

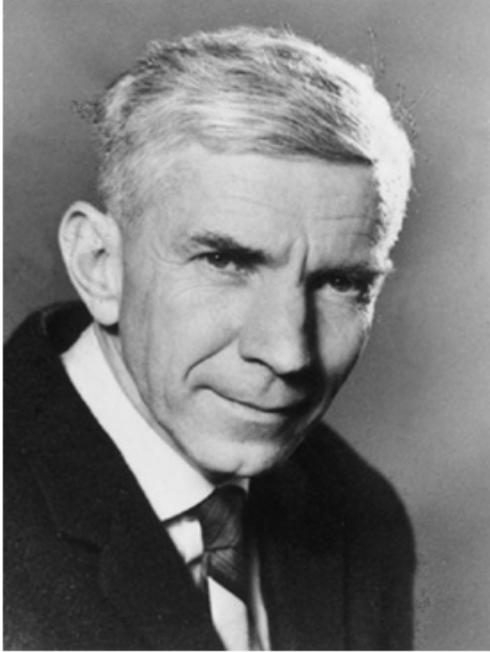
Introduction

I drove to Scherzingen on the shores of the *Bodensee* (Lake Constance) on a cold spring afternoon. Professor Kuhn's cottage was in the outskirts of this village. It had all the charming characteristics of the Swiss countryside, with perfect green lawns covering rolling hills, and grazing cows. The door was opened by an old woman of few words who took me through the house that had seen many important visitors in the past. The cottage was simply furnished, functional, elegant, and perfectly in keeping with the local taste. Professor Kuhn was waiting in his office in a sort of a basement with a low ceiling and a large window. He sat behind a desk untidily covered with papers and books. The only decoration was a beautiful impressionistic painting reminiscent of Renoir. I was invited to sit in front of him. He had a slender figure and a calm voice which made me feel at ease with the interview. The overall sobriety of the place and the man was in contrast with a somewhat prideful tone of his words. Nothing was subject to doubt and his discovery was the only topic that seemed to count.

His best comment was:

“Nobody in psychiatry actually reads because the majority of psychiatrists are unable to read. They are unable to read a scientific text, my counsel is to read classic psychiatric texts with one's pupils”.

He probably was correct. A more detailed interview of Roland Kuhn is reported in David Healy's book *The Psychopharmacologists II* (Healy 1998b, pp. 93-118).



Roland Kuhn, M.D. (1912-2005)

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Scherzingen, April 4, 1990

LT: I would like to know about how the discovery of imipramine¹ came about. When and where did it happen?

RK: It happened in the 1950s at the Psychiatric Clinic of Münsterlingen, near here.

LT: How did it happen? What was your interest at that point?

RK: Everything is described in a book... Do you read German?

LT: Not much; actually almost nothing.

RK: The whole history is described. The book is quite recent and it has the complete history going from opium treatment up to imipramine. I think you should take this text also; it eventually could be translated into Italian.

LT: This is quite interesting, indeed. Are you one of the authors?

RK: It is a very important paper, it shows the problematic role of antidepressive treatment from the past right up until today.

LT: Do you think you could actually add something to what is written in the book?

RK: Concerning the history of the discovery of imipramine, I think that all is said in these two books. There is actually a German pharmacologist who is interested in this question and who was here.² She will write a dissertation and I gave her the original papers I had written. However that is all in German you see. It is not suitable for translation but will be published in German. The important problem is the idea that a substance like morphine has a specific antidepressant effect on clinical manifestations of depressed states. I have searched for this effect with other substances.

LT: Similar to morphine and not to chlorpromazine?³

RK: In the beginning I searched for a substance like chlorpromazine but I always thought that it must be possible to find a substance which had the specific effect of morphine on the depressive state. It was clear that chlorpromazine did not have this effect. Our experiences with chlorpromazine showed that there was no antidepressant activity in such a neuroleptic. I am of the opinion that still, today, no neuroleptic drug exists which has a specific antidepressant effect.⁴ A neuroleptic drug can have a sedating effect as well as other effects which diminish the suffering of the patient, but that should not be confused with a specific antidepressant effect. It's the effect on what I call vital depression.⁵ That concept was published in my first report at the International Congress of Psychiatry in Zürich where I said that the specific effect of an antidepressant is the action on vital symptoms of depression – fatigue, inhibition, loss of humor, a sense of oppression. These

Notes

¹ The first tricyclic antidepressant discovered, and among the most efficacious to this day. A section at the end of this interview discusses imipramine and some controversies about its discovery.

² Information not available.

³ It is the first antipsychotic drug, a phenothiazine, initially introduced to psychiatry in France by Jean Delay and Pierre Deniker in the early 1950s. The first publication of their results was in 1952 (Delay & Deniker 1952).

⁴ This statement may be contradicted since some antipsychotics have positive effects on at least some depressive symptoms such as agitation and insomnia; it is less certain how such drugs, especially second-generation agents affect core features of depression syndrome including anhedonia and melancholic features.

⁵ A syndrome that today would be defined as major depressive disorder sometimes with somatic or psychotic symptoms.

symptoms are better in the evening and worse in the morning. That is the problem. All other things are of secondary value but what is particularly important is that this syndrome of symptoms is worsening in the morning and improvement in the evening.

LT: These are actually the symptoms which indicate the presence of melancholia according to DSM-III.

RK: DSM-III. I am of the opinion that it is an absolute catastrophe. It is impossible to make an indication for treatment of depression by medication – it is not possible. I attended a conference in Galway, an excellent conference with Carroll⁶ from Duke University. He said that if you choose a patient with a history of depression, you will not find any difference between the action of imipramine and placebo because the real specificity of the symptoms is introduced only if you include melancholy, a psychotic form of depression with delusion, great anxiety and suicidal thoughts. Depression, alone, is not an indication for antidepressants. In every case of real melancholy you treat the patient with drugs like Ludiomil^{®7} or Anafranil^{®8}, but these must be given with a neuroleptic because delusions are not specific symptoms of vital depression. If you have depressive delusions or hypochondriacal illusion, or fear of loss of money,⁹ then you cannot treat with antidepressives alone. When you have epileptic psychotic states with delusions, you give antiepileptic drugs for the seizure attacks but you must add neuroleptics for the delusions and other psychotic symptoms.

LT: You mentioned that you were studying a compound which was similar to morphine for depression: did you think that morphine was actually a good drug for the treatment of depression?

RK: Yes, you see, before imipramine, we had a lot of patients with vital depression without psychotic manifestations. We saw them in the General Hospital for Internal Medicine for various manifestations of the neurovegetative system. It was necessary to treat these patients but it was not justified to use electroshock. It was necessary to treat them with drugs and, at first, there

was only one possibility – the ancient treatment with opium extract. We used this treatment for more than 20 years and found that morphine had a specific antidepressant effect. The first difficulty with morphine is that its effect is not rapid: it takes weeks, if not months to act. Second, the intestine is affected – opium causes constipation. Third, administration of morphine was not simple; one began with 1 drop a day, 2 drops the next day, 3 drops the 3rd day, and so on, up to 30 drops 3 times a day. Then, after a patient has taken opium for a time and you wish to discontinue it, you are forced to reverse the dosing in the same way, and that is almost impossible, especially in depressed patients. We were forced to have a family member charged with this complicated gradual administration. Morphine can create dependency and it was strange that, in general, this treatment seemed not to cause dependency in depressed patients, although we were never sure about this important potential problem of the treatment. I was always of the opinion that morphine treatment of depressed states must be improved – that was my idea. It proved that imipramine was a substance which was able to do that without any risk of dependency.

LT: Is there a chemical relationship between imipramine and morphine?

RK: The connection was only the idea that there must be a substance which had the same effect as morphine but without the disadvantages.

LT: Were you studying chlorpromazine when you discovered the effect of imipramine?

RK: I studied chlorpromazine and found that it had no antidepressant effect at all. It has been the same with all neuroleptics since.

LT: What was your interest in research before imipramine?

RK: My interest was especially in the Rorschach test.¹⁰ I have a very good knowledge of the Rorschach test and I continue to hold the opinion that the Rorschach test is one of the most important tests and, indeed, one of the most important methods used in the formation of

⁶ Bernard J. Carroll, M.D., Ph.D., a native of Australia, is Scientific Director of the Pacific Behavioral Research Foundation in Carmel, California, which promotes research and community education in mental health. He served as Chairman of the Department of Psychiatry at Duke University Medical Center from 1983 to 1990, Chief of Staff from 1988 to 1990, and remains Emeritus Professor of Psychiatry there. His major contributions are on the biology and treatment of depression; he pioneered neuroendocrine research strategies for depression as well as developing laboratory markers in psychiatry. He is also known for his conceptual analyses of mood disorders, especially for the Carroll-Klein model of bipolar disorder. He is widely consulted on the development of drugs for depression, bipolar disorder, psychosis, Alzheimer's disease and geriatric anxiety-agitation.

⁷ Brand name of maprotiline, a tetracyclic antidepressant, with a strong norepinephrine-reuptake inhibiting effect.

⁸ Brand name of clomipramine, a tricyclic antidepressant discovered in 1960 that is particularly effective in obsessive-compulsive disorder.

⁹ To be distinguished are *delusions* arising from psychotic thought disorder, largely unassociated with experience, and *illusions* arising from reactions to, and interpretations of real experiences distorted by depression.

¹⁰ Hermann Rorschach (1884-1922), Swiss psychiatrist and psychoanalyst, developed a psychological technique known as the Rorschach inkblot test with the idea that the ten figures would help in revealing unconscious material through the psychological mechanism of projection. He was famous at school for his passion for *Klecksographie* (Kleck: German for inkblot). He published details of his test in *Psychodiagnostik* (Rorschach 1921). He died at 37, of peritonitis.

psychiatrists. Current opinions that the Rorschach test is not valid are absolutely ridiculous. It is true that the Rorschach test is not psychodiagnostic and is related to diagnosis only in a secondary way. It is more concerned with the examination of interhuman relationship between the physician and the patient. It gives the possibility of objectivizing problems of this relationship which cannot be objectively evaluated. Even today, I always have patients who do the Rorschach test. I recommend that every young psychiatrist study it.

LT: You may be pleased to know that my medical dissertation was on the Rorschach test. But that was my first interest when I started psychiatry. Did you happen to know Rorschach?

RK: No, he died in 1922 and I was born only in 1912.

LT: Do you think there are any problems with the Rorschach test?

RK: It is in the style of speaking to patients and is of fundamental importance. If you present the ink-blot tables to a patient and you say “What is that?” he will say, “That is an inkblot” and the test is over. If you ask, “What could that be?” then you have an interpretation. I was in Vienna recently and on a Saturday afternoon I took part in a conference where I discussed the case of an 11 year old girl whose father had died of suicide when she was two years old. Now the girl was affected by a severe depressive state. At the time she was preparing her examination for maturity¹¹ and I had one week to treat her for the preparation of this examination. She was sitting where you are now, and in two hours she told me her story. I was not sure how to judge this case, so I did a Rorschach. The girl said that the first plate was an angel. Another psychiatrist who treated this girl over the years also did a Rorschach test. He thought he was rather an expert Rorschach user, but she told him that the first plate was a butterfly, you see. After completing the test, she asked me to see the first plate again. She knew she had said it was a butterfly, but now saw an angel. If a scientific psychiatrist is faced with an experiment in which, in one situation the plate is interpreted as a butterfly and in another as an angel, and states that it may be both of these things, then that

is not a scientific statement. The main problem is that a human being is constantly changing. In psychiatry it is not important that you follow the book which establishes a fixed state because it is in every case false because human beings change continuously. As your relationship to me changes as I speak; that is what is important and not what is fixed in one moment.¹²

LT: But there is another difference: the relationship. The girl saw an angel with you and a butterfly with the other psychiatrist.

RK: That is also the reason why the other psychiatrist couldn't do anything for her as her state worsened for months up to the point that she told him of her suicidal ideas. He was then afraid and she told him: “I will never come again”, and she came to me. I have not done anything great, I only gave her some explanations and then I was an angel.

LT: Since your interest was in psychodynamics and Rorschach test, how did you get interested in psychopharmacology?

RK: It was nearly three weeks after the beginning of my studies in the University Clinic of Bern, with Professor Kläsi,¹³ who was the first to use narcosis in the treatment of schizophrenia patients. Here I was introduced to the first problem [probably the choice between studied insomnia with Prof. Kläsi]. The second was that after the beginning of my studies at the university, I met an excellent anatomist and pathologist who told us that he would present us some cases. He presented a case in which Professor Grünthal¹⁴ had diagnosed as hysterical paralysis. The patient was a young girl who was treated in the clinic for some months. Subsequently she died of a meningioma. I thought then that, in psychiatry, it was particularly important to differentiate between psychic and physical illness.

LT: When you discovered imipramine, were you working for Geigy?¹⁵

RK: Yes. I was working for Geigy in the early 1950s. They gave me a substance, an antihistaminic product which they were interested to investigate to see whether it could be employed as a narcotic. I told Geigy

¹¹ High school final examination.

¹² Although change from one moment to another may sound like a rather obvious consideration, it also has important implications from an existential-phenomenologic perspective which Kuhn believed should be more considered in psychiatry.

¹³ Jacob Kläsi (1883-1980) was a Swiss psychiatrist. In 1921, working at Burghölzli Hospital in Zürich, he introduced the treatment of schizophrenia with sleep therapy using a barbiturate (a mixture of diethyl – and dipropenyl-barbituric acid; Somnifen®). It is unclear whether it was an effective treatment and it was less and less used with the advent of other treatments such as insulin and cardiazol shock therapies about ten years later.

¹⁴ Ernst Grünthal (1894-1972). German psychiatrist who fled Germany in 1934 and found a new career at the psychiatric hospital in Bern, Switzerland. Considered a pioneer of neuroscientific research in psychiatry, he thought that human behavior has definable localizations in the brain. He collaborated with Geigy in the experimentation of new drugs usually tried first on his own staff and students.

¹⁵ Geigy was founded in 1758 in Basel, Switzerland, to extract pigments from plants and later to manufacture synthetic dyestuffs. It started a pharmaceutical branch in 1939 and became famous in the 1940s for the discovery of the Nobel Prize-winning pesticide DDT (Healy 2000). It merged with its Swiss competitor CIBA (*Gesellschaft für Chemische Industrie Basel*) in 1970, and finally merged, along with Sandoz Laboratories, into Novartis Corporation. Ciba-Geigy continues as a drug manufacturer in India.

it was not possible since the drug had specific antipsychotic actions, but Geigy was not interested and refused to give me more specimens. Then, in 1955, at the Clinic of Basel, I presented the results of the research with Geigy, and reviewed all that I had seen concerning Geigy's substance but I did not know the formula. I knew that chlorpromazine was also antihistaminic but it was difficult to obtain sufficient amounts of it and so I told my director that we could use the substance from Geigy and could have it at no cost. I acquired the substance again and it proved to be a neuroleptic but it had two bad side effects. I told Geigy that we needed to change the formula and as I had searched for a substance to replace chlorpromazine, I proposed a formula which was nearest to chlorpromazine with a side chain of 3 carbons and another chain of 2 carbons.¹⁶

LT: Did you hope that in changing the substance that way, it may become antidepressive?

RK: No, that it would be a neuroleptic. However, it had no effect of that kind, but it did have effects on vital depression.

LT: Imipramine was a major breakthrough in psychopharmacology. Why did the monoamine oxidase inhibitors (MAOI) not enjoy the same destiny?

RK: First of all, MAOIs have very disagreeable and dangerous side effects. That was the main problem with Marsilid (iproniazid).¹⁷ A lot of people died because of taking Marsilid. Moreover, MAOIs prevent the disintegration of noradrenaline and dopamine whilst antidepressant drugs improve the action of no-

radrenaline and dopamine. This is an important difference.¹⁸

LT: But why were the new MAOIs after Marsilid, very little used used?

RK: I think that there are rare cases which can be helped by MAOIs, although in my experience this effect is very elusive.¹⁹ It is the reuptake inhibitor imipramine which has antidepressant action and the action is durable.

LT: It's also strange that the first MAOI was discovered in the same period, actually a few years before imipramine.

RK: It is not absolutely clear when it was discovered, I am not sure of the date but it is in the same year.²⁰

LT: It was in 1952 by Crane,²¹ if I remember correctly.

RK: It was in the same year [as my discovery of imipramine].²²

LT: I understand that you continued to be interested in psychopharmacology. Were not you involved in the discovery of maprotiline (Ludiomil®)?

RK: I gave the formula for maprotiline. That was with Ciba.²³ Ciba had a substance, a benzocetamine and I can show you the formula (he showed it to me).

¹⁶ Prediction of an effect based on the chemical formula is highly improbable, even for an expert in pharmacology (Prof. Ross J. Baldessarini: personal written communication, April 2012).

¹⁷ Iproniazid (Marsilid®), a monoamine oxidase-inhibiting (MAOI) drug used as an antidepressant, and chemical analogue of the antibiotic isoniazid. It was discovered serendipitously in 1952 when patients with tuberculosis in sanatoria were found to become peculiarly cheerful and activated when treated with iproniazid as an antituberculosis drug. At the same time, the Swiss-American chemist E. Albert Zeller, at Northwestern University in Chicago, discovered that iproniazid inhibited the action of MAO. The first publications on the mood-elevating effect of iproniazid were by J. A. Smith (Smith 1953) and by George Crane (note 20), but the largest study was carried out by HP Loomer, JC Saunders and N Kline (Loomer et al. 1957). For this discovery Nathan Kline received his second prestigious Albert Lasker Prize (the first was for use of reserpine to treat psychotic disorders). However, his collaborators on the study of iproniazid sued him; Loomer eventually dropped out of the action, while Saunders received a third of the Lasker prize. Iproniazid was withdrawn from the market in 1958 by the FDA because of hepatic toxicity and replaced by less toxic MAOIs including isocarboxazid (Marplan®), phenelzine (Nardil®), and tranylcypromine (Parnate®).

¹⁸ Both types of drugs increase concentrations and duration of monoamines in synapses.

¹⁹ The impression is that Professor Kuhn was promoting imipramine over MAOIs. In fact, MAOIs are quite effective antidepressants, although less used than tricyclics owing to concerns about their safety and tendency to interact with other drugs and natural, indirect sympathomimetic amines in foods and beverages that can lead to dangerous elevations of blood pressure, cerebral hemorrhage, or toxic cerebral intoxications.

²⁰ Iproniazid was synthesized in 1951 by Herbert Fox and John Gibas at the Hoffman-La Roche Laboratories in Nutley, New Jersey (Healy 1997). It was soon found to inhibit oxidase enzymes that metabolized monoamines. Within the next two years, there was clinical interest in Paris in its behavioral effects among clinical investigators who developed chlorpromazine (Delay et al. 1952), as well as in the United States (Baldessarini 2012).

²¹ George E. Crane published results of his study on the effect of iproniazid on depression in 1956 (Crane 1956).

²² This timing is not correct.

²³ The first selective serotonin-potentiating (serotonergic) antidepressant drug was zimelidine in 1981 (following initial work with the toxic agent indalpine in Paris and New York). Zimelidine was effective in depression, but almost immediately withdrawn during clinical development because of flu-like adverse effects, liver toxicity, and rare association with Guillain-Barré syndrome of ascending paralysis. Another serotonergic drug, fluvoxamine (Luvox®) appeared in 1983, and the serotonergic agent fluoxetine (Prozac®) was marketed as an antidepressant in 1987, and became the first psychotropic drug to generate more than one billion US dollars in annual sales.

LT: This is the formula?

RK: That is the formula of benzoctamine as Geigy first gave it to me. I then told them that it was neither an antidepressant nor a neuroleptic; I just could not characterize it. However, I told Ciba-Geigy to add another ring to the structure of imipramine [he showed me a sheet with a chemical formula].

LT: Is this maprotiline?²⁴

RK: Yes. I gave this formula to Ciba and they did the research. The substance was not available and it was necessary to produce it.²⁵

LT: Do you think there has been a major change in the treatment of depression in the last 30 years, following the discovery of imipramine?

RK: I think so, especially for people who know what to do, and there are just as many who don't know. Many are not able to correctly diagnose vital depressive state and they therefore diagnose neurosis, obsessional states, hysterical states and will not see that the fundamental trouble is a vital depressive state. For this reason, many patients are not treated as they should be.

LT: But when diagnosis is correct, do you think that in the last 30 years, since the introduction of imipramine, there has been a major change in treatment, or does imipramine remain the best antidepressant?

RK: Today we have not only imipramine but also clomipramine (Anafranil®), maprotiline (Ludiomil®) and lithium. These are all drugs used in the treatment of depression. Not all antidepressant drugs are good, and some have more side effects and become less effective and lose efficacy after a few weeks or months.

LT: What do you think of the atypical antidepressant drugs – the second-generation?

RK: I have never seen any advances achieved by the use of these newer drugs.

LT: What about the unpleasant side effects of tricyclics?

RK: The side effects that everybody knows are represented by dryness of the mouth, disturbed sight in the aged, urine retention, constipation, tremor, and agitation. The last is probably the most important as well as unpleasant side effect.

LT: What would you consider the major indications for treatment with imipramine and tricyclics?

RK: Vital depression. These drugs are not at all effective if the patient is obsessive, hysterical, schizophrenic or alcoholic. It is important to correctly diagnose a vital depressive state. If such a state is diagnosed even in connection with any other psychiatric state, then antidepressive drugs are indicated.

LT: It is now generally acknowledged that imipramine is the drug of choice in the treatment of panic disorders where there is no vital depression – what is your opinion of this?

RK: In cases of panic disorders and anxious neuroses, if you make a good and clear examination, you will find the basic trouble in the vital sphere but you must search for it; it doesn't come up and present itself.

LT: I see. But you mean you have to look for vital depression in a psychodynamic way or objectively?

RK: I don't make this distinction. When I make a psychiatric examination, I ask the family to be around, and if the patient says: "I am always good in the morning", I ask the wife or the husband about the patient. Sometimes you find that the patient is horrible in the morning and good only in the evening. If you don't ask – and psychiatrists often don't ask – you are unable to ask the most simple questions; the questions can be put and answered in a few minutes. This is no good, but psychodynamic and theoretical constructions sometimes are not good as well. All this is the consequence of absolute inability to learn. Everything is in the books by Kraepelin²⁶ and Bleuler,²⁷ but who reads them today? Nobody in psychiatry actually reads because the majority of psychiatrists are unable to read. They are unable to read a scientific text, and for this reason, my counsel is to read classic psychiatric texts with one's

²⁴ Maprotiline is *N*-Methyl-9,10-ethanoanthracene-9(10H)-propanamine.

²⁵ According to Healy (1998a, pp.139-141), Paul Schmidt and Max Wilhelm from Geigy collaborated with Kuhn in his clinical trial of the new compound following the same protocol used for imipramine. Since the first trials, maprotiline was as effective as amitriptyline and was first marketed in 1972.

²⁶ Emil Kraepelin (1856-1926). German psychiatrist known as the founder of modern psychiatry. He believed in a biologic origin of psychiatric diseases and through careful follow-ups of many patients he systematized major psychiatric illnesses in two main groups: manic-depressive (later called bipolar disorder) and *dementia praecox* (later called schizophrenia by Eugen Bleuler). His *Compendium of Psychiatry* first appeared in 1883 (Kraepelin, 1883) and continued through nine editions to 1927 (Kraepelin 1927). His classification of psychiatric disorders has strongly influenced most current classifications.

²⁷ Paul Eugen Bleuler (1857-1939) was a Swiss psychiatrist who worked mainly at Burghölzli Hospital in Zürich; he is famous for his studies on schizophrenia (a term he coined to replace *dementia praecox*), although his approach has been criticized by some colleagues with Kraepelinian views for being insufficiently systematic.

pupils. In one hour you will maybe read one page but you cannot make reference to the seventh chapter of Freud in one hour. You cannot speak about it in one hour about the seventh chapter: it is absolutely impossible. If you read this chapter, it will take one year and you must give a course and a lecture every week and then you can give an introduction to this way of thinking. This cannot be done as, in general, you cannot learn psychiatry and psychology in the same fashion as popular literature which appears now in hundreds and hundreds of libraries. If you go into scientific libraries, you see hundreds of books on psychology, psychodynamics, psychiatry; this is impossible, it does not serve any purpose.

LT: You mentioned Kraepelin and Bleuler, but they had very different views...

RK: Not as different as is generally thought. They are different because they have different methods. That is a problem; you see, Kraepelin practiced psychiatry through thousands of observations and Bleuler made one after the other – he never had thousands of observations but his observations were very different. Kraepelin was more superficial. It is very interesting to compare the two. Kraepelin made some excellent observations. You can learn very much from Kraepelin, and you must read him, as I also must do. Also my course in Zürich was about existential psychiatry, especially that of Binswanger. Currently, my interests have turned to Henry Maldiney²⁸ who was Professor of Philosophy in Lyon and wrote psychiatry texts. Here is another of his books containing an article about Erwin Straus and notes about Binswanger.²⁹

LT: I do not think that this book is available in Italy.

RK: You can buy it in Switzerland, in Lugano. Every bookshop will be able to get it. This book is not available; it is very good. That is an edition from Switzerland. I think that the problem is the phenomenological approach. It is a pity that we have no studies by Binswanger³⁰ available in reprint. That is an introduction to modern psychology, with a philosophical point of view which is most important. This is a reprint from the Netherlands on the history of modern psychology by Binswanger from a philosophical point of view [Kuhn went back and forth to his bookshelf and showed me several books and papers].

LT: How do you put everything together, the Rorschach test, existential psychiatry, psychopharmacology. How is it possible to do so?

RK: I think that it is absolutely necessary if we wish to practice psychiatry because every case has its neurobiological and psychological aspects.

LT: Were you more interested in the treatment of patients or in research?

RK: More in the treatment of patients.

LT: What do you think about the treatment of depression through psychotherapy?

RK: I think that psychotherapy of depression is possible and even indicated in some cases. However, it requires a new methodological approach; the psychoanalysis recommended by Freud is not the method to use.

LT: What would you suggest as the best method?

RK: An existential and analytical approach. That is absolutely so. With psychoanalysis the only common factor is represented by the patients' illnesses. If you would help the depressed, you cannot just rely on free association. This is not possible with depressive patients.

LT: Not even with patients affected by mild depression?

RK: It's not satisfactory. There must be quite another approach but I think that such an approach still remains to be discovered.

LT: What do you think about Jungian psychoanalysis?

RK: I think Jung was a genius, but he was undisciplined. He had excellent ideas but he was not able to develop these ideas in a fruitful way. I also think that his successors are too excessive in their admiration. Admiration like that does not help them to develop professionally.

LT: Did you work with Binswanger?

RK: Oh yes; he was in Kreuzlingen near here. I think he was the most important psychiatrist I know of. The questions he asked represent the main questions present in psychiatry.

LT: What kind of person was he?

RK: He was very intelligent, very kind, extremely comprehensive, and one could immediately understand

²⁸ Henry Maldiney (1912-). French philosopher influenced by Binswanger, Heidegger, and Husserl. His main interest was in mental illness as an existential possibility and in psychiatry as a study of human expression. He collaborated with Kuhn in writing a foreword to Ludwig Binswanger's *Introduction to Existential Analysis* (Maldiney & Kuhn 1971).

²⁹ Erwin Straus (1891-1975). Phenomenologist, psychiatrist, and leader in anthropological medicine.

³⁰ Ludwig Binswanger (1881-1966). Swiss psychiatrist whose grandfather founded the Bellevue Sanatorium in Kreuzlingen, Switzerland, of which he was medical director from 1911 to 1956. He combined existential philosophy with psychiatry and psychotherapy. His most famous book was *Basic Forms and the Realization of Human "Being-in-the-World"* (Binswanger 1942) and he also wrote *Melancholy and Mania* (Binswanger 1960).

what he meant... [Doctor Kuhn continues in French, his second language] he was very kind, very warm, very understanding, understood all, forgave all. It all depended on his immense knowledge, immense knowledge of philosophy, psychology, and his enormous experience; that was the true difference.

LT: What were his relationships with patients like?

RK: He was very understanding.

LT: Was his existential position in psychotherapy a development of existential philosophy?

RK: Yes, he had a philosophical formation but not academic because he did not have the time to follow courses at the university; he was more interested in his psychiatric patients and had his private hospital.

LT: What type of treatments did he use?

RK: He used a kind of psychoanalytic treatment but with some existential elements. The foundation of the treatment must include the vital elements in almost all psychiatric conditions.

LT: It seems to be a psychotherapy which tries to develop some patients' energies and improve their understanding of their existence

RK: Both. One thing follows the other.

LT: Any particular memories of your relationship?

RK: It's very difficult to think of one particular moment. For a period of about 10 years we talked every week on the telephone, and I saw him often. He was an excellent musician – he played the piano very well.

LT: Was he an outgoing person or more reserved?

RK: He was both. He was not particularly

extraverted. It all depended on the type of person he was with, and he could adapt to different situations and to individual patients. It is very interesting.

[Back to English]

LT: Can you remember any episode involving Binswanger that particularly impressed you?

RK: In particular, I recall that he claimed that the clinical features of endogenous depression are observed in patients taking antidepressants. He stated that the aetiology of depression does not play any role in the indication for antidepressants.

LT: The aetiology is not important?

RK: Of no importance at all.

LT: Not for psychotherapy either?

RK: Yes, it's not important.

LT: Returning to antidepressants, several researchers maintain that antidepressant drugs, particularly tricyclics, can induce hypomania and mania and can actually worsen the course of manic-depressive psychosis. What do you think?

RK: I don't think that this is acceptable. We observed manic phases in depressive patients before the discovery of antidepressants. If you administer lithium and use carbamazepine (Tegretol®), these phases can generally be dominated without any problems.

LT: So you do not think that tricyclics induce mania?

RK: I don't think so. Manic phases are hereditary. Of course, it is possible that some patients would not have become manic if they hadn't taken antidepressants, but this is of little importance.³¹

³¹ Many studies have confirmed the role of antidepressants, in particular tricyclics, in favoring the emergence of mania or hypomania. Even Kuhn recognized that phenomenon in his first papers.

Roland Kuhn, M.D. (1912-2005)

Brief biography³²

Roland Kuhn was born one hundred years ago on March 4, in Biel, Switzerland in a family with local roots and medical tradition. One of his maternal ancestors had founded the children's hospital in his birth town. His father and grandfather were booksellers and publishers and other paternal relatives were pastors and poets. He married in 1957 his long-time colleague Verena Gebhart with whom he worked until his old age. They had three daughters, Regula, Beatrix, and Ursula.

Kuhn studied medicine in Bern and Paris, graduating in 1937 with a dissertation on *Iodine Excretion in Cretins*. He wanted to start a residency in surgery but the program in Berne was canceled so that he chose psychiatry and studied with Jacob Kläsi (see note 13) and Arnold Weber,³³ Ernst Grünthal (see note 14), and was introduced to the study of psychotherapy by Otto Briner.³⁴ He learned the Rorschach technique in the regular evening seminars organized by Arnold Weber and Hans Zulliger,³⁵ both pupils of Hermann Rorschach (see note 10). He collected over 30,000 Rorschach protocols. In 1939, Kuhn was appointed as consultant and deputy director of the psychiatric hospital at Münsterlingen in the canton of Thurgau on Lake Constance. He was director of this hospital from 1970 to 1980 (year of his retirement), giving up more prestigious appointments that included his candidacy for the Chairmanship of Psychiatry at the university of Würzburg. From 1957 to 1983, was Docent of Psychiatry at the University of Zürich and honorary Professor until 1998. He established a close friendship with Ludwig Binswanger (see note 30), director of the Bellevue Sanatorium in Kreuzlingen, a few miles from Münsterlingen. Binswanger supported Kuhn's clinical, psychopharmacological, academic talent as well as his work with Rorschach test, and facilitated his study of the phenomenology of Edmund Husserl.³⁶ They gathered several times in Binswanger's house with great thinkers and scientists, including Martin Heidegger,³⁷ Wilhelm Szilasi,³⁸ Eugène Minkowski,³⁹ and numerous artists. In addition, he held fortnightly courses in his own residence on philosophical and phenomenological topics keeping records of all meetings, collected in thousands

of pages by his secretary, Ms. Rutishauser⁴⁰.

In the early 1956 a chemical compound, G-22355, from Geigy (later named imipramine; initial brand-name: Tofranil[®]) was tried at the the Münsterlingen Hospital and proved to be effective in patients suffering from melancholia (see below the section *Discovery of imipramine and its controversies*). In September 1957, Kuhn reported the finding at the second International Congress for Psychiatry in Zürich to very few listeners, and in the same year published his observations in the Swiss Weekly Medical Journal (Kuhn 1957). The article was followed five years later by a follow-up study published in the same journal (Kuhn 1962). These two articles are significant, among other reasons, because they reported that the medical treatment of depression may be important and that recognition of depressive symptoms that may be helped by pharmacological treatments. Kuhn presented his discovery on various lectures. Last occasion was at the award ceremony for the Hans Prinzhorn medal in Berlin in 2004, later published in the *Swiss Archives for Neurology and Psychiatry* (Kuhn 2005).

A few years after the discovery of imipramine, Kuhn collaborated again with Ciba-Geigy Laboratories in the synthesis of a tetracyclic antidepressant molecule (later named maprotiline [Ludiomil[®]]). He repeatedly emphasized the specific activity and the main indication of these antidepressants in vital-form [endogenous or melancholic] depressions when emotional and physical symptoms are present. Kuhn stressed the importance of practicing a combination of pharmacotherapy and psychotherapy, mainly based on existential analysis (*Daseinsanalyse*) practiced by Binswanger and, in fact, he was more recognized as an expert in phenomenological psychiatry and in Rorschach psychology than in psychopharmacology. Kuhn's published and unpublished scientific works dealt with broad areas of psychiatry and psychotherapy as well as philosophical, sociological, ethnological, educational, theological, aesthetic, and artistic aspects associated with psychology. His broadly ranging titles included, for examples: *Evil from a psychiatric point of view*, *Errant question of pathological art*, *Miraculous healing in the New Testament*, and *Freud's essay about the Uncanny*. Other publications are more revealing of a free spirit

³² Biographic notes based on published accounts (Cahn 2006 [reprinted by permission from Macmillan Publishers Ltd: Neuropsychopharmacology]; Bossong 2008).

³³ Arnold Weber (1894-1976). Swiss psychoanalyst who contributed to the diffusion of Rorschach test, providing protocols of professional musicians and other talented persons.

³⁴ No information available.

³⁵ Hans Zulliger (1893-1965). Swiss school teacher and child psychoanalyst. His main interest was in understanding children's difficulties at school. He is also the inventor of the Z-test, which is analogous to the Rorschach test that allowed otherwise impossible re-testing.

³⁶ Edmund Husserl (1859-1938). German philosopher, founder of the phenomenology, which later applied in psychiatry tried to explain the meaning of behavior.

³⁷ Martin Heidegger (1889-1976). German philosopher, famous for his work on existential philosophy studying the relationship between the individual and the world. His most famous book was *Being and Time* (Heidegger 1927).

³⁸ Wilhelm Szilasi (1889-1966). German-Hungarian phenomenologic philosopher.

³⁹ Eugène Minkowski (1885-1972). Russian-French psychiatrist who merged psychopathology and phenomenology. He moved with his family to Zürich after World War I, and again to France in 1926. His most famous book was *Lived Time* (Minkowski 1933).

⁴⁰ No information available.

(Kuhn 1967, 1985). For Müller's *Lexicon of Psychiatry*, Kuhn wrote contributions on existential analysis, shame, and grief.

Kuhn's combination of clinical, scientific and humanistic work and this versatility was considered a model for future psychiatrists (Bossong 2008). His clinical efforts were focused on patients he sometimes treated over decades, with knowledge of their families. He stressed that *Psychiatry for the Future*⁴¹ (Kuhn 2004) should not rely only on purely biological research with scientifically-oriented methods but also on the development of an aesthetic and phenomenologic dimension of the existence. He also warned that significant effects of psychotropic drugs may not need large-scale studies or meta-analysis but sometimes it is sufficient in studying the relevant characteristics of each patient.

Although psychopharmacology was not his main interest, paradoxically, imipramine gave him international recognition. His dearest interests included efforts to integrate philosophy, psychology, and psychiatry. These interests included considering psychological effects on patients treated with psychotropic drugs. In 1992, on the occasion of Roland Kuhn's 80th birthday, a Colloquium was held in Münsterlingen. The main themes of this meeting were ethics and aesthetics in philosophy and psychiatry.

Roland Kuhn was much in demand as a visiting lecturer in many countries. He received honorary medical doctorates from the Universities of Basel and Louvain, and a doctorate in philosophy from the Sorbonne (Cahn 2006). At the introduction of 1997 symposium on the 40th anniversary of the discovery of imipramine, Professor Karl Rickels from the University of Pennsylvania, concluded, "Progress needs two things: ideas and good primary clinical observations: We need more Kuhns!" (Rickels 1997).

Despite the importance of his discovery he was never awarded with a major prize. Although he may have deserved to be a candidate for a Nobel prize for his work on imipramine, Kuhn thought that his work as a psychiatrist from a rural Swiss hospital would hardly be considered for prestigious recognition. However, some controversies about the discovery of imipramine may have played a role in his not receiving a prestigious prize, as are considered below. It is also noteworthy that none of the major clinical discoveries in psychopharmacology during the 1950s was awarded a Nobel prize. Thuillier (1981) reports that, in that era, only chemists and biochemists received the prize for medical research, whether or not their discoveries brought important clinical benefits. Roland Kuhn died at the age of 93 on October 10, 2005.

The discovery of imipramine and its controversies

In the early 1950s, Robert Domenjoz (Healy 2000, pp. 357-369), chief of pharmacology at Geigy

Laboratories, showed interest in antihistaminic drugs similar to the phenothiazines that might replicate the success of chlorpromazine. A candidate substance had to be similar but not so similar as to infringe on patents for the phenothiazines. For this purpose, Geigy reviewed compounds from its collection of older substances, and considered an iminodibenzyl synthesized in 1898 by Thiele and Hölzinger. At first, they had no idea about its possible uses, but eventually it had been used as a dye (*Summer Blue*). Among 42 compounds synthesized at Geigy by chemists W. Schindler and F. Haefliger from the iminodibenzyl nucleus, one (G-22150) was selected for further testing as a hypnotic. Two representatives from Geigy, Otto Kim and Paul Schmidlin visited Roland Kuhn at the Münsterlingen Hospital which he directed. It was a large psychiatric facility with 700 patients at the time. Kuhn, despite his main interest in existential analysis and the Rorschach test, did not show any opposition to the trial of a drug. According to Kuhn, it was he who asked Geigy to try a new possible antipsychotic due to the limited budget of Münsterlingen Hospital which did not allow for the purchase of chlorpromazine, which was being recognized increasingly as a very effective antipsychotic agent by the mid-1950s. Geigy's version, in the words of Alan Broadhurst (Healy 1996, pp. 111-134) who worked at Geigy at the time, is that Geigy asked Kuhn to try a different drug as a potential neuroleptic. In one way or another, G-22150 was tested. However, in March 1955, Kuhn announced that it had serious adverse effects and that it was not only ineffective but also disastrous for many patients whose symptoms heavily deteriorated owing to agitation and worsening of psychotic symptoms (Baldessarini & Willmuth 1968, Baldessarini 2012).

Early in 1956, Kuhn met Domenjoz in Zurich and reports that he picked one possible substance (G-22355), out of at least 40 other chemical products with a tricyclic structure and a side-chain similar to those features of chlorpromazine, hoping for another neuroleptic medicine. He gave the substance to about 300 patients with different diagnoses. Some became more agitated and others hypomanic, so that the company decided to interrupt the trial. Kuhn, along with Alan Broadhurst and Paul Schmidlin from Geigy, realized that G-22355 may induce some mood elevation and decided to try it on melancholic patients. The first patient (initially treated on January 12, 1956), Paula J. F., was depressed and delusional; she improved in three weeks. Results in the other patients given G-22355 were so positive that the entire hospital staff had no doubt that the new treatment was effective in depression (Healy 1996, 1997, 2000; Shorter 2009).

Kuhn described his first observations as follows: "In the first two patients who received the drug, there was identified quickly and clearly, an effect that had never been seen before! It was so impressive, and close observation of these patients revealed the essence of the new substance." Therefore, he switched the prescriptions of G-22355 from patients with schizophrenia to those with depression. Within a period

⁴¹ This book contains a selection of unpublished lectures by Kuhn, the speeches of his colleagues and friends on the occasion of the 90th symposium on his Münsterlingen birthday in 2002, with a brief biography and list of his published scientific works to 2004.

of three weeks, the depressive symptoms improved in most patients, especially those with what Kuhn described as “vital depression” (similar to or coinciding with “endogenous or melancholic” depression). However, he repeatedly emphasized that he had discovered the effect of imipramine, not with statistics or double-blind trials, but by carefully observing his patients in their familiar environment. In addition, he gave particular importance to “vital depression”⁴² manifesting physical symptoms (dysfunction of appetite, sleep, and sexuality with diurnal variations) which should alert physicians to candidates for the new treatment. In fact, he attributed his discovery to Ludwig Binswanger’s distinction between “life function” and “inner life story”, which allowed him and his staff to detect the dissimilar effects of imipramine and chlorpromazine by clinical observation. Binswanger and Kuhn had predicted in the 1940s the discovery of a pharmacological treatment of depression after observing that the disease could be effectively treated with electroconvulsive therapy (ECT) and with opium derivatives (Bossong 2008).

Kuhn communicated to Domenjoz that melancholic patients felt less tired, became less inhibited, and that their mood improved after taking G-22355 for several weeks (CINP 2002). However, Geigy sent the compound to ten Swiss⁴³ clinics, of which only six tried it, and concluded that the drug was ineffective. Largely based on this experience, Geigy lost interest in G-22355 as a potential antidepressant, and insisted on pursuing it as a possible antipsychotic. Kuhn presented his results at the 1957 Congress of Psychiatry in Zürich, but stirred very limited interest. In the spring of 1958 G-22355 was given the generic name imipramine and it was soon introduced in the market in Europe with the brand-name Tofranil[®]. In the same year, the drug was given to, and was effective for, the depressed wife of Robert Boehringer, an important shareholder at Geigy, who soon influenced the company to show more interest in it. It is interesting that Kuhn met Boehringer in Villa d’Este in Tivoli at a dinner for the International Congress of Psychiatry in September 1958 (CINP 2002). In the same year, Kuhn published the results of his observations based on 500 patients with a follow-up of about three years.

Imipramine was not an immediate success for

several reasons pointed out by Healy (1997). One is that, unlike chlorpromazine, which was discovered in Paris, and iproniazid, whose effect was formally recognized at Rockland State Hospital, near New York City, findings on imipramine came from a hospital in a small Swiss village and Kuhn did not have the scientific and academic status of Jean Delay (chlorpromazine) or Nathan Kline (iproniazid). Kuhn was not even invited to speak at the 1958 Congress of Neuropsychopharmacology in Rome; instead, a colleague from Heidelberg presented on imipramine. On that occasion, Kuhn reports that Jean Delay approached him asking why he had not sent the compound to Paris to be tried, and Kuhn replied that he had sent it a year before to Delay’s associate, Pierre Deniker, who apparently had not tried it. Kuhn claims that once Delay heard this, he made a public scene with Deniker in Rome (CINP 2002).

In addition, Kuhn was interested in associating the clinical effects of imipramine with his concept of vital depression and denied any attempt to characterize the new agent as a “stimulant.” However, these aims were not well matched with marketing strategy being planned for imipramine by Geigy (Healy 1997).

David Healy⁴⁴ (1997), reports that in 1956, when the first depressed patients were successfully treated with imipramine, Geigy was not convinced of the importance of an antidepressant. Indeed, the discovery of the first monoamine oxidase (MAO) inhibitor, iproniazid, was not considered interesting by its manufacturer, Hoffman-La Roche, also of Basel. In addition, reserpine, whose antidepressant (as well as antipsychotic) action had been shown by Kline and others, had not been supported as an antidepressant by its manufacturer, CIBA (as Serpasil[®]). Healy concludes that, in order to sell the new drugs (including Merck’s highly effective antidepressant, amitriptyline [Elavil[®]]), “the companies had to sell the illness.” Accordingly, they bought and distributed 50,000 copies of Frank Ayd’s book *Recognizing the Depressed Patient* (Ayd 1961). The first major review on imipramine and other tricyclic antidepressants appeared in 1965. It was based on all available international studies that included a total of 502 depressed patients and 449 depressed controls given a placebo or not given an antidepressant (Klerman & Cole 1965). The reviewers found that 65% of those treated with imipramine improved, compared with 31%

⁴² Kurt Schneider (1887-1967) of Berlin coined this term, following the philosophy of Max Scheler. “Vital” depression describes a condition characterized by complaints of fatigue, oppressive feelings of heaviness, and constriction or inhibition of thinking and acting, more obvious in the morning than in the afternoon or evening, as well as inability to experience pleasure and to pursue interests. These symptoms apply to endogenous and melancholic as well as vital depressions (Kuhn & Müldner 1986).

⁴³ One of these was the Viarnetto Clinic in Lugano, Switzerland (founded by Drs. Giovanni Bolzani and Bruno Bariffi), at the time managed and supervised by Dr. Luciano Bolzani, son of the founder and father of Lorenza Bolzani, the current director. Doctor Luciano Bolzani still recalls the trial with imipramine and the satisfactory results obtained with it. He also recalls that Dr. Kuhn was a gentle person, but “Swiss-German,” implying an admixture of correctness, kindness, formality, and rigidity.

⁴⁴ David Healy (1954-). Irish psychiatrist, currently Professor of Psychological Medicine at Cardiff University School of Medicine, Cardiff, Wales. His writings focus on the extent of the *unhealthy* influence of pharmaceutical industry on academic institutions and on clinical practice. Healy has a critical view about the excessive use of modern antidepressants which may not be as useful as they are publicized to be, and may also lead to suicide behavior. He is also author of several books including *The Psychopharmacologists*, Vol. I–III (Healy 1996-2000), *The Antidepressant Era* (Healy 1998), *The Creation of Psychopharmacology* (Healy 2002), *Let Them Eat Prozac: The Unhealthy Relationship Between the Pharmaceutical Industry and Depression* (Healy 2004), *Mania: A Short History of Bipolar Disorder* (Healy 2008), and *Pharmageddon* (Healy 2012).

of controls, although the methods involved in many of the studies were not as well developed as in modern, controlled drug trials.

The controversies

Three points remain unclear about the discovery of imipramine. One is whether its effect was discovered by chance; the second is whether the crucial clinical observations were made originally by Kuhn; the third is whether Kuhn was alone in the discovery or was helped by collaborators who were not included in subsequent authorships or acknowledgments.

Kuhn rejected the idea that the discovery was serendipitous. He probably chose one of the compounds presented by Domenjoz in Zürich for clinical testing, but it is very likely that he expected it to be a neuroleptic-antipsychotic and not an antidepressant. Also notable is his repeated assertion that “vital depression”, as an endogenous form of depression, largely independent of environmental factors or life circumstances, should respond uniquely to pharmacological treatments, as it had to opiates, ECT, and perhaps iproniazid, before the discovery of imipramine. Probably there was a favorable combination of events when a drug with some mood-lifting properties fell into the hands of a man who knew depression well from a clinical point of view.

For the second point, Healy (1997) questioned who actually discovered the antidepressant effect of imipramine. Broadhurst (Healy 1996, CINA 2002) claimed that, after long discussions with Kuhn trying to explain why some schizophrenia patients had become excited (probably manic or hypomanic, and possibly misdiagnosed cases of bipolar disorder) when given G-22355 (imipramine), the Geigy team thought of trying the drug in depressed patients. Broadhurst is said, further, to have added that the idea imipramine might have antidepressant properties was proposed specifically by Paul Schmidlin at Geigy in the 1950s as the company was planning its development of one or more of its older iminodibenzyl compounds (Kuhn vehemently rejected this proposal). Broadhurst (CINA 2002) concludes:

I do not want to detract in any way from Kuhn's pivotal role in the discovery of imipramine. Clearly, he was the first to notice the antidepressant effect of the drug in his patients. However, the idea to carry out a trial of imipramine in depressive illness was ours, based upon our rather naïve theory of why its extraordinary side effect of mood activation had occurred [in schizophrenia patients].

Apparently Kuhn was rather unenthusiastic about trying it and did so reluctantly; in fact, in a correspondence with David Healy (CINA 2002), Kuhn again strongly rejected this idea. This version of the discovery of the antidepressant effect of imipramine is, in part, contradicted by Jean Thuillier who, in his book (Thuillier 1981), recalls that during a meeting, Domenjoz, after telling him that a new product (G-22355) was unsatisfactory as a neuroleptic, added:

I have a problem to solve. I gave one our products

to a psychiatrist who works in a small cantonal hospital. I know him well; he is a conscientious man and a scrupulous observer whose intuition and clinical experience I have often made use of for other drugs. Now, contrary to the big customers, he is insistent that clinical experiments should continue with one of the tricyclics [imipramine]... Roland Kuhn has never misled me... He states he has obtained spectacular results in depression... according to him, the drug only works on depression.

In 1955, 40 patients were studied but the effect was so compelling that Kuhn wrote to Geigy reporting that the drug had a potential antidepressant effect. On February 4, 1956 he wrote Domenjoz:

We had a quite a few cases in which the effect can be characterized as positively favorable. This applies first and foremost to depressions. Unfortunately, our group of these cases is rather small since we had relatively few cases to treat.

Further, on April 18 of the same year, he wrote:

Since depression is not only one of the most frequently occurring mental illnesses, but one of the most frequently occurring illnesses in general, and since the effect of Lergactil® (chlorpromazine) against depression, as generally accepted, is rather limited and most cases not sufficient at all, I see an immense potential here.

However, Kuhn, rather than focusing on the clinical effects of imipramine, emphasized confirmation of his idea that “vital” depression has some characteristics that may be treated with medication. Nevertheless, Domenjoz confirmed that Kuhn was the actual discoverer of the antidepressant effects of imipramine, based on correspondence that they exchanged (Thuillier 1981, Healy 2000, CINA 2002). Kuhn sent Domenjoz long, detailed reports of the results of his trials, in which imipramine appeared to be clinically effective in depression. Whether there was some envy on the part of members of the Geigy team or the pride of a discoverer is hard to disentangle. Certainly, Geigy Corporation had a clear interest in self-attributing the proposal of the initial trial which first found and documented antidepressant effects of their new drug.

Third, it seems fair to state that virtually all discoveries of novel psychotropic agents in the remarkable decade of the 1950s resulted from the collaborative efforts of several persons. However, Kuhn consistently made no reference to input from staff or collaborators at his hospital or from Geigy in recounting the discovery of the antidepressant effects of imipramine. In addition, none of them was included in his publications or lectures on imipramine. Kuhn always claimed that he made the discovery of the effect of imipramine in the treatment of a particular type of depression – vital depression – and that, if the agent was effective in other forms of depression, it was because they, too, had “a substantial vital core”. Moreover, in his view, the drug seemed more important to him for validating the psychopathology that he

associated with vital depression, than for its potential clinical therapeutic value. However, Kuhn claimed that he wanted a rapid publication in order to present it at the Zürich Congress of Psychiatry in September 1957, and so he delivered the manuscript for publication in June of the same year. He added that Paul Schmidlin of Geigy had started his trial with imipramine only in February, 1957, and that four months were insufficient to obtain any results. However, he did not explain why Schmidlin's name was not included in *his* publication. Kuhn also had given imipramine to Klemenz Faust of nearby Freiburg (Germany) and wanted to include this collaborator's observations and include him as a co-author. However, it is reported that Kuhn's superior, Professor Ruffin, did not permit the co-authorship (CINP 2002). Broadhurst (Healy 1996) reported that the initial trial of imipramine was a collaborative project, not only with a team from Geigy but also from Kuhn's hospital at Münsterlingen. Kuhn rejected this view, saying:

The team had its place, and discussions took place, but it was again the discoverer who gave these discussions their importance and special significance. In this way I identified a "particular kind of depression" which led to treatment with a particular kind of drug.

David Healy is well aware of details of the imipramine story, and conducted a detailed interview with Kuhn (Healy 1998). I asked Healy (April 2012) why Kuhn did not receive a Nobel prize and whether he had to be the only person credited with discovery of the antidepressant effect of imipramine. He replied:

He did not get a Nobel because Delay did not get one due to squabbling in Paris over chlorpromazine. Alan Broadhurst, who was present at the time, thinks Kuhn was not the only one to discover imipramine's antidepressant effect and that very few if any of the others who were around give Kuhn much credit. They really did see him as a country doctor, and Kuhn got fiercely proprietary about it all.

I also asked Healy about the apparent inconsistency regarding the treatment of Robert Boehringer's wife. According to Kuhn (CINP 2002), he was asked by Mr. Boehringer to treat his wife in September 1958, but at that time imipramine was already marketed. Healy replied, "Boehringer spoke up in favor of the discovery long before he met Kuhn. He was aware of it early and only met Kuhn later".

As David Healy not only interviewed Kuhn for one of his books, but also carried out an intense correspondence with him, I also asked about his final impression about Kuhn. His reply was⁴⁵:

I have interviewed a large number of people who had dealings with Kuhn, and views are mixed. Alan

Broadhurst, Robert Domenjoz, Hans Hippus, Merton Sandler, Peter Waldmeier and others were very dismissive of his role. Jean Thuillier and Frank Ayd gave him credit [as has Edward Shorter: see below]. Those closest to industry play down Kuhn's role. Those who agree with his views on the nature of melancholia give him credit. There was intense antipathy to him. This is perhaps well symbolized by the meeting in Galway where he was not initially invited to even though it celebrated *Thirty Years of Antidepressants*. He himself requested to attend, and the organizers felt they couldn't avoid having him if he was willing to come. In part his lack of an initial invitation may have come from his approach. Whether it was a matter of his personal style from the start, or his insistence on priority in the face of efforts by others to downgrade his efforts, the upshot was that he was considered someone who gave little credit to others and who insisted on a point of view that increasingly seemed contrived to suit his claims. He also made claims about being able to see likely efficacy from molecular structure that people like Domenjoz flat out contradict. His views in these areas are perceived as being shaped, as we might say today, by a conflict of interest. While very pleasant for the most part, and not at all obscure for someone with an interest in psychopathology, although very obscure to most psycho-pharmacologists, Kuhn could be quite difficult when challenged. I attempted to bring a number of competing views into the frame in some of the accounts I have offered as to what happened (Healy 1998), and was sent a letter threatening to sue me (CINP 2002). This is what led to the lengthy, 70-page, Imipramine Dossier in the book, *From Neuropsychopharmacology to Psychopharmacology* (CINP 2002). This difficulty was used by Tom Ban, Ed Shorter, and me to try to get more information from Kuhn. Ultimately, however, Kuhn kept hinting at records and documents which he did not make available. His views also were couched in a language increasingly at odds with the language of psychopharmacology. And finally he was crucially a decade older than the others in the field and so never developed the network of friends one needs who can lobby for recognition and credit. Having said this, Kuhn's papers on imipramine were eloquent and contain most of what we know about this drug (Kuhn 1957, 1958). If he was also as involved in the discovery of maprotiline as he suggests, this would make an impressive record of discovery. His predictions of the efficacy of later SSRIs were correct. His impact on our culture – although mostly in ways he would not approve of – have effectively been enormous. People have got Nobel Prizes for less than his contributions. So the verdict is that he was correct on a lot of things and played an essential role, but the discovery of the antidepressant effects of imipramine is almost an object lesson in how *not* to make a discovery.

⁴⁵ Received on April 21, 2012

I also asked the same questions of Professor Edward Shorter,⁴⁶ historian of psychiatry at the University of Toronto, who had an opportunity to visit and interview Kuhn with Healy, and wrote extensively on the history of early antidepressants before the serotonergic agents (Shorter 2009). He replied to my query about his overall impressions of Kuhn⁴⁷:

The discovery of the clinical utility of imipramine was very much Roland Kuhn's own work and not the result of a team effort. I consider him a pioneering figure in the history of psychopharmacology, and resist talk of "team efforts" that might lessen his own role in the epochal discovery of the utility of the tricyclic compounds in the treatment of what was, essentially, melancholia. The discovery was serendipitous in the sense that Geigy had set out to find an antipsychotic they could patent. It was owing to Kuhn's clinical acumen that the importance of imipramine was recognized – despite the resistance of the company! My personal impression of Dr. Kuhn is that he was a dedicated scientist and clinician. In the manner of many of his generation, he had initially become bogged down in psychoanalysis, but he followed the trail of science, and ended up making a major contribution to biological psychiatry. He was a modest man and not inclined to seek the spotlight, which is why recognition has come to him rather belatedly. I assume that you are familiar with the imipramine correspondence in volume 3 of the CINP series edited by Thomas Ban (CINP 2002). David [Healy] and I enjoyed the hospitality of Roland and Vera Kuhn that remains to me to this day, unforgettable.

Shorter's recognition of the fundamental role of Kuhn on the discovery of imipramine is furtherly supported by a brief note sent me by Jean Thuillier⁴⁸, which states: "Yes, I agree with you that Roland Kuhn is the only discoverer of the antidepressant effect of the imipramine"⁴⁹.

If these scholars, who interviewed Roland Kuhn, wrote about him, and know about the history of psychopharmacology as very few others do, disagree so evidently, there should be very little to add to the

imipramine dossier. My conclusion, however, is that there are incongruencies in Kuhn's recollection about the discovery of the antidepressant effect of imipramine. In fact, contrary to Kuhn's claim, it is nearly impossible to predict the effect of a drug based on its chemical formula,⁵⁰ especially for a man whose main interest was existential psychiatry, even at a time when eclecticism in psychiatry was prevalent. It is also somewhat suspicious that Kuhn published his results in a hurry without including in the authorship at the very least the name of Paul Schmidlin and one of his German colleagues, whom he recognized as collaborators with whom he shared the idea of treating depressed patients with what was later called imipramine. Kuhn's explanation regarding Schmidlin was that the colleague had insufficient time to collect data for them to report together at an upcoming congress. It would be speculative to suggest that, at that point, Kuhn realized he had made an important discovery and was not willing to share it. Nevertheless, such a reaction would be understandable for a rural, but erudite, psychiatrist receiving such unexpected luck that may bring him to fame. Moreover, Kuhn claims that Boehringer, knowing of the effect of imipramine, asked him to treat his wife and when she improved after three weeks, Boehringer decided to encourage development of the new drug by Geigy. However, Kuhn stated in our interview that the meeting with Boehringer occurred in Rome in September 1958 when imipramine had already been on the market for nine months in the same year. Finally, Kuhn said that Jean Delay scolded him at the congress in Rome for not having sent his group imipramine to try. Kuhn replied that the drug had been sent a year before but Deniker did not try it, leading to an angry public encounter in Rome between Delay and Deniker (CINP 2002). This picturesque situation is at odds with a report by Thuillier (1981), who was in Paris at the time and claimed that Delay and Deniker tried imipramine but were dissatisfied with the results. It is possible that memories of events that occurred thirty or more years earlier may not be accurate, but several hints suggest that Roland Kuhn built his own version of events that may not have been entirely consistent with their actual development. Critical comments that have been directed at Kuhn during his lifetime and since may derive from a lack of personal "likeability" and from the

⁴⁶ Edward Shorter (1941-). American-born psychiatrist, currently Professor of the History of Medicine and Psychiatry at the Faculty of Medicine of the University of Toronto (Canada). He is author of 24 books on several topics associated with the history of psychiatry. His forthcoming book is *Big Footprint: The Story of Medicine in Toronto, a History of the Faculty of Medicine, University of Toronto, and its Affiliated Healthcare System* (Shorter 2012). He is also author of more than 130 papers.

⁴⁷ Received on April 21, 2012

⁴⁸ Jean Thuillier (1921-). French psychiatrist, formerly a Chef de Clinique at the Faculty of Medicine in Paris. He was one of the founders of the International College of Neuropsychopharmacology (CINP) in 1957. He wrote *Ten Years that Changed the Face of Mental Illness* (Thuillier 1981). He also devoted himself to fiction, history and poetry, some of which received literary awards.

⁴⁹ Received on May 6, 2012

⁵⁰ Indeed, it was not immediately apparent that the pharmacology of the phenothiazines and the iminodibenzyls is markedly dissimilar, and the latter are, in retrospect, unlikely to have been congeners of the antipsychotic phenothiazines. They share superficial chemical structural similarities, with markedly dissimilar pharmacodynamics, probably arising from the planar conformation of chlorpromazine and the non-planar conformation produced by the seven-member central ring of imipramine that evidently prevents its action as a dopamine receptor antagonist and contributes to its activity as an inhibitor of the neuronal transport of norepinephrine and serotonin (Baldessarini RJ, personal written communication, April 2012).

striking contrast between his work with imipramine and his professional background marked by psycho-analytical training and philosophical interests. His views about selective benefits of imipramine and other antidepressant medicines in what he termed “vital depression” is a concept that seems more biological than the result of developmental and environmental stressful factors that might be expected of someone with his training and interests.

It is very tempting to speculate that Kuhn may have been dealing with a conflict between his background and clinical experience versus his observations of the clinical efficacy of imipramine. He was not alone in being surprised by the ability of medical treatments to provide beneficial clinical effects in depression in the 1950s and early 1960s, as is underscored by the use of Ayd’s book (1961) on the treatment of depression as part of Geigy’s marketing campaign for imipramine, as well as by sentiments expressed in the early review of research on imipramine by Klerman and Cole (1965). These authors reported significant beneficial outcomes from all studies included in their review, but concluded that “depression” could not be considered a single nosological entity and that subgroups characterized by responses to treatments could not be defined. Despite this and other research evidence, many traditionally trained psychiatrists remained skeptical about the clinical value of antidepressants. Despite the earlier success of ECT and the reported beneficial effects of opioids and of iproniazid, many psychiatrists of Kuhn’s generation held to a developmental-experiential and psychodynamic view of the etiology of depression. To some extent, differences between such psychologically based views and more biomedical conceptions probably reflected differences in clinical experience between the minority of hospital-based clinicians who treated severely ill patients with disabling, melancholic or psychotic forms of depression and those based in clinics and private offices who worked with much larger populations of moderately ill and more highly functioning patients. Possibly, Kuhn attempted to resolve the proposed dilemma between his background and training versus his unanticipated experience in the clinical use of imipramine to treat depression. This effort may have included his striking preoccupation with explaining his imipramine experience as being selective for a particular type of depression (“vital” depression), which is more similar to the severe and melancholic illnesses then found mainly in hospitals, but might be found in milder forms even among outpatients.

Finally, regardless of the extent to which Kuhn’s observations were aided and supported by observations of other colleagues, whether he may have exaggerated his own part in the imipramine story, or how to understand his efforts to limit the efficacy of imipramine to patients with vital depression, his contributions to the advancement of modern clinical psychopharmacology and psychiatry were of enormous importance and it is difficult to understand the impact of the tricyclic antidepressants on psychiatric theory and practice without taking note of his seminal contributions.

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