology of the Soviet Union in the IUPHAR General Assembly and Executive Board meetings. Russia will always remain for a foreigner one of the most enigmatic countries of the world.

There were many many other but I will just mention Merton Sandler and Gerald Stern. I am sure that Merton Sandler played a leading role in the development of psychopharmacology, not only with his important contributions as a sharp and intelligent scientist, but probably even more as the man who exercised on the highest level the art of bringing together the best people in wonderfully organized meetings and creating for them the proper atmosphere for fruitful discussions. Gerald Stern, a clinician with high international reputation in his field, put a charm on me from our first meeting with the extensiveness of his knowledge in science, philosophy and art. To read his sophisticated papers is always a special delight.

Can I ask you about the introduction of the psychotropic drugs to Hungary during the 1950s? Did they have much impact, were they delayed, did you have to make you own versions cause they were too expensive?

I think generally even in the 60s what was new in the West was reported and because of the highly developed pharmaceutical industry here, they either copied very quickly or made some small changes to make it possible. The

Hungarian population even under the communist regime had access to the important psychotropic drugs in good time

I think what people forget is that in the 1950s, most of the pharmaceutical companies, even firms like Ciba or Geigy were quite small. They were into dyes and all sorts of chemicals but their pharmaceutical divisions were actually quite small. They are now huge, but then perhaps they were roughly the same size as you say the big companies here were.
I think the pharmaceutical industry in Hungary in comparison to other industrial lines was a little bit more developed because of the history and because the Soviet Union and its satellites needed pharmaceuticals. It was more convenient for them to buy from Hungary and therefore it was reasonable for the government here to support this line because it was productive.

I think that those who worked in this business like me, were lucky in a certain sense because we had especially in this field better opportunities than many other people in other fields had. And because this was a small country, which supplied the big nation and all the others, the drug supply here much better and we had even some money to buy new and really important new drugs earlier than others. For about 25 years or more I was the president of the committee in the middle of the Hungarian drug administration from this perspective it seemed to me that we were in a more advantageous situation than others

Did thing change in the mid-1980s because in the West drug development costs got much bigger? From then on the SSRIs all get produced by Western companies and not by Eastern ones...
We have never had the resources to compete on an international scene. But if you look at deprenyl, I think we may say that it proved to be an important discovery. It cost almost nothing. We synthesised only about 30 structures. I selected (-)PPAP from altogether 40 new structures and (-)BPAP out of 65 structures. It was more brain work. This shows that sometimes even without a great industry you can develop something very important. But in this time of high investment research, which now characterises the West, it was never possible to do that here. We never have had the resources

So up till the 1970s you kept pace with things in the West but there was a change- at the clinical level?
It's like the football team. In the 1950s we were the best in the world. After 56 our stars emigrated. We continued to be good but not as good during the 1960s and 1970s. After the big change everyone thought it would all come back now that we could afford to pay the players but it hasn't yet.

We had very good, very clever clinicians, experts in some fields. But we never had and I think we still miss the resources needed for the highest level of clinical work. I think that the circumstances for the brain work were always better. This has its advantages and disadvantages of course but we always lost a lot of our best scientists and clinicians. The brain drain worked here very

substantially and very efficiently. On the other hand, I have had to make much of my work in collaboration with outsiders. So it is reasonable to say that this is a small country, a poor country, with an unhappy history and we just hope that the future works. We have had good intelligent people, whether they will come back to Hungary to work again in the future depends on what the future of this country in this capitalistic system will be. Will it be productive enough - because everybody likes to live in his native country. But on the other hand, it is good to know that famous scientists of Hungarian origin work almost everywhere in the world, and this was always very helpful to us

Now you are obviously a high performing person so maybe there is no need for you to take deprenyl yourself but do you take it?
Yes I take it. I'll tell you why. I started taking deprenyl when I finished that 88 study which was the first longevity study. It was published in December 88 and I started January 1st 89 to take deprenyl. I started taking two, later three tablets per weak, but than changed to 1 mg a day. I take deprenyl simply because I think as I showed you each system is running down. If you were someone who had a higher performance when young, there might be no need to take it but even he too can benefit. I'm convinced that there is no limit in the good to say it is good enough. What can be made better should be. I believe we should live as long as possible and maintain the quality of life as high as possible. If you find a technique to change that for the better, all individuals can make a profit from this.

My personal opinion is this. Very probably too much psychopharmaca are consumed in the world at this moment and on the other hand too little are consumed. Some are over used, some are not given enough. This varies from country to country but essentially its true for everywhere in the world. The main representative drugs we have now are not in my opinion very good for the healthy. For example, it's very important that the mild forms of depression are treated. I think there are thousands who have committed suicide who could have been probably prevented from that just by the treatment of a mild depression. So in this context probably we need to do more. But I'm not so very happy for example with the reuptake inhibitors which are very active or with the receptor stimulants because I believe that when we change something continuously by a drug, we may have benefits but we will also have a lot of noticed or unnoticed consequences of unphysiological situation we created.

Also, we need to pay more attention to a problem, which we almost neglect at the moment, which is the individual difference within the population. In the brain work, in the psyche these individual differences are quite fantastic so that gives us a huge frame work within - to make lower performing individuals into better ones. This is unknown territory for most people. Its a new thing. I'm so sorry that I have had so little effect in this effect. Deprenyl is the first example of something that will bring about change within the range of physiological variation, that will convert the normal or low performing to the normal or high performing without doing anything else physiologically. This cannot be done by the stimulants. I think the psychopharmacological agents of the future will have to be different in this way. The big firms at the moment

are restricted to diseses, they are not investing in the way I'm outlining partly because you can't make developments of this sort that will get through the bureaucracy

Would you get rid of the FDA?
I would like to get rid of the clumsy, narrow-minded bureaucracy which slows unnecessarily and in some cases even inhibits reasonable breakthroughs. I now more and more realise that the thalidomide disaster brought an other disaster - namely the over-regulation of the problem. This may have caused at least as much a problem as anything was saved by developing along this route. We have paid for that bureaucratic view. As I mentioned the bureaucrat is never asked to account for not giving to tens of thousands a remedy but is immediately punished if a good remedy makes some ill. This is wrong. And the pharmaceutical industry now in the world know that the regulatory mechanism are not interested really in improving the quality of life. They immediately believe that this is wrong. As a physician my oath compels me to think that this issue of the quality of life is important but this is in contradiction with the general interests of the governments and the bureaucratic systems and because of that its in conflict with the big pharmaceutical companies who have the money.

Two of the things that go together are this focus on disease and a failure to take into account individual variation. With a disease approach you get the notion of a right dose, which gets rid of individual variation
Absolutely

When you go to meeting in the West, you must see these huge marketing exhibitions where the industry buys the physicians with a few pens rather like was the white men bought Manhattan with a few beads
It's big business. Money spoils everything because money is power. Power corrupts and absolute power corrupts absolutely as Lord Acton said. Has our society changed in essence?

A true scientist is always in conflict with power. I don't like that money is so powerful but we have accept that it is. I remember I was asked by the Journal of the American Geriatric Society to make a review of deprenyl. This was very nice of them. They recognised that this is so important. So I wrote a manuscript and send it to them. They wrote back 'thank-you, we don't want to change anything other than minor editorial changes in the language but we need to add to the end a paragraph'.

The addition says: The proposal in this final paragraph is the author's opinion and does not reflect the mainstream view point at the present time. It is a hypothesis, testable by a long term randomised controlled trial treatment. Treatment of individuals in this way, outside a randomised control trial, would be considered premature in the United States.

They were scared
They said 'thank-you, this is very good but we have to add this small little piece in'. And this is the reason why you can't give a small dose of deprenyl

now as a prophylactic agent. My problem is I know that if those patients who are going to precipitate into Parkinson's disease were to take just 1 mg of deprenyl per day for 10 to 15 years before hand they could either avoid this or shift it in time substantially. All the evidence points this way but despite all this work, despite the clear cut evidence, they cannot say that everybody who is afraid of getting Parkinson's disease should take 1 mg of deprenyl just to remain on the safe side. Why can't they say this? Because this is the system. This is how life is now organised. This is how society works. As a physician however I think I'm responsible. The evidence as it stands is that if you give a de novo Parkinsonian deprenyl instead of about 300 days to l-dopa need, he takes 550 days. What would happen if you give it to him 15 years earlier?

Maybe if we develop techniques to measure the rate of decline of dopamine in the brain, we will be able to pick out those for whom it is more than normal and we will be able to give it to them. That would be beautiful. Then we can select who should get it but in the mean time isn't it reasonable that something should be done for such dangerous diseases as Parkinson's and Alzheimer's. Why should people wait until they have the condition. We know this loss is going on anyway in normal aging even in those who are not going to end up with the disease precipitated. The DATATOP study data are there. Part of the reason for the delay, I think is because people cannot explain the finding but just because you don't know how it is working doesn't mean you shouldn't do it. You did not have to know how aspirin acted to realise it was an analgesic.

Donald Buyske was the man who finally brought deprenyl onto the market to US. He knew about these things. He died of an heart attack shortly after it came on the US market. He told me Joseph there is only one way to win this war. You have to go on television in the United States as a showman. You must talk about it everywhere because only public pressure can bring about what you want for this drug. I told him that I had several times been asked by the Hungarian media to talk about deprenyl on television but I never did it. I have only done it on one or two occasions and then only on serious programs because I don't like it, its to much trouble. Maybe he was right. Maybe the world now is different and is working more the way he said and I have to reconsider my position. I now believe more the scientist has to be involved in these things but I don't know how. I give lectures and the lectures are very successful always but nothing happens no matter how successful they are. I believe still that important things are simple. I like to hear other opinions, to learn from different points of view. When it comes to this work, however, the main problem is that nobody when they hear it says this cannot be right because of this and this and this. If they did I could go and think it over.

If there is no response, then it must be important

This is the problem. Polemic is good in order to change ideas. I never think I am right for sure. Maybe I am wrong but I have to be shown by somebody that here this is wrong for this and this and this reason. That neurone is not acting like that, its acting like this. If he is right, I shall admit it. I sleep with my ideas. I haven't married them. So argument is no problem. The main problem is that there is no argument, no debate. Nothing happens.

References

Knoll J, Ecseri Z, Kelemen K, Nievel J, Knoll B (1965).Phenylisopropylmethyl-propinylamine (E-250) a new psychic energizer. Arch. int. Pharmacodyn. Thér. 155, 154-164.

Knoll J, Vizi E Sz, Somogyi Gy (1968) Phenylisopropylmethylpropinylamine (E-250), a monoamine oxidase inhibitor antagonizing the effects of tyramine. Arzneimittelf. 18,109-112.

Knoll J (1969) *The theory of active reflexes. An analysis of some fundamental mechanisms of higher nervous activity.* Publishing House of the Hungarian Academy of Sciences, Budapest, Hafner Publishing Company, New York, p. 131.

Knoll J, Magyar K (1972). Some puzzling pharmacological effects of monoamine oxidase inhibitors. Adv. Biochem. Psychopharmacol., 5, 393-408 This Week's Citation Classic, January 15 (1982).

Knoll J (1982) Selective inhibition of B type monoamine oxidase in the brain: A drug strategy to improve the quality of life in senescence. In: Strategy in Drug Research (Ed. Keverling Buisman, J.A.) Elsevier, Amsterdam, pp. 107-135.

Knoll J, Yen TT, Dalló J (1983) Long-lasting, true aphrodisiac effect of (-)deprenyl in sexually sluggish old male rats. Mod. Probl. Pharmacopsychiat., 19, 135-153.

Knoll J (1988) The striatal dopamine dependency of lifespan in male rats. Longevity study with (-)deprenyl. Mech. Ageing Dev., 46, 237-262.

Knoll J (1994). Memories of my 45 years in research. Pharmacology and Toxicology 75, 65-72.

Knoll J, Yen TT and Miklya I (1994) Sexually low performing male rats die earlier than their high performing peers and (-)deprenyl treatment eliminates this difference. Life Sciences 54, 1047-1057.

Knoll J and Miklya I (1995) Enhanced catecholaminergic and serotoninergic activity in rat brain from weaning to sexual maturity: Rationale for prophylactic (-)deprenyl (selegiline) medication. Life Sciences, 56, 611-620.

Knoll J, Miklya I, Knoll B, Markó R and Kelemen K (1996) (-)Deprenyl and (-)1-phenyl-2-propylaminopentane, [(-)PPAP], act primarily as potent stimulants of action potential - transmitter release coupling in the catecholaminergic neurons. Life Sciences, 58, 817-827.

Knoll J, Miklya I, Knoll B, Markó R and Rácz D1996) Phenylethylamine and tyramine are mixed-acting sympathomimetic amines in the brain. Life Sciences, 58, 2101-2114.

Knoll J (1998) (-)Deprenyl (Selegiline) a catecholaminergic activity enhancer (CAE) substance acting in the brain Pharm. Toxicol. 82, 57-66.

Varga E et al (1967). Clinical trial of a new type of promptly acting psychoenergetic agent (phenyl-isopropylmethyl-propinylamine. HCl), E-250, Acta Med. Acad. Sci. Hung. 23, 289-295.