

## FROM DDT TO IMIPRAMINE ROBERT DOMENJOZ

**(This interview was facilitated in German by Dr Claus Langmaack).  
Where were you born and where did you train?**

I was born in Lausanne on the 23.12.1908, so I am 89 years old now. My father was working in the German industry as a merchant and was responsible for contacts with French-speaking countries in Europe and Northern Africa, mainly Morocco and Egypt. My mother was of German extraction. In 1910 we were living in Frankfurt am Main, where I started in the Liebig-Oberrealschule, later concentrating on mathematics, the natural sciences as well as with French, English and optional Latin. During the last three years of school, I had the opportunity to work in my spare time at the Geological Department of the Senckenberg Museum, where I learnt from Professor Richter and Dr. Runzheimer how to prepare fossils of the Lower-Devon period. At the end of those three years I summed up the work done in a 110-page typewritten paper titled "*Variationsstatistische Untersuchungen an Merista herculea Barrande*". I finished school after passing my final exams, the "*Abitur*", with distinction in March 1929

In April 1929 I was admitted as a student of medicine at the University of Frankfurt. My student-book reported that I was "*Nichtmitglied der deutschen Studentenschaft*". During 1930 I fulfilled my military obligations in Switzerland (*Sanitaetsrekrutenschule* and incorporation in the Swiss Mountain Infantry). I completed the propaedeutical exam ("*Physikum*") in the natural sciences in March 1933 with good results. In these years the political situation in Germany changed as Hitler had just come to power. There had been demonstrations of young people in SA-Uniforms against Professor Bluntschli, the Director of the Institute for Anatomy, who was a Swiss national. Two professors, whom I both appreciated very much, were removed from the University because they were Jewish, Professor Ph. Schwartz, who later moved to Istanbul, and Professor E. Goldschmied, who moved to Lausanne. I felt that the changing political environment in Germany was not conducive to a foreigner studying medicine in Germany and decided to return to Lausanne in 1933.

In Lausanne, because of my excellent references and my limited economical means, I was awarded a grant from the Government of the Canton de Vaud, which covered my living expenses and exempted me from paying tuition fees to the University of Lausanne. I was, however, forced to repeat my "*Abitur*", the propaedeutical examination in Anatomy and Physiology, as well as having to complete an examination in Swiss history and Swiss geography. Nevertheless, in the spring of 1935, I was admitted to the Swiss Federal Examination for Physicians after having studied for 12 Semesters and gained my Diploma in Bern in June 1935.

After the obligatory training as a physician in the Swiss Army, I started to work as an assistant of Prof. G. Delay, director of the Policlinic of the University of Lausanne. I had an appointment for 2 years. These 2 years in internal medicine were a happy and successful time for me. Prof. Delay was also satisfied with my work and wanted me to stay on. He wanted me to work on

some interesting physiological problems and contacted Prof A. Fleisch at the Institute of Physiology in Lausanne, so that I could work as an assistant there.

Unfortunately Prof Delay died from a heart attack around the time I finished my 2 years at his department. I had already started on my thesis which was titled "*l'hypotension arterielle essentielle, frequence et symptomatologie*". I started to work for Professor Fleisch at the Institute of Physiology till 1941. At the Institute I control-analyzed vitamin preparations which were sold in Switzerland. Prof Fleisch then directed my interest to the venous system and its function in blood storage. In my experiments I used a method devised by Prof. Fleisch himself, where I measured the perfusion in situ of the Vena colica of narcotized cats. These cats were maintained in a waterbath with automatic temperature regulation and the perfusion was controlled by Fleisch's Differentialstromuhr and continuously recorded with a photokymograph. The drugs – we had a long list of vasoactive substances - were added to the perfusion liquid. The results obtained by these experiments allowed us to correlate chemical structure of the substances to their biological activity. It was quite a similar design to the classic experiments of Barger and Dale.

Another series of experiments concerned the role of the spleen in the regulation of the volume of circulating blood. In narcotized dogs I continuously recorded blood pressure, respiration and the volume of the spleen. The latter was done plethysmometrically and the vasoactive substances were injected into a branch of the Arteria lienalis. All these results were presented and discussed at several physiological meetings and were then published in Naunyn-Schmiedeberg Archiv.

Just before the beginning of the war in 1939, the firm IR Geigy in Basel had decided to start a pharmaceutical branch. This included a complete research division for synthetic chemistry with the corresponding laboratories for the biological evaluation of the substances produced by chemical synthesis. The branch also included a commercial Pharmaceutical Division.

In 1939, because of the war, I was mobilized and I became an officer in the border-troops. During that time Geigy was looking for a man who was able to organize a pharmacological laboratory for them. Until then they had only made pigments and chemicals for use in the tanning industry and had no pharmacological expertise. They contacted Professor Fleisch who established contact between I.R. Geigy and myself. I was eager to take on this job, as I felt I was wasting my time in the Army. After extensive discussions in Basel with Dr. Peter Peiser, director of the commercial Pharmaceutical Division and Dr Laeuger, director of the newly created Chemical Division, I was hired with the task to set up a complete Pharmacological Institute within the Research Department.

In order to enable me to supplement my previous experiences in experimental pharmacology by learning new specific experimental procedures, Prof. Fleisch and Dr Peiser organised study-visits to various well known Institutes abroad. Geigy had arranged for me to be released from my military obligations for a

period of 12 months. During my study-visits I was informed about the ongoing work at the Institutes and the experimental methods in use there. My journey started in June 1940 and I was able to work at the following institutions:

- Karolinska Institutet for Pharmacology in Stockholm directed by Prof. G Liljestrand. I analysed gases with by the methods of Haldane and van Slike's. I also did self-experiments with Grollman's acetylene-method in order to determine the cardiac output. The results were published in Acta Physiologica Scandinavica ("Die Wirkung des Atropins auf das Herzminutenvolumen am gesunden Menschen").
- Statens Farmazeutiska Laboratoriet Stockholm, directed by Professor H. Rydin. I was able to learn evaluation techniques on isolated organs and later how to work up the results in a statistical manner.
- Pharmakologisches Institut der Universitaet Berlin, directed by Prof. Dr. W. Heubner. With Professor M. Kiese I experimented on the Starling-Heart and on a heart-lung preparation. I also learnt to use the Havemann-Colorimeter and Rein's Flowmeter.
- Pharmakologisches Institut der Universitaet Bonn directed by Prof Dr W. Schulemann. I was introduced into the experimental evaluation of the effects of an antimalarial on infected hens and canary bird hearts. Because Prof. Schulemann was working for the pharmaceutical industry, as opposed to a University environment, he was able to give me much advice, which I found useful later on.
- Pharmakologisches Institut der Universitaet München directed by the Privy Councillor Prof. W. Straub. I worked on the relationship between speed of injection and the toxicity of morphine in the guinea pig. I also worked on some problems connected with de-caffeinated coffee and did experiments on caffeine-induced rigidity in frog-muscles. The latter work was published in Naunyn Schmiedbergs Archiv.

When I returned from Germany, I started working for Geigy on 31 March 1941. There was plenty of money, so it was not too difficult for me to set up the pharmacological research Department. It all went very quickly. Finding staff also posed no problems and we very soon started to analyze and evaluate the chemicals, which came from the large chemical research department. This department was also newly set up and was designed to feed us chemicals for pharmacological testing on animals.

### **Why do you say I.R. Geigy?**

At that time Geigy was called IR Geigy, or sometimes JR Geigy. The letters stand for Johann Rudolf Geigy, who founded the firm in 1758 in Basel. He called it a *Drogenhandels-gesellschaft*. This "drug company" among others imported coloured woods, blue-woods, yellow-woods and red-wood, which were sold. These trees were used in the dye-works of the day, where they were crushed, the dyes extracted and then used for the dyeing of textiles.

From 1833 onwards IR Geigy, after having bought a timber mill, produced the extracts themselves and in the latter half of the 19th century the then-owner of Geigy very deliberately steered the company towards the synthetic production of dyes. These dyes became very successful, not least because of Sandmaier.

**Let us go back the Geigy of the 1940's. Were you in charge of the whole pharmacological research department?**

Yes I was. The research division (*Forschungsabteilung*) was headed by Dr Paul Laeuger, who was succeeded by Dr Hartmann Koechlin, and afterwards by Dr. Hentrich. The chemical department had 6 different research programmes (*Arbeitsgruppen*) with about 20 chemists. Dr Hans Gysin headed the group, which worked with analeptics. Together we brought Geigy's Micoren to the market. Dr Franz Haefliger was group leader for the group concerned with spasmolytics, antihistamines, iminodibenzyls and the iminostilbenes. Dr Fritz Mueller was in charge of the barbiturate-*Arbeitsgruppe*, and Dr Stenzl was group leader for the chemists working with analgesics and antirheumatics, including butazolidine. Dr Paul Mueller was in charge of insecticides, including DDT. The *Forschungsabteilung* also had a bacteriology section and a department of physiological chemistry apart from my own pharmacological department.

The other newly established division was the commercial division (*kommerzielle Abteilung*), which was located in the administrative building. Dr Peter Peiser was in charge, where he was later succeeded by Dr. W. Faber. Dr Boehringer acted as a consultant for the director of the *kommerzielle Abteilung*. The commercial division also had a so called medical division, which consisted of Dr Otto Kym, Dr Paul Schmidlin, Dr Conaud, and Dr Meyer, among others.

Our teams obtained good results pretty quickly. Geigy discovered DDT and it was evaluated in my department<sup>1</sup>. I myself tested it on lice. I asked the Salvation Army to bring me two paupers, who slept with them and I bought their shirts from them in order to obtain lice to work with. With these lice I started the research-programme. I put the lice in small boxes, which could be sealed with a sieve so that the lice could breathe. I then attached the boxes on my arms so that they could live off my blood. This went on for weeks and they obviously multiplied. We then had enough lice and could start our investigations with DDT on them.

This was a big success and we published. DDT was then used by the Swiss army and I presented the results to representatives of the American embassy in Bern. When the Americans invaded Italy later, they used DDT in order to prevent typhus.

**You worked with anti-cholinergics as well?**

Yes, one of the groups worked on spasmolytic anti-cholinergics. They were semi-synthetic derivatives of atropine. Geigy synthesized them. I evaluated

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<sup>1</sup> For further details of Robert Domenjoz's role in the discovery of DDT and phenylbutazone see Thuillier J in this volume. These were unknown to the interviewers at the time.

them and later Geigy brought out a compound, which could be used in Parkinson's disease, Parpanit.

Another group worked on non-steroidal analgesics, which were of value in rheumatism. The animal tests were easy, but we had great difficulty in extrapolating the results of the analgesic tests obtained in animals to humans. I then stumbled on a paper by Ernst Grünthal in Bern. This was a few years after I started at Geigy. At that time Ernst Grünthal was working as an assistant collaborator at the psychiatric Department in Bern. He looked at how morphine affected the sense-organs in the skin, i.e. temperature, touch, and pain.

I got my supervisor, who was in charge of the money, to talk to Ernst Grünthal's supervisor, who was Professor Jakob Klaesi, the psychiatrist. We gave him an EEG machine - a whole EEG laboratory, in fact - which at that time was worth about 50,000 Marks. We could then discuss our problems with Ernst Grünthal. Geigy collaborated with Ernst Grünthal for as long as I was with them. He started testing our analgesics, antiphlogistics - everything we made which in any way was pain-relieving - on humans. Later we gave him other substances - not necessarily painkilling substances - which he tried on humans.

**Can you tell me more about Ernst Grünthal.**

I think that he came from Breslau originally, but I am not sure. Before he came to Bern he worked in Würzburg in psychiatry. He was a neurologist and a psychiatrist. He also worked at the Waldau in Bern at the Psychiatric Institute there. He was thus in contact with the younger assistant collaborators who also worked there. Roland Kuhn was one of them and he later worked for Ernst Grünthal or Jakob Klaesi at the Waldau. That is before Kuhn went to the psychiatric hospital in Münsterlingen. I cannot remember when I met Roland Kuhn but it was pretty late, maybe between 1948 and 1950.

**Apart from analgesics and anti-cholinergics you were also working with anti-histamines at that time?**

Yes, our basic model was histamine-induced spasm in the guinea-pig. It was not too difficult. Our research led to the introduction of chloropyramine. Because of our work with chloropyramine we were aware of the side-effects of these compounds, e.g. drowsiness, which was prominent at even relatively low doses. Ernst Grünthal's work on humans was invaluable in elucidating these side effects.

**What indications were you looking for at the time for the antihistamines?**

It had already been discovered that histamine's actions could be attenuated by these substances. The antihistamines were commercially interesting for Geigy. There were several anti-histamines on the market already. Ciba, Rhône-Poulenc and the Americans also had one, I think. It was a competitive area. The antihistamines were used in the treatment of urticaria and also for some forms of asthma. They were also used as an anti-emetic, in airplanes for instance.

**Tell me about how a prospective drug was tested at Geigy at the time.**

The prospective candidate drug was synthesized by the chemical research department and then given to me. I tested it in the pharmacological research department, but only on animals. If it was still interesting it was given to Ernst Grünthal so that he could give it to humans. We could give any drug we wanted to Ernst Grünthal, there were no controls, no "ethical commissions" like today. Ernst Grünthal then paid students to take the drugs. He paid them for their time. He had a little group of students for this. The drugs were not tried on mentally ill people in the first instance. This was the way it was done with the psychopharmaceuticals later as well.

Once we wanted to launch the drug on the market, it had to be approved by a commission, of course. It was complicated and time-consuming to get a drug approved by the FDA in the USA. But also in Germany and in Switzerland the drug had to be approved by a governmental agency, although this was somewhat easier compared to the USA.

**What sort of animal tests did you run for CNS compounds then?**

Only those that you find in the publications of that time. We did not know that this reserpine-like effect is characteristic for some of the aspects of the neuroleptic effects and we were not able to use animal tests in order to identify compounds with possible neuroleptic effects in man. When imipramine came along, we knew about the reserpine test and we used it then. As far as I know we did not do the rope climbing test early on.

**In 1945/1947 promethazine, an antihistamine, was released on the market. It was only in 1952 with chlorpromazine that there was any indication that there might be uses for these compounds in mental illness. Before that you had made Synopen in 1949 and also G22150 as I understand it. But what led you to the iminodibenzyl-nucleus as an antihistamine. It seems to me that you got to that before chlorpromazine became the phenomenon it did. Where did the idea of the iminodibenzyl-nucleus come from? I understand it had been made first in 1898, that it was a dye - Summer Blue - and that it was in a sense lying around in the basement of the Company.**

It is very difficult for me to remember - it is over 40 years ago and I have no papers. All the letters to Ernst Grünthal, all the reports that Ernst Grünthal sent back, everything is in Basel with Geigy.

It is true that the group of substances started with the anti-histamines and especially after the success of promethazine and diethazine. Apart from this I am not aware of the sequence that you just presented. As far as I remember we made the iminodibenzyls in response to the enormous commercial success of chlorpromazine. In this particular case it was not possible for us to bypass the patents by just finding a different method to synthesize chlorpromazine. It was also quite difficult to come up with a similar drug, because of the patents protecting chlorpromazine. At one of the meetings of the chemical research department they came up with the idea of substituting the sulphur-atom in the phenothiazine nucleus with an ethylene-bridge. They tried to make a structural analogue of chlorpromazine. In essence, it was

hoped that the derivatives of the iminodibenzyl-nucleus might copy the pharmacological effects of Chlorpromazine but not infringe on the patents.

Franz Häfliger was the supervisor of the chemical research department at that time and also the group leader of one of the 6 research teams of the chemical research department. Willi Schindler, the other chemist involved in synthesising the series was a member of Häfligers research team.

After I left Geigy AG they tried swapping the ethylene-bridge in the iminodibenzyl-nucleus with a stilbene moiety, i.e. they introduced a double-bond into the middle nucleus of the compound. The phenothiazines and these iminostilbenes are iso-steric - they crystallize in the same manner. Unfortunately the iminostilbene-compounds proved to be relatively uninteresting.

### **So who came up with the idea of looking at the iminodibenzyls for any antipsychotic action?**

I would imagine it was the chemists. The group leaders of the chemical research department had meetings, where these things were discussed. We then had meetings with Franz Häfliger, who was supervisor of the chemists, myself, as the supervisor of the pharmacological research department, and also the supervisor of the Geigy research department. An additional one or maybe two people were present at these high-level meetings. It was there that the decision was taken to commence work with these substances.

### **Can you tell us more about the Geigy research department at that time.**

The whole Geigy research department was housed in Draugut. The name of the house was Sandmaier, the *Sandmaierbau*, which was built in 1939-1940. Traugott Sandmaier himself was born on 15.9.1854 and went through an apprenticeship in precision engineering. In 1882, he was hired by the chemist Dr Viktor Meyer at the Swiss Polytechnic Laboratory in Zurich as a permanent assistant lecturer. Sandmaier had an intense interest in chemistry and followed Meyer to Goettingen in 1885, when Meyer was offered a chair there. He later returned to Zurich and in 1888 he was offered a position in the field of technical chemistry by Geigy. In 1891 he was awarded a *Dr honoris causa* by the University of Heidelberg for his research in the field of organic chemistry. In the same year he invented a new method for producing synthetic indigo for Geigy. He was appointed into the board of directors because of this. He left the board in 1919 for reasons of age. They called the building after him.

But to get back to your question, as I mentioned, the commercial department had a medical research department. Dr Peiser was the head of both this department and the commercial department. He had previously been working for Bayer in Germany. He was Jewish and an important man, so when Hitler came into power, he was sent by Bayer to their Chinese branch and when this manoeuvre did not work any more he was taken over by Geigy.

No experiments were done in the medical research department. The department was staffed with doctors who were responsible for staying in

contact with the various hospitals, where the clinical research was executed. Otto Kym and Paul Schmidlin worked in this department. Otto Kym came from Zurich. Paul Schmidlin had previously been working under Bucher at the Pharmacological Institute of the University of Basel. Schmidlin wanted to become a pharmacologist but it did not happen. Then I became Professor in Bonn and Paul Schmidlin took over at Geigy.

Now, when a pharmaceutical still had commercial prospects after having gone through the pre-trials in the medical research department, it was taken over by the marketing department. New trials were started in many different clinics. Dr Boehringer worked in this department. He had previously worked for Hoffman-la-Roche, but wasn't getting anywhere. He came to Geigy as a consultant. He did not have specific job but he played an important role especially in business decisions. He was not involved in research. Dr Boehringer was a member of the Mannheim family branch. He was not involved with Boehringer-Ingelheim, as Roland Kuhn has suggested. Dr Boehringer had studied German and was part of the circle surrounding Stefan George, the famous poet. When Stefan George died, Dr Boehringer was the executor of his estate and organized Stefan George's burial in Switzerland. He also posthumously published a large book with Stefan George's previously unpublished works.

**In his interview with me Roland Kuhn says that when it became clear that G22150 didn't work or seemed to cause too many side-effects, he met you in a hotel-room in Zürich and said "why don't we try G22355, the one with the same side-chain as chlorpromazine"?**

I cannot remember that a meeting like this took place. I don't believe it either. This would also not be the normal course of events. I gave the substances to Ernst Grünthal who investigated them and then sent them to Roland Kuhn, among others. Roland Kuhn was not involved in selecting the substances for trials.

There are actually a number of things in the interview with Roland Kuhn, which do not correspond to facts<sup>2</sup>. He misreads the circumstances surrounding my departure from Geigy. When I went to Saarbrücken, Geigy lent us laboratory equipment and they paid for all our animals. When I came to Bonn they paid two of my laboratory assistants. I worked with non-steroidal analgesics there and my work was very interesting for Geigy because of the pending release of phenylbutazone in America. He also made a connection between caramiphen - Parpanit - and imipramine but in reality there is no connection at all between caramiphen and imipramine. Caramiphen was also run through Ernst Grünthal and I think it was given to Roland Kuhn and to another Psychiatrist who had previously been working at the Waldau-Clinic. But it was tested as an agent for the treatment of Parkinson's Syndrome only, not for anything else.

**Tell me about Caramiphen.**

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<sup>2</sup> Kuhn R (1998). The Discovery of Antidepressants: from Imipramine to Levoprotilene. In Healy D, The Psychopharmacologists Vol 2.



We published our work on caramiphen in 1946. Shortly before our publication I had held a lecture for the Belgian Academy at the request of Professor Heymans in Gent which was the first time the work was outlined. Caramiphen was developed because we were looking for a treatment of Parkinson's Syndrome. At that time Parkinson's Syndrome was treated with an infusion of an extract of Belladonna-leaves. This extract was made in Homburg and maybe elsewhere as well. When we were looking at the spasmolytics, we prepared a number of very potent chemicals with atropine-like activity. This was done partly with the thought of finding a synthetic product, which would substitute for this Belladonna-extract. We had great difficulties with caramiphen. I travelled to London and to Bristol where it was tested clinically, and it was found to have too many side effects. I think it has been taken off the market now because of these side effects. When I looked into my pharmacology-book the other day it wasn't mentioned any more. Hoffman-la-Roche has levo-dopa now and caramiphen has become obsolete.

**Roland Kuhn reported the antidepressant effect of imipramine to Geigy in February 1956. There was an almost 2 year delay from this report and to the time that the drug was actually released on the market. At the same time other companies were able to get drugs from the first human studies on the market within 2-3 months. Why did it take so long for Geigy to release the compound?**

I think that Geigy had no idea about the commercial value of an antidepressant. No idea about the size of the market for a drug like this. It certainly was not a problem from a research department point-of-view to put the drug through the necessary trials quickly. Another point, which Roland Kuhn also mentions, is that other clinics in Switzerland had found G22355 to be of virtually no value at all as an antipsychotic. And we were looking for the new chlorpromazine, weren't we? Like the others, Roland Kuhn also found that G22355 had much less anti-psychotic activity than chlorpromazine. In our minds, imipramine was a poor anti-psychotic, not a good anti-depressant. We did not test it for an anti-depressant effect, we did not think of making an anti-depressant out of G22355.

**Alan Broadhurst who was working for Geigy at the time and Sylvia Schmidlin, the wife of Paul Schmidlin, say that the idea of an antidepressant effect was first Paul Schmidlin's and that Kuhn was almost unhappy to try the compound for this at first.**

I cannot say who thought of the idea of making an anti-depressant out of G22355. Who decided that it might be possible to make something out of this side effect of G22355 on a commercial level I have no idea. It may very well be that Paul Schmidlin pointed out that this antidepressant effect had a commercial value. But one thing is certain, Roland Kuhn was the person who discovered the anti-depressant effect. Without a shadow of a doubt. No-one else realized this.

The decision to investigate G22355 further for its antidepressant action was taken around the time I was leaving Geigy. When I was offered a chair in Bonn in the late autumn of 1957, Paul Schmidlin and Otto Kym started working with Roland Kuhn. They were in charge, supervised him, visited him,

wrote him letters etc. Previously it had been me, who co-ordinated the work with him. I officially left Geigy on September 1, 1958.

**Can you tell me about what you did after Geigy?**

In 1950, after my publications, I was offered a chair in Saarbrücken. The University had just been founded. The Saarland was under French administration then. The administrating body was in Paris and they were looking for someone who could speak French of course. And that played a role in me being selected. I became full professor and had to build up a pharmacological institute. By that time I was quite good at doing this after having done the same thing for Geigy. The pharmacological institute and the clinics were in Homburg. I was employed there from 1950 to 1958 but I was still working for Geigy in Basel co-ordinating the work between them and Ernst Grünthal and Roland Kuhn. So every week I drove from Basel to Homburg. I stayed in Homburg for two days and lectured, trained my assistants etc and then drove back to Basel.

Walter Theobald was one of my collaborators in Homburg. He did his doctorate under me. Geigy took him on in 1957. Other researchers were Otto Büch, who went to Switzerland, Karl Mörsdorf who came with me to Bonn and Ernst-Georg Stenger who went to Hoffman-la-Roche later.

In the autumn of 1957 I was offered chairs in Lausanne, in Marburg and at the University of Bonn. I chose Bonn and took over the directorship of the pharmacological institute in September 1958. I had to leave Geigy then as it was not possible for me to commute between Bonn and Basel any more, because of the distances involved.

After I left Geigy I continued working with antiphlogistic and antirheumatic substances. We used cell cultures and molecular biological methods. My main interest was the elucidation of the mechanism of inflammation.

Shortly after I left Geigy I wrote a large piece about chlorpromazine which I presented at the Academy of Science in New York. I did another important presentation of the results of our experiments about inflammation at the Society for the Advancement of Science in America. All this was still in continuation of the collaborative work I did with Geigy. I also did other research for Geigy, studies on side-effects of drugs and long-term effects of insecticides.

**When you left Geigy, had they already made chlor-imipramine, later to become Clomipramine?**

We had quite a number of compounds, which still had to be sent to Ernst Grünthal for testing. I was involved in di-chloro-imipramine, but not in the work with desipramine, clomipramine and opipramol. They were made or tested after I left Geigy.

**In 1956 the company was slow to develop the antidepressants partly because it seemed as though there were very few people who were depressed. Now half the world is depressed and millions of people all**

### **taking antidepressants. You are partly responsible - how do you feel about this?**

In a way I am responsible, with our first experiments and the chemistry, yes. But we did it without looking at depression. We knew nothing then about serotonin, noradrenaline and dopamine. I do not feel that I am one of the discoverers of the anti-depressants. It was pure chance. And anyway, it was Roland Kuhn who discovered the anti-depressant effect. Although I do not know anything about these things, it seems unlikely to me that there are more depressives now than in 1956. However there is no doubt that antidepressants are much more interesting now from a commercial point of view than they appeared to be then.

One thing is certain. The way in which we did things at that time would not be possible today. That I would contact someone doing research on skin and sense-organs and that this person then would give drugs on a large scale to students and all that. It was all right to do it then, there were no laws against it but these things would be illegal today. There are ethics commissions and controls everywhere. On the other hand it is quite clear that animal models are not enough and that psychopharmacology has to be done on humans in the end.

### **Did you work together with other people in the field of psychopharmacology?**

I worked together with Thuillier for a long time both in Homburg and in Basel on a narcotic. He was a pleasant, honest man, a friend of mine. He worked at the clinic Sainte-Anne on "hibernation artificielle". I gave him a few hundred tablets of imipramine in the winter of 1957. I visited Paris and he picked me up from the Gare de l'Est. It was morning and we had coffee together. I told him about Roland Kuhn's findings that imipramine worked as an anti-depressant and told him that I did not know what to make of this finding. That all of the other senior investigators said that it was without usefulness but this clinician whom I had used before and whose judgement I trusted said that it had antidepressant effects. When Thuillier heard this he said that we should immediately go to Jean Delay at the clinic Sainte-Anne and talk to him about imipramine and that we should talk to Pierre Deniker as well. We did this. It is all written up in his book *Les Dix Ans Qui Ont Change la Folie*<sup>3</sup>. Working with the tablets I gave them, they found that imipramine had to be given for several weeks before the antidepressant effect became apparent. Roland Kuhn had stressed this important point as well. It was quite atypical, for instance, for Frau Boehringer to become well after only 5 days.

### **What narcotic did you work with Thuillier on?**

Thuillier had a Eugenol-derivate, which he offered Geigy. Eugenol is found in oil of cloves and it was used as a dental local analgesic. However, when Thuillier's derivate was given intra-venously the patient became unconscious for a short while. The Eugenol-derivate, which was never given a name, was broken down within a few minutes in the blood and not by the liver. It was quite unlike Hexobarbital. It also did not affect respiration. I did experiments

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<sup>3</sup> Thuillier J (1999). English translation: *Ten Years that Changed the Face of Mental Illness*, Martin Dunitz, London, See also Thuillier J, this volume.

with that drug and published on it. We had great hopes for the drug and it would have been a big commercial success if it had come on the market. Geigy started clinical trials. But a company in East Berlin synthesized the drug because we were not able to patent it. They did trials as well and one of their clinicians gave an intra-arterial injection to a patient by mistake. They had to amputate the arm. That was the end of this drug. We would never have been able to launch it. Later Bayer modified our compound chemically and launched their analogue as an ultra-short acting anaesthetic. I do not remember the name they gave it, but that was around 1958.

**Do any other people who worked with antidepressants spring to mind?**

Well there is Kline. Everyone was very surprised when patients with tuberculosis received isoniazid and became much happier, even though their tuberculosis did not get better as measured by X-rays. Also this was initially not recognized as an antidepressant effect of the drugs. Kline worked with both iproniazid and isoniazid.

**Roland Kuhn told me that when Geigy was not very interested in imipramine the Russians took the drug and did a lot of work with it. Are you aware of this?**

No. But I can tell you that I attended a scientific meeting at one time in Berlin and met this Professor from Moscow. Later one evening, when we were all in high spirits, he told me that they had synthesised caramiphen immediately after I had published about it and started testing it clinically. I can imagine that they have done this with other substances as well.

**May I introduce a very tricky little subject here? Kuhn feels that the reason he did not get a Nobel Prize, was because Thuillier and others characterized him widely as "a country doctor", and one does not give Nobel prizes to country doctors.**

I don't believe Thuillier said that. I cannot imagine that. But really, does Roland Kuhn think he should get a Nobel Prize? I do not know what other people think, but it seems to me that Roland Kuhn judges himself wrongly. Although I would not object to him getting a prize, I personally would not propose him for one, either. In any case, I think it is a bit late for a Nobel Prize now.

**Did you work with Professor Bernard N. Halpern?**

Halpern made the phenothiazine anti-histamines and later worked for Bayer and Rousell when they made their version of chlorpromazine soon after the news of its effects were published. Thuillier worked with him on this project, too. When Halpern was admitted as a member to the academy I paid for his sabre, as a friend. I don't think he was French, but I know he was Jewish. I was once in his clinic and we did open-heart surgery on a dog in hibernation artificelle. You will remember that chlorpromazine was initially tested for surgery<sup>4</sup>. That was before it was given to psychiatric patients. It was Pierre Deniker who did the psychiatric testing. They also did open heart surgery in humans in "*hibernation artificale*". They gave the patients drugs, then put

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<sup>4</sup> See Thuillier but also Cook L (1998). Chlorpromazine, Psychopharmacology and Behaviour. In Healy D, The Psychopharmacologists Vol 2

them into a cold bath, and after a certain temperature was reached, the operation was commenced. There was something wrong with the refrigerator for the bath and one day it broke down completely. They then discovered that the cold bath was not necessary and that chlorpromazine was hypothermia inducing in its own right. This made things easier.

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