

## 5 Roland Kuhn

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### *From imipramine to levoprotiline: the discovery of antidepressants*

#### *What led you into psychiatry?*

Accident. Not totally but partially. It was a second love. What I really wanted after my finals was an assistant's placement in surgery. I had an appointment with a professor with whom I was friendly and who was very good but shortly before my final exams he told me he was retiring and he had no use for me. So then I had no placement and that was one of the reasons. I had to find a new position. My colleagues had already all been placed and the best positions had gone. Another reason to think of psychiatry was that I had done my dissertation on iodine metabolism in cretinism and because of this I had become aware that the neurovegetative nervous system and the psyche have a great influence on the endocrine system. So I thought why not do a year in psychiatry, maybe I would be able to get a position there. I thought I would try it for a year and then I would also have time to look for a good place and change. So I went to Professor Klaesi and he was immediately very enthusiastic and welcoming. Of course I could come!

#### *Where was Professor Klaesi at that time?*

In Berne. I've studied in Berne and Paris – I was one semester in Paris. So I went to Berne. In the beginning I was a ward doctor and I had a ward of one hundred beds, all men, with five hundred admissions alone in a year. You had to work till evening and half the night and in the night you had to get up of course. As a result I had so little time that it was impossible to look for another place. So instead of one year I stayed another year. That was in the Waldau. After two years, even before I was finished I was asked whether I would be interested in becoming consultant here in Münsterlingen.

I made inquiries and I heard that a new director doctor Zolliker had come to the clinic. I also inquired about the possibility for scientific work there and it happened that the clinic had an excellent scientific library. That was one reason I came. Also not five kilometres away was Ludwig Binswanger. Binswanger was one of the most important Swiss psychiatrists at that time, no doubt about it and I was told that if I went to Münsterlingen I would surely have contact with him and would be able to learn a lot. So it came about: I

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came here for what I thought was two years. I thought then I would go traveling but that was in the year 1939 and the war came and there was no possibility to travel. So I stayed. In time I saw that it was a great advantage to stay in one place in psychiatry and I lost my interest to do surgery. I decided to remain a psychiatrist and essentially I have never regretted it.

When I came into psychiatry, in Berne we were already doing sleep therapy with Klaesi and also cardiazol shock treatment and insulin therapy. By the time I came to Münsterlingen we also did it here. So in this way I learnt biological psychiatry very early in my career. In Berne there were two consultants who were both psychoanalysts – Arnold Weber and Otto Briner who was trained in psychoanalysis in Berlin. From these two I learnt psychoanalysis. I also learnt to hypnotise – at that time we still used hypnosis. That was a terrific business. I got acquainted with the Rorschach test from Weber. He was an analyst with Rorschach and he had been taught by Rorschach himself. Weber was also psychopathologically excellent. He also had a child observation ward where I learnt child psychiatry. There was also Jacob Wyrsh, who was a general clinical consultant who was absolutely brilliant in psychopathology – not in this modern psychopathology as we have it today but in the psychopathology of that time. He was an immediate pupil of Eugen Bleuler. He was very good at exploring patients and he showed us how to do this. He was Director of the Polyclinic. So by the time I came here I had a complete overview of contemporary psychiatry, which I had got in a very short time – in two years – and all from people with excellent credentials.

Then there was Max Müller who was in Münzingen; he arranged seminar evenings there. There was also Walter Morgenthaler, the man who had the case of Wölfli, the artist who painted these famous pictures, that along with Prinzhorn was the start of the dealing with art of the insane. Max Müller invited Walter Morgenthaler who talked about education in psychiatry and Storch who was interested in philosophical psychiatry. I was also made aware of the modern philosophical psychiatry, of course because of Ludwig Binswanger that was foremost figure in philosophical psychiatry. At Binswanger's I met Kurt Goldstein and got to know him personally, as well as Gebattel, Heidegger and numerous other people with some of whom I corresponded.

So when I joined this establishment, I did mainly biological psychology in the clinic and philosophical psychiatry with Binswanger. I started at the same time to do psychotherapy with Binswanger checking my therapy. It was an absolutely unique education. I knew Kretschmer through Klaesi and I also heard a lot from Viktor von Weizsäcker.

*But he was never in Switzerland*

No Weizsäcker was not, that is I never knew him personally, but I had the first edition of the Gestalt Circle, that is when the edition first appeared I got it within the first half year. As part of my training I was told I had to read it. Every two weeks also I went to Binswanger for dinner in the evening and afterwards

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there was a demonstration of a Rorschach protocol and I had to interpret the protocol. After that the consultant presented the case history and Binswanger with his knowledge of the case produced a synthesis.

*A psychoanalytical interpretation.*

Yes, an interpretation. He was already then producing his Daseins-analysis. So here, then, the Daseins-analysis originated. It took decades to evolve. In this fashion I always got to know new people who came to our clinic. I have to mention something here. Binswanger as the owner of a private clinic had an unrivalled grasp of depression and manic depressive illness. He was treating very severe cases in famous people. He regularly had professors and heads of departments as patients – these highly intelligent people with their depressions. He also had alcoholics and drug dependence – everything in psychiatry and of course we got to know these cases.

*Were these patients presented to your seminar?*

Not the patients but the case history along with the Rorschach test and maybe other psychological tests. We discussed all this and in this way we learned an incredible amount and we gained enormous experience. These meetings took from 7.30pm till 11.00 o'clock at night. Additionally Binswanger visited us now and then in the clinic here and we presented cases to him and he gave us his opinion. In this way I learnt a great amount. I also had contact with Hans Binder, who was professor in Basel and Director of the Rheinau clinic. He was an excellent psychopathologist.

*You mentioned some of the treatments that were being used when you came to Münsterlingen; were there any drug treatments being used and what were the prospects for drug treatment?*

Drug treatment was the treatment of choice with sedatives, morphium and scopolamine and sleep therapy as Klaesi did it modified by Cloetta. Very early on we used Trional which was taught to us by Ernst Grünthal who came from Reichhart in Würzburg – he was an anatomical brain neurologist and psychiatrist. So we did Trional sleep therapy, that was wonderful. It lasted six weeks. One gave Trional up to a certain dose and then came down, like with opium. Very early on, as soon as I joined, we did malaria treatment. It was very difficult during the war because we couldn't get malaria from the tropical institute in Hamburg where we used to obtain it. So we cultured our malaria base in chronic schizophrenics, so that we were able, during the war, to provide the whole of Switzerland with malaria blood. By the way, this developed from the experience of its effects on chronic stuporous catatonics where it helped a lot. Malaria treatment really helps these people. I would say they got better; not completely well, but they got better.

*I thought these malaria treatments were only used for paralysis?*

Well it's possible that nobody else did this. This idea arose out of necessity.

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*Where did the idea of introducing Trional treatments come from?*

It came from the Würzburg Clinic and Grünthal brought it from there. He had the expertise of how much to give, up to a certain maximum dose. It was a good preparation to pacify some of the raging women on the open wards who simply screamed for 24 hours a day. In this way we managed to significantly improve the atmosphere in the clinic. Also we used electro-shock treatment and cardiazol shock treatment. At that time, I gave the treatment three times a week between 10 and 12 to between eight and twelve cases with cardiazol shock.

*Why did you prefer these to insulin shock?*

Insulin shock was much less effective. Insulin treatments helped in those cases when a spontaneous epileptic fit occurred – then one would say ‘all right, then it will help’. Following this idea we treated people with an additional cardiazol shock when there was no epileptic fit when they were in the insulin coma. But of course the disadvantage was that after about eight shocks you got a psycho-organic syndrome, which was the beginning of the relapse. After three months these psycho-organic syndromes stopped and the psychotic experiences reappeared.

*In 1949 Geigy produced G22150 – the forerunner of imipramine. What do you understand they were hoping to treat when they first produced it?*

The true beginning was that I had a connection with the Waldau clinic, where Grünthal was. He had a Brain Anatomical Institute which Klaesi had founded and he had contact with Geigy and had tested an anti-parkinsonian drug for them. He wished to expand the trials and asked me whether I was willing to take part. This is how I came in contact with Geigy.

*Which year was that*

That was around ‘49. Geigy had at that stage a brilliant pharmacologist, Domenjoz. Geigy let him go later, foolishly – it was one of their stupidities. He then went to Saarbrücken and became professor of pharmacology and did some highly interesting work there. It is incomprehensible that nobody took much notice of this work. Anyway, Domenjoz came to me and said I have a new sleeping pill, would I try it out. I told him I would be interested to try it.

*Did he ask anyone else?*

Yes, there were other people. Exactly who, I cannot remember – not at least concerning this specific drug. Afterwards I told him: ‘This is no sleeping pill, but this substance has curious effects on chronic schizophrenics, not on their sleeping pattern, but on their schizophrenic symptoms’.

*At the time when Rhône-Poulenc produced Chlorpromazine, they had no idea what the pill would do and they gave it to respiratory physicians and cardiovascular physicians as well. Do you think Geigy also gave this to respiratory and cardiovascular physicians?*

No, no. Geigy’s drug had the structural formulation of an anti-parkinsonian drug. The anti-parkinsonian drug they had introduced together with Grünthal

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was Parpanit and it was from this family of drugs that the suspected sleeping pill came from. It had a formula already similar to Tofranil with a seven molecule central ring. I had tried Parpanit out with people suffering with Parkinson's but we had very few Parkinson's cases and there were no new ones. The ones we had all originated from the epidemic of the encephalitis lethargica. The Waldau also had a few but we were always looking for more cases. That is how this whole thing developed. At this point I already realised, that these anti-parkinsonian drugs work better if you give iron. I observed that during treatment where I did a blood analysis all the patients developed a slight anaemia. So I thought to myself I would treat these patients with iron and I realised that if you add iron the neurological symptoms improved, more than if you didn't. When I looked into this, I learnt that the nucleus niger is the most iron rich in the whole brain. From then on I've never treated Parkinsons Disease without iron. I've always said this but even today nobody believes me. I've always been concerned with such metabolic phenomena.

Anyway then I wrote to Geigy, to Domenjoz, to ask whether he would make available more of this trial drug, because I had an idea to try it on patients with schizophrenia, who had had psychosurgery. At that moment Geigy thought it is clear Kuhn has gone mad, he is not quite right in the head. Now, he wants to treat schizophrenics, whereas we only want to treat Parkinsons. So they sent me these little bottles with tablets and I said this is stupid – that I had to have more and so I gave up.

*Did Geigy come round to the idea that it might be useful for schizophrenia after Paul Kielholz had held a meeting in Basel in 1953.*

The first meeting of the Swiss Society for Psychiatry did not take place in Basel – it was in Biel. It was the spring meeting, where Kielholz reported for the first time on Largactil. At that point in time I said to myself that I had seen what he was reporting two or three years before with the preparations from Geigy. It was immediately clear to me and I still remember where it happened – I remember where I sat and I remember how he spoke about it and how I thought it is exactly that which I have seen two to three years ago.

Following that meeting we got Largactil gratis – for half a year – and the whole clinic was swallowing Largactil as one could imagine. Then one day a company rep came and said 'The trial phase is over, now you will have to pay for the Largactil'. Well we were a poor county; these were poor people and we only had a pharmacy budget of 6000 SFr a year, which we needed first and foremost to buy morphium and scopolamine. You couldn't get much for it and we needed it in great amounts. So we had no money and we couldn't buy Largactil. This was when I said to my boss 'You know I've seen all this with a drug from Geigy. I will write to Geigy and tell them that I know their drug has the same effect.' This is how I went into business with Geigy and they sent me huge bottles!

So I tested it for a whole year and showed that it was truly a neuroleptic, but that it had a lot of unpleasant side effects and that it was not as good as Largactil. So then the question was 'How does the formula differ from

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Largactil? Because in those days one thought if the formula is fairly similar it should have the same effect. I said that it obviously depended on this side chain, which was different in G22350, that they should use the same side chain as Largactil. As it turned out the substance already existed, it had been synthesized. When I told Domenjoz about my idea in a meeting in Zurich hotel, he spread out his samples and I said "That is the substance which has the side chain of Largactil, that is the one I want". He was immediately agreeable.

*They also gave this compound G22355 to lots of other people to try, and you were the only person to pick up the anti-depressant effect?*

They wanted a neuroleptic. The problem was that I was also looking for a neuroleptic as similar as possible to Largactil. I wanted a formula which was as close as possible to Largactil, so the most obvious thing was to look for the compound with the same side chain, and I tried the compound as a neuroleptic and observed that it was not so good, that it didn't work as well. But I saw that it was different, so then I used it with depression and in particular with clearly endogenous depression.

*There were also reports that not only was it not awfully good for schizophrenia but it actually seemed to be unhelpful for some people. You said in your essay in the Pongratz volume that it had a disinhibitory effect on schizophrenics, that people got almost manic*

Yes in any case it didn't do the schizophrenics much good, that was very evident. It was certain that it was no replacement for chlorpromazine.

*Where did the idea that it might be useful for treating people who were depressed come from? Was it from hints that one or two people, who were on the study for schizophrenia, went 'high'.*

Yes, yes. It is like that. Tofranil affects schizophrenics and the reason is, in my opinion, that schizophrenics often start with a depression, we may be dealing with an Einheits-psychose. Many schizophrenics have depressive symptoms and with these it worked, of course, but at this time I didn't understand how it worked.

*At that time you were of the opinion that you were dealing with two separate illnesses.*

That was the other thing. I knew what depressions were and that you could heal them with electric-shock. So I reasoned that depression is not reactive, that it has to have an organic basis because otherwise electric-shock would not work. That was clear. So in principle there had to exist a drug against depression. There were other pointers to the same realisation... it would lead too far here, to explain this now, it has to do with the psychopathology. In 'vital' depression the most important fact is that the depression is worse in the morning and better in the evenings. Healthy people who work are tired in the evening and fresh in the morning, but if somebody who does not work is tired in the morning and fresh in the evening than this can only be explained on biological grounds. It cannot be psychogenic; there has to be something biological at work.

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*I know that you have a different philosophy of drug discovery to the currently prevailing one. Can I ask you to expand on the methods of clinical observation you used to discover the antidepressant effects of imipramine?*

Given that there has been no discovery of more efficient drugs than imipramine in the last forty years, I am impelled to ask how I was able to discover these effects and later was in a position to offer to Ciba a modification of the chemical formula of a substance synthesized in its laboratories which was later called maprotiline. My methods were entirely different from those which are nowadays applied in clinical research. I have never used 'controlled double-blind studies' with 'placebos', 'standardised rating scales' or the statistical treatment of records of large numbers of patients.

Instead I examined each patient individually even every day, often on several occasions, and questioned him or her again and again. Many of the patients were also under the observation of my assistants and nursing staff and I always regarded their proposals and criticism seriously and their observations and considerations were also recorded.

Thus, in 1957, I published the results of treating 40 patients for at least 1 1/2 years. Some years later the outstanding Belgian psychiatrist, Bobon said to me 'the results of your research are surprising. Even more surprising, however, is the fact that in your first publication, you discussed 95% of everything there is to be said in essence about imipramine'. Even today, at the most, only a small modification would have to be made to the original text.

The essential result of the first publication can be expressed in the following quotation 'a particularly good effect is achieved with typically endogenous depressions... as far as they present symptoms of vital depression'. Furthermore at that time I pointed out that reactive depressions also respond to antidepressant medications.

But it has turned out that most psychiatrists did not know what is meant by the term vital depression. It is a syndrome which consists of tiredness, often combined with disturbed sleep, psychomotor retardation and difficulties with thinking, deciding and acting. Patients have physical and psychological sensations of oppression and narrowness and they have lost the ability to experience joy. But the most important feature is that all of these symptoms are much more marked in the morning than in the evening.

One needs to realise that the symptoms of vital depression are often not spontaneously mentioned by patients and cannot be found easily through questioning. They are often concealed by other symptoms which may seem to be more severe. They may not come to the patients mind even with questioning. Patients admit to these symptoms only as the links of an integral whole in a dialogue that is free and comprehensible. Isolated questions of a standardised scheme cannot be understood by many patients. He or she may be unable to make any connections between them and his or her former experiences and as a consequence may answer 'no'.

Nowadays you can read in ICD-10 that 'it is acknowledged that the symptoms referred to here as 'somatic' could also have been called melancholic,

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vital, biological or endogenomorphic but that the scientific status of this syndrome is somewhat questionable. The classification is arranged so that this somatic syndrome can be recorded by those who so wish but can also be ignored without loss of any other information'. That is exactly the opposite of what I wrote in 1957 and have stated again and again ever since. Vital depression is based on a correct observation and it can be very often found in almost any psychiatric disorder. But to conclude that this symptomatology is to be considered as a non-specific syndrome which has no meaning is a fundamental error. In any psychiatric disorder which includes vital depression, this syndrome responds to treatment with an antidepressive medication, whatever the other psychopathological diagnosis may be. It may be interesting to note that this comes close to an observation made by the Belgian psychiatrist Guislain 150 years ago, who put forward the idea of a unitary psychosis which always began with a state of depression. I pointed out in 1964 that some support for such views has been shown by the generally acknowledged fact that many patients with obsessional disorders respond to antidepressants.

I have never been urged to change my methods or the interpretation of my results. I have continued to practice and to research as I did before and have obtained significant results. However, they have not received much notice. As long as there is no willingness to understand that psychiatric illnesses, especially affective disorders which form the basis for states of depression cannot be reduced to mathematics, nothing is going to change.

In the future the researcher needs to turn away from computers. In clinical research, most of the statistics are useless and reliance on them can be severely limiting. It is necessary to turn toward our patients, examine them as individuals, study them and then begin to draw some conclusions based on solid clinical experience. Negative results can prove to be as fruitful as positive ones and can point to the discovery of new facts. The discoverer does not need to go to congresses in order to gain information but does need to examine every patient individually, to talk to them in familiar surroundings and not just in the doctor's office. The doctor has to have a free and open, not preconstructed conversation with the patient, adapted to their situation in a manner that can be easily understood by them. It is necessary for the doctor to continue in that way until the necessary and important information has been obtained and this work has to be done by the researcher himself and not left to assistants.

*You mentioned that you always depended on the observations as well of ward staff and the other people working with you. Now it is quite clear in one sense that the response that you describe to imipramine is something that the ward staff couldn't have fully appreciated in a sense that what you actually described was the response of a vital depression to this treatment, and they wouldn't have been trained to appreciate concepts such as vital depression but what role did the observations of the ward staff play in alerting you to what was going on?*

I have to explain something at this point. In Münsterlingen we had an outpatients in the general hospital and the consultants in surgery and gastroenterology, gynaecology and obstetrics were well disposed towards us and sent



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us cases which were ambiguous and even those which did not show obvious psychological disorder. Every Wednesday we went to the general hospital together with an assistant. We then had to examine six to twelve patients, and decide whether the psychiatrist could have anything to offer to these cases. And often we could. These were average hospital patients who came to hospital with everyday kinds of physical complaints and did not come because of psychological reasons.

*Why were these patients referred to a psychiatric outpatients department?*

Because the consultants of the departments, when they received a patient who complained about stomach pains and nothing was found during the examination, said 'let's see whether the psychiatrist can find something'. And what did the psychiatrist find? Mainly there were two diagnoses which we came up with, the first was alcoholism which had been missed by the physicians and the second was vital depressive mood disorder. Here I learnt to ask questions which are decisive in finding the underlying vital depressive mood disorder.

*I can see this but how much did the people under your supervision, other personnel, nurses for instance understand this and help with their own observations?*

Well what I learnt in the hospital I did not keep to myself. I showed the assistants who came on the rounds with me. They would show me their patients when they couldn't find anything, or else found something very odd and then I would explain to them: 'this woman has a depression and that is why she is in hospital'. This is how the assistants learnt from me. In the same way I taught the nursing staff how they have to observe the patients in order to see vital depressive mood disorder. It happened for years like this. The discovery dates from the year '57 and I came here in '39, so I had worked on this for eighteen years before I made the discovery.

*So these insights came from you to others and obviously not the other way round?*

Yes and when these people noticed a response to treatment, of course, they then told me 'You were right'. Even my boss, the director who, of course, also got to hear about it, observed the same thing.

*How much was the actual discovery of this drug at this time an accident of history in the sense that if you were to give Tofranil to people who were being treated today for being depressed, it possibly couldn't be shown to work as well, maybe because community cases of the kind we have today are milder cases while on the other hand if you look at the drugs that are used today for people who are depressed, the SSRIs, they mightn't have worked as well for the more severe cases you had in the 1950's in hospital?*

It is certain at that time of course that we had a different kind of patient than today. They were people with a more severe depression. Today the depressive comes for treatment only after their general practitioner has already done everything possible with them. The cases then were much better suited for trials because those today who are suitable for trials don't come anymore to the

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psychiatrist and even less into clinic. The clinical picture has completely changed because of treatment.

The second remark reaches very far and it is very complicated. It's because of the fact that catecholnergic as well as serotonergic active drugs work as antidepressants. In my opinion, the number of people who are affected by catecholnergic drugs only is larger than those on which serotonergic drugs work only. There is a third group that is affected by both. Purely catecholnergic-responsive cases are probably a quarter of all cases, at a guess, purely serotonergic are probably 10-20% and the others are mixed and the composition is not always the same. During treatment the effectiveness of one or the other drug may change. Under certain circumstances you can get a pure catecholnergic effect in the beginning, with Ludiomil, but after a while you have to add something else or vice versa. There are probably 10% of all cases where the catecholnergic drugs don't work at all (Ludiomil), who respond very well to serotonergic agents. That doesn't mean that after half a year it is still like this – it might be that you have to add Ludiomil after half a year in order to maintain the good effect because the inner dynamic is changing all the time. This has to do with the fact that the serotonergic and the catecholnergic systems are most intimately connected with each other. So you see the serotonergic system can induce a reaction in the catecholnergic cells. And the opposite is possibly also true.

*Now, you actually discovered the antidepressant effects of the drug at the end of '55?*

No. It is absolutely clear, the date is fixed – it is one day and that I can tell you. I have here a copy of the case history of the first patient.

'On the 12<sup>th</sup> of Jan 1956 the treatment has begun with 100mg of Tofranil. On the 14<sup>th</sup> of January there was an acute symptom of delusion... Ah here, 21<sup>st</sup> Jan '56: For three days the patient is a totally changed person. So since the 18<sup>th</sup> of Jan, six days from the beginning of the treatment ( I added that afterwards), all her manic behaviour and restlessness has disappeared. The day before yesterday she remarked herself, that she had been terribly confused and as stupid as she had ever been before and she didn't know where it had come from but she was only glad that she was better now.' – That was the 18<sup>th</sup> Jan '56.

*O.K. but why this long interval between your first report of antidepressant effects to Geigy and the final marketing of the drug? Why did the company hesitate so long?*

That is another story. In Jan 1956 I made the discovery and shortly afterwards sent a report to Geigy. After this report, Geigy sent the compound to ten Swiss clinics. Of these ten clinics, I think six replied. All six said that the drug was completely useless. Following that, Geigy said that they would not proceed and that I didn't know a thing. But then there was a very prominent person at Geigy Robert Böhringer, who was part-owner of the company Böhringer Ingelheim, it was a family concern, who was also a shareholder at Geigy. He had some influence in the running of Geigy. He was known as the 'grey emi-

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nence'. He constantly moved around in the company, opened every door and asked everybody what they were doing. He had an office employing two secretaries who wrote reports for the attention of the management. Now a relative of Robert Böhringer became depressed and he had heard that there was something about that might help and he asked whether he could try the drug. So Robert Böhringer went with Tofranil in his pocket back to Geneva and gave it to his relative. After five days she was actually healed and he came back to Basel and said Kuhn is right – it is an antidepressive. So then the firm introduced the preparation. But this is not publicised anywhere.

*Extraordinary.*

This is absolutely authentic because Böhringer himself told me. At that time there did not exist any government departments who concerned themselves with these things, anybody could put onto the market what he wanted without asking a soul but Geigy still thought it was not true. So they said 'Okay we will introduce it but only in Switzerland and only for psychiatric clinics'. Then Kielholz who was working at the psychiatric clinic in Basel said how wonderfully well it worked and after that other people said how excellent it was – for instance Lieser, in Haar, near Munich, where there is still a big clinic.

But on the other hand there was also somebody else, for instance, who summoned me after about a year, who told me it was terribly painful for him to have to inform me that everything I had said about Tofranil treatments of depression was untrue. It was all incorrect. He had made trials with his colleagues and he found that it was all untrue. I said, 'I have to ask you what kind of patients did you test it on'. He replied patients, of course, with unambiguous depression – depression with melancholic delusions. I answered that 'I had never claimed that it would work with these kinds of depressions but I have always said that the important part was the vital depression'. To which he replied that this was such an ambiguous expression that he didn't know what to make of it. So, I explained to him what I understand vital depression to be. He said that now it was clear to him and I told him 'Now go and please do not treat that other kind of patient because the drug will not help there. You have to use it with the right kind of patient. If the patients are manic you have to also give a neuroleptic'. Today everybody knows these things.

*Was another reason for the hold up the fact that the effects of the drug were counter-intuitive, in the sense that everyone expected an antidepressant, if there was such a thing, to be something of a stimulant but here you were proposing that a sedative drug was antidepressant?*

That again is a very complicated question. The idea of stimulus and inhibition, these opposite activities, of course is a scientific idea which has been carried into the debate artificially. It is much too simplistic in order to explain what happens. One needs a very intricate exploration in order to know exactly what is happening.

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*Certainly but from a naïve point of view, people within the company would have thought that if there was a drug that was going to be antidepressant, that it would be more likely to be a stimulant. Within Geigy were there other reasons to hold back apart from the reason that many other clinicians did not believe in it*

That I do not know. Of course nobody at Geigy knew what a depression was. Now the whole world talks of depression but then depression, as an illness, was predominantly only known of in specialist medical circles. Everything I said sounded to these people highly curious.

*Was it seen as a rare disease at this time?*

Yes, there were the great melancholias with delusions, with suicidal ideas, with stupor, with agitation, with food refusal, the classical great melancholia which was then, as is today, a rather rare presentation while vital depression, as I have described it, is the most common illness over all although at the same time it is the least well known – exactly because it occurs together with hypochondria, with obsessive-compulsive disorders, hysterical manifestations, manic behaviour etc. And then people only treat these symptoms, nobody thinks to look beneath it.

*Were you aware that they called in other experts to help them assess the drug. People like Frank Ayd were asked in.*

That is true, when it got around, of course everybody came to Basel.

*But not before?*

No, before there was nobody. Before there were only these ten Swiss clinics which were asked and all of them were told it was a new neuroleptic, the same as Largactil and they were to try it out. Six replied it were totally useless, there were only side effects.

*All tried it as a neuroleptic and nobody tried it for depression?*

But nobody thought that they could use it for depression, nobody thought of it, of course.

*But by then your report was with Geigy saying that it helped against depression?*

Geigy didn't notice that there was anything new within this report. Geigy was only looking for a neuroleptic, they only wanted a competitor to Largactil. They said to themselves those French are earning big money with Largactil and we want to have a share of the money.

*They only realised after Böhringer*

Well, even then they didn't fully. Only very few believed it at that time. But it was the case that Böhringer could prevent them from telling me to terminate the trials.

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*That was the key moment then?*

What Böhringer said was the most important factor at Geigy, at least this is how Böhringer presented it to me. Böhringer was a poet from the Stefan George Circle. He was an extraordinarily educated man. He owned one of the few original marble images of Plato. I do not know how he was paid by Geigy, but one day Geigy gave him a painting by a very famous renaissance painter, Montegna, in order to reward his services to the company. He was an amazing personality. And he was the one without whom Geigy would have let the whole thing drop and nobody would have ever known about it.

*Some additional evidence for what you are saying comes from the fact that in 1958 Geigy produced G34568, which was later clomipramine and they gave it, as I understand it, to Walter Pöldinger first and asked him to try it out in schizophrenia. They still weren't looking for a compound for depression.*

I tested clomipramine and also dichlorimipramine – Geigy had a compound dichlorimipramine where both phenyl rings had a chlorine atom. This preparation was also effective. The specific effect of clomipramine on obsessive compulsive behaviour I saw in 1964 when I said that you could use this compound to heal OCD. In 1964 I wrote to Geigy about this but it is the case that I also only realised later that clomipramine has a specific effectiveness in OCD.

*How does this link with the idea of a unitary psychosis.*

The same thing applies to hysterical manifestations. Only that with hysterical manifestations even more than with others, in addition to the manic depressive constitution, a paroxysmal symptom of the epileptic kind is present as well. This is why women with hysterical manifestations – of the notorious kind – have to be treated with additional Tegretol. In these kind of cases I give Tofranil, Ludiomil or Anafranil, and depending on how big a part the obsessional behaviour plays, I give Tegretol. I had very good successes but you cannot leave it out.

*To come back to 1957 and Geigy's dilemma about whether to market this compound as an antidepressant: Did the fact that Nathan Kline in 1957, came out and said I have an antidepressant and there is a big market out there for that kind of compound, make any difference to the way they thought?*

I do not know how much that played a role. I came to America in 1958 to the American Congress in San Francisco, when there was a great deal of news about Nathan Kline and Marsilid. It was printed in the American daily papers that the congress commission had interviewed Kline and that Kline told them that the Russians with their Sputnik were way ahead of the Americans in the Arms Race. Now it was important that America should get ahead of the Russians and they could only do it by increasing the psychic abilities of the American researchers. So he said that everybody should take Marsilid, in order

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to help with their psychic powers, so that America could catch up with the Russians in the space programme. And this was printed in the newspapers in May 1958 at the time when we were in America.

*Was Kline's name known in Basel?*

Yes, yes, Kline was known in Basel. Kline was widely known, he himself saw to it that he was well known. .. And at this congress in San Francisco, he made a big show and tried to impress everybody. Hoffmann La Roche were also there with Pletscher, who stated that the benzodiazepine compound, Librium, would do exactly the same as Kline had promised. He gave a major lecture on the point that if one was to change this or that on the benzodiazepine molecule and I don't know what else.. that then there was a prospect that you would find a wonder drug as well. This lecture by Pletscher I heard myself. I guess that there are records from this congress, it was in May 1958.

I also had to give a lecture on Tofranil, which I did but I had very few listeners, just like in Zürich. In Zürich there were fewer than a dozen people, when I gave that lecture at the World Psychiatric Congress in September of 1957. But it was published in the Swiss Medical Weekly. That was the original publication. The Russians, who were there, read that and they went home and declared through diplomatic channels that they had to obtain this compound immediately. They got it through diplomatic channels and in Moscow the pharmacology of the compound was reproduced and I had the impression that it ended better than when Geigy produced it. Basel was then two to three years behind in the work of their pharmacologists.

Later I went to Russia and talked to the relevant pharmacologist and he told me the whole story. It was a very embarrassing one. When the congress in Zürich took place the Russians had recently invaded Hungary. Following that the Swiss Society of Psychiatry canceled the invitation to the whole Russian delegation. So then the Russians took the issues of the Swiss Medical Weekly where everything was published. They read it and instantaneously translated it. Then they realised that of everything that was in the issue about new developments that were being debated at the congress, the most interesting was the publication of Tofranil. Which was true! And they immediately – the pharmacologists told me this for sure – switched a whole institute to the analysis of the pharmacology of the substance. The original compound from Basel was bought through the embassy in Berne in large amounts and went to Russia. And there they realised its importance, long before America realised it .... that also is part of this story. Psychoanalysis was very influential in American.

*When you gave your talk at the World Psychiatric Association Meeting in Zürich in '57 this was the first public talk on the use of Imipramine for people who were depressed. Why were there so few people in the audience? Why do you think there was so little interest?*

Because it was one of several hundred presentations, you see. And that was for twenty minutes. And there were a lot of other people who spoke. I was myself the chairman of this session, because it was of such little interest. Nobody thought that it was of any importance to us. One of the psychiatrists, he was

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the professor in Lausanne knew it. He himself treated depressed patients and he had had Tofranil before it was on the market, I sent him the medicine, and he was cured in five days. There were some people who noticed but it was a very small percentage of the many people who were there.

*Why was the level interest so low?*

Because nobody believed that there could be a drug against depression. One drug rep from Geigy told me he had been to see one of the heads of department in Germany. He had wanted to introduce Tofranil and the professor listened for a while to him and then said 'Well my dear colleague we are clear about something here, depression is a reactive illness and nothing else and you can go with your drug back to where you came from, it doesn't interest me'. This was a famous German professor.

*When did it come on the market here in Switzerland?*

I believe the first of November 1957.

*Were you at the CINP meeting in 1958 in Rome – you're not listed as one of the speakers?*

I was there. There was a meeting one morning with I think eight papers. I did not speak, I was not invited to speak but the meeting was a singular triumph for Tofranil.

*Why weren't you invited?*

That I don't know. I thought it was curious but Geigy obviously still did not believe that I was right.

*That's strange.*

Yes, it was like this. I was not invited by Geigy to speak but I was invited in order to help write for the journal in which the congress proceedings was reported. So then I wrote the papers on depression. They are mine. I've got copies of this paper if you are interested and if I can find them you can have one.

*It is curious that you did not take the stage – others gave talks on imipramine? Did you talk to Geigy about it?*

I thought it was strange but that simply is how it was. It may have been connected to... I can't remember who chaired the meeting, I would have to look it up, but I suppose that the chairperson of the meeting had to organise the symposium for the congress management and he did not know me. He only invited famous people instead. And there were very famous people there. For one there was Hoff from Vienna amongst the audience and then Jean Delay from Paris.

Jean Delay came up to me after the lectures. I knew Jean Delay and he knew me. I had been working several times at his clinic and I was friendly with his EEG specialist. He made me explain why I had gone ahead with this, without letting him and his clinic know. I said that I was very sorry but his consultant Deniker had been in the possession of the drug for a year and had up till now

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refused to test it. When he heard this Jean Delay challenged Deniker and made an huge scene in public in Rome.

I had been previously introduced to Hoff in the Engelsburg but he took no notice at all of me. But after the lecture, which he had been present at, he suddenly came towards me and greeted me and said to me, 'How highly interesting it was'. I had to come to Vienna and give a talk. That same year (or the year after) he invited me to a meeting of the Austrian Society in Graz. We were late, because the train was late, so we just crept into the lecture theatre, where Hoff, who chaired the meeting, interrupted the proceedings, greeted me with all his Viennese charm and politeness and spoke of 'his dear colleague whom he'd been intimately connected with for many years'. But I have to say that he was very nice to me. He invited me several times to his clinic in Vienna, where I stayed in his private quarters. In the morning a sister came with an enormous breakfast, and I came and went into his clinic as if I were at home. He then showed me the clinic, introduced me to the patients and so on and was very, very nice to me. He planned at one point to make me his successor – he once approached me. Nothing came of it – I didn't really actively pursue the matter. He then approached Kielholz but Kielholz did not go. I presume that Hoff thought I would not go.

*Were you at the CINP meetings in Basel in 1960 or the USA in 1962? You are not listed as actually being a speaker. Why I ask is that one of the odd things about the whole story is why there was no prize for the discovery of the antidepressants? Do you have to go to conferences and be seen in order to be proposed for prizes?*

I don't know. I always say in psychiatry you get a prize not for the biggest successes but for the biggest disasters. It is just like that but why this is so I cannot tell you, you probably know better. I never got a prize, I did once get a prize as a fresh young man. I got 300 SFfr from the Lucerna Foundation for my work on the interpretation of the Rohrschach test. Otherwise, I never got a penny. I am an Honorary Doctor of the University of Löwen (Louvain) for Medicine, and Honorary Doctor for Medicine at the University of Basel – I received this one two or three years ago. It was Pöldinger's doing. Also I am an Honorary Doctor of Philosophy at the Sorbonne in Paris for my works on the Daseins-analytical philosophy. Not for medicine. I got in a yellow gown of the philosophy faculty rather than the red one of the medical faculty.

*How do you account for that?*

Well. Envy plays a very big role. That is certain. I am convinced. Constantly people say that I have only made these discoveries by accident. And this I deny. It was not an accident. It was an accident that I happened upon this compound but I did chose it.

*If you hadn't had the insight about vital depression then you wouldn't have been using it on these patients.*

I wouldn't have found it. That was no accident. It was the result of a long historical development. The fact that nobody will accept this is inconceivable.





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Everybody thinks 'it's a pity that this accident didn't happen to me'. Everybody thinks it could have happened to him just as well. I'll tell you a good anecdote about this. There is a frenchman who wrote about this history of this, Thuillier, who put it like this ' Un petit psychiatrie de campagne, foutu dans ses montagnes, a fait par hazard le decouverte de Tofranil'. The point is nobody gives a prize to someone like this.

*But even before that weren't you involved in introducing the EEG into Switzerland?*

No. It was introduced in Waldau. If I hadn't come to Münsterlingen, then I might have been the first, because Klaesi offered me an EEG apparatus from Tönnis. This was before the war, it was a machine with three connections. Incomprehensibly I did not follow this career and went to Münsterlingen. But after the Waldau, I was the second psychiatric clinic in Switzerland which had an EEG in June 1950.

*How did you get involved in the maprotiline story?*

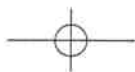
Yes the Maprotiline story went like this. After Tofranil was a success, there were several pharmaceutical companies who turned to me with the idea that if they gave me a compound, then something would come of it. This was the case also with Ciba. Ciba offered me a compound and I told them that I was agreeable to try it. The thing was, Ciba wanted a competitor to the benzodiazepines. They had a compound which acted as a muscle relaxant and they suggested to me that I should try this compound. I tested it and said it was slightly anxiety reducing and slightly sedative. But for clinical usage in psychiatry it was much too weak. They then introduced this compound anyway, and it was a flop. So I said to Ciba the ring system was in my opinion very interesting, but one should alter it, and give it the side chain of Tofranil which is the same, as in Largactil. They should attach this to the ring system and they might have a useful psychopharmacological drug.

The pharmacologist said Kuhn should try our compounds and not suggest compounds. But later, after the first meeting where we talked about this, I got very friendly with this pharmacologist – Hugo Bein. Then he told his chemist – who was Wilhelm – to create this substance which had not been already produced. So then Wilhelm had to obey Bein although he was highly appalled that a psychiatrist would suggest to a chemist what kind of substance he had to produce! And that compound was Maprotiline.

*You are responsible for it. But you do not participate in the profits?*

Well I have received something. It wasn't riches. I had a share in the turnover for twelve years. It wasn't a great deal but never the less.. Of course the compound would never have been produced if I hadn't told them.

*When you looked at Maprotiline clinically you looked at it in the same way as you describe Tofranil, you looked at it in depth with a large number of patients. At the same time the company were beginning to do clinical trials with placebo controls. That was fine then, but the interesting story comes about later on with Levoprotiline. Can you fill us in on that*



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*story. How did the idea come about first of all that it might be an antidepressant. What did you discover when you used it and what in your opinion went wrong in the company?*

This is a complicated history. The complication lies in the fact that Levoprotiline was produced as a racemate. It was found that one of the compounds was biochemically active and the other inactive in all the usual tests. They decided to separate the two isomers, which you can do, with the intention of using the inactive substance as placebo whilst testing the other one. But it was evident that the placebo was more effective than the actual substance which was on trial.

The thing was this, Levoprotiline had been given to half the world to try. I also received it and I started Levoprotiline in a large investigation with over 100 cases. I produced a study which was ripe for publication but still today is a manuscript that has never been published. Then Ciba gave America Levoprotiline. From America came a damning report, which was as expected. This experts report I have never seen. It was explicitly denied to me. But a friend of mine, a very good psychiatrist and pharmacologist in Germany, a man of good renown, saw the report and he told me it was completely unqualified, absolutely. Without asking me, or telling me anything, Ciba decided not to pursue the matter any further and the last stocks of the compound which had been synthesized were burnt last year.

*Why has your manuscript never been published?*

Ciba did not want to keep the analysis; they wouldn't know what would become of it and so on. Germany was very interested in it and insisted on importing it. I said one should license it because it is a compound that has no effect on either the serotonin or catecholamine systems but it is an antihistamine. I had an interesting case with a lady professor, the wife of a very wealthy Swiss gentleman, who told me how treatment with an antidepressant I was giving her had diminished her extreme allergy. She called me to tell me that her cat allergy had gone. One can summarise that the biochemistry of depression and the antidepressants and the histamines and the antihistamine drugs affect each other. That is very probable but nobody is interested in it, even though it is extremely interesting that a substance that is active on neither the catecholamine or serotonergic systems is without a doubt antidepressive

*You are sure of that?*

Yes, yes, absolutely. It is less active than Tofranil and less active than Anafranil or Ludiomil but it is almost the same as lithium and without a doubt specifically an antidepressant, without a doubt.

*You were very angry with the company? And with the FDA? I've heard you say that we have got to resist the regulators.*

Yes, it is terrible. The reason why Levoprotiline was not licensed is this, the drug was not shown to be effective in a placebo controlled trial and the FDA implied it was just sugar, so it could not be licensed. It was impossible. But Astra in Sweden wanted to buy it. Three representatives from Astra came to

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Switzerland to talk to me. I had a long conversation with them, explaining the situation, and they refused it in the end because it could not be tested under any of today's methods.

*Was that before or after the catastrophe with Zimelidine?*

It was after. The Zimelidine catastrophe was another chapter, I tried Zimelidine as well.

*What can you tell us about it?*

I can tell you the following. I was given Zimelidine to try out, and I tried it but I didn't see any effect. Then I was invited to Stockholm to take part in the launching of Zimelidine. I listened to the whole thing. They had a very good biochemist who gave a very good introduction, then there was a good biopharmacologist. But after that there was a disastrous clinical report, totally unsatisfactory. The longest trial lasted four weeks, well, I can not say anything after four weeks. I reckoned they would find out even less than I. In any case I was of the opinion that one couldn't be responsible for recommending this drug for license, on the grounds of the clinical trials which had been done. It was impossible to judge whether it could be licensed. That is the proof for the total inefficiency of bureaucratic regulation. I thought if they are lucky they will get it through but they have to have undeserved luck. And they did not have the luck.

*There is a drug you have here for a condition you have or have had here – and we have neither the drug nor the condition in the Anglo-Saxon world. The drug is Opipramol-Insidon and the condition vegetative dystonia. What is this condition and what is the difference between it and vital depression and between opipramol and an antidepressant drug?*

Opipramol is in fact a very good antidepressant. It is weaker than Tofranil, that is clear. It is given usually in doses of 50mg and not 25mg which is the normal dosage. It is very well suited for menopausal women especially when they experience sleeplessness. If there is depression with sleep disorder then Insidon is an excellent drug. It is for instance excellent for reactive depression also with severe bereavement reaction after a death in the family. Excellent. The bereavement reaction is not interfered with but the ability to overcome the mourning process is enhanced. It is an excellent compound against anxiety and has practically no side-effects with normal dosage. We still use Insidon with certain cases and, then, it is a very good drug. But Ciba Geigy never advertised it at all, they never went to anybody to ask them to test the drug with a larger trial base. It is mainly a drug for outpatient usage, it is not a drug for severe psychotic depression. For primary care it is ideal. It is really very good and somebody should speak up for this preparation. One should do the proper tests but Ciba Geigy doesn't contribute a cent for any such trial.

*And Vegetative Dystonia?*

This refers to an abnormal frailty of the vegetative nervous system, that is people whose pulse increases quickly, people who very quickly collapse, who eas-

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ily break out into sweats, who, because of this vegetative instability, tend towards panic attacks. They also become depressed quickly, because depression goes hand in hand with the whole neuro-vegetative condition. Many depressions are neuro-vegetatively stigmatised. These people have a vegetative nervous system which is less adaptable, it gets out of balance and has little tendency to get back into balance. They suffer from severe dizziness for instance vertigo and often in old age they suffer badly from travel sickness so that if they are not at the wheel themselves they get extremely sick, very dizzy etc. It is simply a very generalised instability and a relatively poor performance of the vegetative system which should equip man for the demands of the world.

*How do you explain the fact that it seems to be only a Middle European disease – it's not found in the Anglo-Saxon world?*

I don't know, what I know is, there is such a thing. I've seen it. In America drugs are given as a matter of course in doses that it would kill somebody in Switzerland. Here in Switzerland if we give benzodiazepines, Valium, we give one milligram or two – in America you give 100. I don't know why. I personally think that one can kill off the vegetative nervous system, roughly speaking, so that it does not function anymore and I guess that in America with such abuse of high dosages of very powerful drugs that the neuro-vegetative reaction in these people is practically non-existent. The cause of this are not only the drugs but also for example noise – that plays a big role – constant stimulation, criminality, also the hectic way of life, etc. so that the neuro vegetative system just cannot keep up. You can get the same thing with caffeine and there are such large doses of caffeine given with drugs in the States which I would think would give people pulse rates of up to 200 and put them at risk of dying!

So many medicines which are given in America ordinarily are clearly poisonous here. I do not know what else causes this or whether this really is the cause – but I have always explained it to myself like this. Of course there is more. Alcohol is drunk there to such an extent which we never see here. I have once seen a statistic on death from acute alcohol poisoning in England – which cannot be compared to here – I have maybe seen two or three in my whole life. I have only actually met one person who really died from alcoholic coma. When I saw these figures from England, I was terribly shocked that there is drunkenness to an extent which we do not usually find here. Another big role is played by smoking. I mean if somebody consumes four packets a day he kills himself, or at least he kills his vegetative nervous system and then you can do anything with him. This is my explanation but I cannot prove it. I can't help you any further.

*When there is only one drug in a class of drugs it can often take a while for that drug to have an impact. But when there are two drugs then it can make more of a difference. How much difference did amitriptyline make to Imipramine, in the sense in the late 1950s there were lots of MAOIs and only one Tricyclic? Then Amitriptyline came along and then there were two and the tricyclics became more prominent after that.*

Amitriptyline was first produced by Hoffmann LaRoche. When the president of Hoffmann La Roche saw the pharmacology he said – I was not present at

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this but I have heard it said – ‘Such nonsense we can’t bring it onto the market’. Amitriptyline has very probably a stronger sedative, hypnotic effect than Tofranil and more side effects than Tofranil or partially different ones.

*But did its existence ease the acceptance of Tofranil and the acceptance of this whole class of drugs. If you have two drugs in one class it often helps.*

That is one possibility. The other one is that it pushed Tofranil into the background because the advertising campaign of Roche and Merck was much more aggressive than Geigy’s. The sedative effect has always been an advantage over the stimulating effect of Tofranil. You can combine Tofranil and Amitriptyline – you can give Tofranil in the morning and in the evening Amitriptyline. Then there is another unpleasant property of Amitriptyline: it loses its antidepressant effect in about six weeks to three months. The sedative effect lingers, this is why people take Amitriptyline as a sleeping pill because of its sedative effect, but with regards to the antidepressant effect people get more tolerant, more indifferent.

There is something else to say here which is that everybody in pharmacology compares the antidepressant effect of a new drug not with Tofranil but with Amitriptyline. Why – because Amitriptyline is less effective than Tofranil and because of this a small effect of the test substance in comparison with Amitriptyline has a bigger chance than if you were to compare it with Tofranil. From this you can indirectly conclude that it is true what I say.

*In the early 1960s, I think there was some recognition in the company, not all these compounds were the same, that Imipramine wasn’t quite the same kind of compound as clomipramine and they were quite different to MAOI’s, but yet the logic of the market place for the companies seemed to be, that all these things had to be the same, they had to be antidepressants and there was to be no particular distinction made among the antidepressants. What role do you think market place logic played in development of the field?*

The differentiation is difficult from a clinical point of view. It is much easier to have everything the same. Everything is antidepressive, and it is of course, the drug reps tell me that general practitioners don’t want specific medicines – they want medicines which they can give three times a day, which work, and that is it.

*Sure but also the logic for the companies is they got to say this pill will treat X million people, they don’t want to be in the business to develop compounds for smaller indications.*

The companies will say my drug works faster than the competitors. Secondly my drug has less side effects than the competitors. Thirdly my drug is just as good as the competitors. These are three factors. But after maybe four of five years nobody hears of it anymore that it works faster than all others – it doesn’t. Secondly nobody says that it has less side effects because it hasn’t and thirdly nobody says anymore that it is just as good as the others because it has been discovered that it is not as good! There is none that is better than Tofranil, Anaframil, Ludiomil and Insidon – nobody has discovered a better drug yet.

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*In your opinion is this also true for fluoxetine?*

Yes with fluoxetine and paroxetine and the other new ones, they are effective in about 50% of cases, that is proven, while under the same conditions, with the same trial base Anafranil is 50-60% effective. All this comes from statistics, I have seen it many times, and Tofranil (if they include it) is even better. This is the situation. Now, concerning fluoxetine I have read that in the USA about a year ago, two million people are dependent on it. Well I don't know but one reads more and more that fluoxetine is addictive. Why it should be addictive is a riddle to me, because Anafranil I'm pretty sure is not addictive. What the position is with the other drugs I do not know. Fluoxetine of course has been pushed much more and so it has been used much more and indeed it is mainly used by people who are not depressed but who use it as a pure stimulant. What the consequences will be nobody knows at the moment, we might know in ten years time, when people cannot come off it.

In any case I have used fluoxetine before this was known. I have seen that it has exactly the same irritating side effects as Anafranil, that is namely impotence with men and frigidity in women. You read everywhere and in every publication that this is the case only in 3% of patients and if you pursue the matter in the literature you will find they must have missed a digit. It is more like 35%. With my patients I find that almost every second one to whom the drug was given ends up with dysfunction in this area. Of course you have to take into account what age you are dealing with, if you give it to a twenty year old it does not crucially diminish his potency but if you give it to a fifty year old who is not quite so potent anymore, he will be much affected by this. A statistic about such matters which does not take into account the age of these patients, you can throw away. It tells you nothing. First of all you have to know the age, then you have to know how many men and how many women there are – impotence will be reported more than frigidity, that is well known. Then you have to know whether the patients have been interviewed about this. Most of them will not have been explicitly questioned so that only those who complain are included in the statistics and so on. The literature in my opinion is totally worthless. You can throw it all into the waste paper bin, you can light a fire with it and science would be not one iota the poorer.

*When you published your paper in 1957 on Tofranil, you said you had people in treatment even then for a year and a half. And in 1958 when you published your paper in the American Journal of Psychiatry you said you had people in treatment for two years at that stage. Where did we get the idea that you only need to treat the depressed for 46 weeks? Somewhere in the early sixties it seems, people got the idea that treatment with an antidepressant was like treatment with an antibiotic, it could be a short course of treatment.*

Of course one has to know what is important. You can ask specific questions if it is as it is described here that after six days the effect is there, then I do not need to wait two years. It is true that the more experience you have the better you can judge it, but in the beginning I had to have lots of time. I did not treat all 40 cases for one and a half years. There were cases which I had treated for

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six weeks. I was in America in the spring of 1958, that was nearly one year after the first publication. Then I already had patients whom I had in treatment during two years, who were included before in the first group, who then afterwards were added, and then continued to be treated. I've got patients who have taken Tofranil over 15 years ...

*Why has taken the field 30 years almost to rediscover that a number of people would have to be treated for months or years?*

It is like this: Chronic depression exists. Chronic depression has always existed. That is one thing. Secondly, cyclical depression which becomes more frequent leads into a permanent depressive state. These are facts that are known since Kraepelin, it was written in the *Psychiatry of Kraepelin* in 1908. This is well known classical psychiatry. That nobody talks about this anymore is purely based on the fact that psychiatrists don't know the old psychiatry anymore. Today the psychiatrist who researches reads literature of the previous five years! Because of this we get discoveries today which have been known much better, and described much more beautifully a hundred years ago. And everybody thinks it highly interesting what Mr X has discovered, when all along in the old literature it had been wonderfully illustrated – much nicer much better. That is so. That is the so called modern psychiatry of which the psychiatrists of today are so incredibly proud.

*Can I ask you though if people have to stay on treatment for two years or more, in some sense the disease is not been cured. What is the treatment then treating?*

Well this is a problem. After a while these compounds use up substances which are necessary in order to function. Amongst these substances are iron, copper, zinc, magnesium and chromium. When you have to treat for a long time then you have to supplement with these trace elements. If you don't do it, it will become worse and worse in spite of treatment with drugs. This is because tyrosine hydroxylase is obligatorily dependent on iron. If it cannot be activated because there is not enough iron then the metabolism doesn't change the tyrosine to dopamine but it goes instead from tyrosine to parahydroxyphenylacetic acid. You can prove this because if you give many of these patients iron the parahydroxyphenylacetic acid will disappear from their urine. In addition noradrenaline is produced from dopamine. This process needs dopamine-beta-hydroxylase which is dependent on copper. And you can check in the urine whether this is working by looking at the ratio of dopamine to noradrenaline metabolites and if the proportion is not right you have to give copper. If you don't, what happens? – after two to three days we have a relapse pure and simple. But to think about that is for the contemporary psychiatrist much too difficult and is rejected as humbug.

The case is very straightforward but it seems these are thoughts which neither the psychiatrist nor seemingly the biochemist thinks. When I told this to the people from Ciba, they said that I was ranting – that I do not understand anything about all this. The strange thing is that these obtuse ideas which I have work very well in the clinic!

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*Have you publicised your own ideas on this theme.*

Partially, partially not. The other day I gave a lecture and in the break I heard two young psychiatrists say 'What Kuhn tells us here is nonsense'

*You worked on Librium do you want to tell us some more about that?*

Yes, I can simply say that I have used Librium with a morphine addicted father-in-law of a very high up employee of Hoffmann LaRoche, before librium was on the market anywhere in the world and after 14 days this man was as addicted to Librium as he had been to morphine. This was the first time that I ever came into contact with this compound which then had no name, I only knew that it was a benzodiazepine. I realised that this compound is addictive and so I have never used it in my practice again. I have only prescribed Valium for the treatment of status-epilepticus, where you can end up in a court case if you don't.

*How do you treat panic attacks then?*

With carbamazepine mainly. With panic attacks you have to make sure whether the attack is the result of a paroxysm, a manic depressive illness or a schizophrenic disorder. That is the first thing. If a schizophrenic breakdown is imminent then of course you give a neuroleptic first of all. If you can detect vital depression behind it then you give antidepressants. Often there is also a paroxysmal component where there is a burgeoning of emotions which are suddenly discharged, then you give carbamazepine.

*The great days of Swiss Psychiatry seem over. The big names like Bleuler and Klaesi haven't been succeeded today. Why has the golden era come to an end?*

All golden eras come to an end! Just like those of the important poets, the great musicians or the great painters. Remember in the Renaissance we had all at the same time Raphael, Michelangelo, Leonardo, Montegna, and now ....

Many professors today would not have obtained a position at the clinic of Eugen Bleuler. You have to know how things were with Bleuler. There are many anecdotes about Eugen Bleuler. A foreign doctor came to the clinic as an assistant, announced his arrival to the porter etc and then somebody came along in a grey coat, took the suitcase of the assistant, and said 'Here is your room, tomorrow morning at 9.00 is Ward Round, you come to the so and so room,' and then he went. The next morning the assistant realised that the porter of yesterday was Eugen Bleuler, the Professor himself.

*Was he a modest person?*

Yes, that he was. He had in his pockets a little notebook into which he wrote all his reports, he would sit in some corner of the ward and write what patient X had said and so on. This is how it happened.... And then there was Kurt Goldstein from Berlin, he appeared at 2'oclock in the morning on the ward, waking the patient in order to give him a neurological investigation in order to ascertain whether something which had occurred to him during his sleepless



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night made sense: if this patient with this particular type of functional disorder did this or that. He would go into the clinic and try it out to see whether he was correct.

*Why are the industry not so interested in the CNS area anymore particularly the psychiatric area. Did Kielholz have any role here?*

Professor Kielholz played a foremost role in pharmacology in Switzerland – much more important in this respect than Angst. Kielholz himself was very clever in the employment of psychopharmaceuticals. But psychiatry was not developed enough to lead the industry in the very difficult area of psychopharmacology. That is the problem.

Kielholz was a clever practitioner. Lately I talked to one of his consultants who said about him that with regards to the practical employment of pharmaceuticals, she had never seen anybody who could have done better. But he stayed completely in the realms of classical psychopharmacology. He also gave benzodiazepines for example, which I have never done, and he never understood that iron deficiency plays a role. When I said, 'listen you have to give people iron' he said 'I'll look into it'. What did he do? Every morning he sent round a phlebotomist to take blood and get the values for iron. He didn't know of course that the iron concentration is lowest in the evening and highest in the morning. This may have something to do with muscle metabolism. But he never noticed this and in his study only one patient of a hundred patients suffered from iron deficiency. So he would say 'It is not true'. Today we do it differently we analyse hair, you get the average value for iron in the organ, for the last three months, you take three centimetres of hair, and then you can properly show whether the patient has iron deficiency or not. You even see whether he has too much, so that you must not give iron.

Further you have to know that magnesium is reabsorbed by the body only up to 45 years of age. Then you have to give magnesium as magnesium orotat and not as magnesium chloride or – hydroxide, or -sulphate. You have to know all this if you give such treatment – you have to know how the preparations are to be given so that they are absorbed and that they enter the cells, so that they can fulfill their functions. Today nobody learns this in psychiatry. A few pupils still come to me sometimes in the evening – they might learn it. Last Wednesday we had two assistants from Würzburg who drove for four hours here in their car, they were here at eight o'clock at night and they left at ten, driving home because they had to be in clinic next morning. Another one comes from Limburg. People say they can learn something here which they can't learn anywhere else.

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See also Interviews with Frank Ayd and Alan Broadhurst in Volume 1

