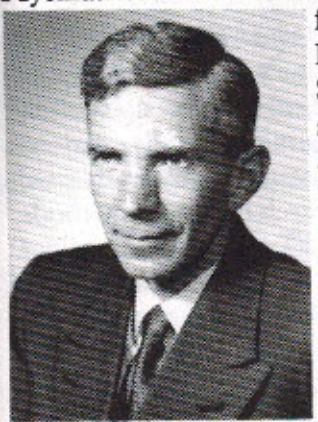
The Discovery of theTricyclic Antidepressants and the History of Their Use in the Early Years

Roland Kuhn

Introduction

The first time I observed the antidepressive effect of a substance later to receive the name imipramine was on January 18, 1956, while at the Psychiatric Clinic of Münsterlingen. It was first reported on in a "section for somatic treatment" of the "Second International Psychiatric Congress" in Zurich on September 6, 1957. The corresponding detailed scientific treatise, dated August 31, 1957, had already appeared in a special edition of the "Swiss Medical Weekly."[1]



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On September 2, 1957, NATHAN S. KLINE spoke at the same Congress about the effect of iproniazid (Marsilid), the first monoamine oxidase inhibitor (MAO-inhibitor), which he called a "psychic energizer." He said the substance was "capable of relieving very severe depressions as well as the milder ones" (Congress Report, volume 1, page 212).

The subject of the Congress was "Schizophrenia"; however, the discussion of drug therapy in conditions of depression was a fitting subcategory insofar as schizophrenics also suffer frequently from conditions of depression responding to corresponding specific treatment. Additionally, the discovery of the specific antidepressive effect of imipramine would not have been possible without the then *new* medicinal treatment of schizophrenics with neuroleptics. The history of its discovery

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and development must be touched upon here in order to understand the strange negative reaction of numerous psychiatrists to the discovery of specific antidepressants, which still persists in many places.

I. Pharmacotherapy of Psychic Disturbances

The pharmacotherapy of psychic disturbances is as old as the recorded history of medicine. The euphoric effect of opium was recognized early on; use of the drug was already well known in Homer's time. In the nineteenth century, a long-guarded secret recipe of a family by the name of ENGELKE, that combined opium with an iron preparation and cascara sagrada enjoyed, great success. Opium was widely used for the treatment of depression until the middle of the twentieth century.

The *sedating* and *sleep-inducing* effect of opium was likewise long ago recognized. Improvements were noted with the use of drug-induced sleep, especially for conditions involving agitation and confusion. A great literary example of this is the medical treatment of the mentally disturbed "King Lear" in SHAKESPEARE's drama.

Out of this context arises the concept, published by JAKOB KLÄSI,[2] of implementing a *"prolonged narcosis"* for between ten and fourteen days in the treatment of psychotic disturbances. This method was also used often in France until the middle of the twentieth century. Usually, various barbiturates were employed to induce sleep. The unpredictable successes, failures, and dangers of this treatment led to the search for better methods of interrupting *pathological trains of thought.* SAKEL achieved this effect in the thirties with the insulin coma. Likewise, the inducement of *epileptic seizures,* initially with medication and later with electric current (VON MEDUNA and CERLETTI), was a movement in the same direction. Psychiatrists in France adopted from surgeons "artificial hibernation"--for which *phenothiazine* was used.

There was, above all after World War Two, another approach besides the interruption of pathological thinking to explain the therapeutic effect of these various methods on psychoses. H. SELYE had in 1936 already begun studies in Montreal that led to his establishment after the war of a *"neuro-endocrine adaptation syndrome"* for stress. This reaction, which occurs along with all disease and is therefore *completely non-specific*, was also present in the course of psychiatric treatments that severely stressed the organism.

On May 26, 1952, in celebration of the 100th anniversary of the "Medical Psychology Society," JEAN DELAY, professor of psychiatry at St. Anne's University Clinic in Paris, gave a talk on "Shock and reaction to alarm [stress]" in which he summarized the then-current developments in

knowledge within the field. There followed at the same session a lecture by his senior associate, PIERRE DENIKER. Deniker placed his own experiments on the treatment of various forms of psychoses with hibernation using chlorpromazine (Largactil) in the category of *non-specific effects*. As with prolonged narcosis, patients remained in bed during the treatment and fell into sleep or dozed without additional soporifics.[3,4]

Seen in retrospect, DENIKER's work raised the *treatment of psychoses* to an *entirely new level,* even if then-current accounts do not suggest that any clear headway was made with the problems. In the beginning, Deniker treated depressed patients as well as schizophrenic ones with chlorpromazine, and he wrote about that in his first report: "Reserving our conclusions concerning the melancholy state until we have followed a greater number of cases, we are simply suggesting that the states of anxiety, depression, and insomnia--whether occurring simply or as complications of psychotic and nervous states--appear to us to be clearly and favorably influenced by the cure we indicated above."[5] At the Congress in Zurich five years later (1957), DENIKER spoke about the effect of neuroleptics on "psychoses and neuroses." In connection with this, we were told without further elaboration of a "flagrant disparity of their action in the opposing phases of the psychoses of manic depressives" (Congress Report, volume one, page 133). Further observations soon revealed the ineffectiveness of chlorpromazine in treating depressions and melancholias.

II. Background to the Discovery of the Antidepressive Effect of Imipramine

The account of the discovery of the antidepressive effect of imipramine goes back to my first two years of training with professor JAKOB KLÄSI at the University Psychiatric Clinic in Waldbau/Bern from June of 1937 until May of 1939. At that time, we treated psychoses with prolonged narcosis and with drug-induced epileptic seizures. My colleagues R. STÄHLI and O. BRINER observed an especially good response to epileptic seizures in late catatonias frequently marked by depression.[6] In the years 1938/39, the two authors went on to note the often excellent effect of convulsive therapy in endogenous depression.

When I came as senior physician in 1939 to what was then called the "lunatic asylum" at Münsterlingen (in the Swiss canton of Thurgau), I already had a clear idea regarding the treatment of conditions of depression with opium for milder cases and with "metrazol shock" for the more seriously ill patients.

My direct superior at Waldau, senior physician J. WYRSCH, had

already laid great emphasis on the investigation and recognition of depressive conditions. From Münsterlingen, I nurtured a close, friendly relationship with L. BINSWANGER, who directed a well-known private sanatorium in Kreuzlingen. He had a lot of experience with depressive illnesses, and he drew my attention time and time again to the problems which depressions present to the psychiatrist. As a consultant to the general hospital in Münsterlingen, I came to realize how often depression was at the root of physical problems. This led to experience in determining the depressive basis of such disturbances. At the same time, however, this diagnosis left one faced with almost insoluble problems with regard to treatment. Invasive shock treatment was scarcely justifiable in light of masked findings of this sort. Opium was, of course, helpful for such patients, but it took many weeks to see improvement. I therefore kept my eyes open for other treatments. This is how I came across iodine, atropine, and manganese, which were recommended at the time. Occasionally, they appeared to yield improvement, but there was nothing resembling conclusive success.

Often, one attempted to address it with psychotherapy. This was prolonged, and, when it led to success, one usually had the impression that it had more to do with spontaneous remission than with the consequences of medical intervention.

There remains one more small episode as background to the discovery of imipramine. While the doctors with whom I was familiar remained at Waldau, I kept up a close relationship with this clinic. Among my teachers at that time was the neurologist and brain anatomist E. GRÜNTHAL. Using normal test subjects, he investigated new substances for the pharmaceutical company of J.R. Geigy in Basel. Through him, I received a substance for clinical testing, which later appeared on the market as an antiparkinson under the trade name "Parpanit." During this investigation, I observed the regular occurrence of a mild reduction in the number of erythrocytes in the blood. This gave me the idea of supplementing the treatment with *iron,* whereby the neurological symptoms further improved. This led me to study the physiology of iron as it was then understood; to search for relationships to the use of an iron supplement to the opium of depressed patients; and to occupy myself with the physiology of especially iron-rich cores in deep structures of the brain.

III. The Discovery of the Antidepressive Effect of Imipramine

The clinical tests of the antiparkinson for J.R. Geigy led them to engage me in the clinical testing of another drug. This involved an antihistamine that, like other substances in this group, produced drowsiness as a

disturbing side effect. The pharmacologist of the company, DOMENJOZ, came up with the idea of increasing this side effect and so creating a soporific.

I tested the substance, G 22 150, with negative results, but I noted a unique improvement with this substance in the condition of chronic schizophrenics. I proposed that this effect be further investigated, but the company was not interested.

When, on June 21, 1953, at a conference of the Swiss Psychiatric Society in Biel, I learned from doctors of the University Psychiatric Clinic in Basel of their successes with chlorpromazine, it seemed to me that I had already witnessed something similar with the antihistamine of the J.R. Geigy company. Our clinic's financial difficulties with the costly procurement of Largactil led me to propose to J.R. Geigy a return to their antihistamine and my earlier idea. As Largactil is also an antihistamine, and since the chemical formula for J.R. Geigy's substance looked very similar to that of Largactil, the company now agreed. The substance proved, in fact, to be a neuroleptic similar to Largactil, but with more disturbing side effects, which resulted in the discontinuation of the experiments.

Now arose the question of testing similar substances. From what was available, I selected the one with the same side chain as Largactil (G 22 355). In this way, I expected to find a drug similar to Largactil.

Contrary to my hopes and expectations, this substance had few neuroleptic characteristics, but rather neurovegetative effects. Instead of rejecting the substance as unsuitable, I administered it experimentally to a severely endogenously depressed female patient. That was the pivotal decision leading to the discovery on January 18, 1956 (see p. 130).

At first glance, the desire described in section III for a better antidepressant than opium explains the decision. Certainly there existed a connection of the sort, but that did not suffice. Just as important was the ability to deviate from a certain mode of thinking--namely, to find a neuroleptic--and to search in a completely different direction. That involves human destiny, which often says "no" to our wishes and efforts. It has to do with the problem of negation, with which the philosophers concern themselves a great deal. I had already looked earlier to philosophy for advice, supported in this by LUDWIG BINSWANGER. *Thus I learned to affirm the experience of negation and to draw the obvious conclusions it yielded.* This realization and action rewarded me with the discovery of the antidepressive effect of imipramine! This was not "only a coincidence," as foolish people never tire of claiming. What they are obviously trying to say is that the fortunate event could just as easily have happened to them, which I doubt.

There is not much left to tell. Two more depressed patients received the

drug, the effect of which was confirmed. Now followed the attempt to stop the medication. In all three cases, this led to relapse after several days, which was remedied with a renewed dose of the medication. With the help of colleagues who had been trained by me for years, and of a staff likewise schooled by me, I treated forty depressed patients with imipramine at the clinic in a year and a half. All of them were examined with purely clinical methods, without "controlled studies, without placebos, without statistics." This yielded the "vital depressive disposition" as an indication for imipramine. This consists of tiredness; feelings of confinement, heaviness, and dejection or depression; slowed and obstructed thinking, decision-making, and interaction; loss of the ability to enjoy oneself and to sustain interests; and daily fluctuations with worsening in the morning. At the time of the Zurich Congress of 1957, I believed that every psychiatrist knew what a vital depression was. Therefore, I did not go into it, which was a mistake. Rather, the description of the "vital depressive disposition," going back to KURT SCHNEIDER and based on the philosopher MAX SCHELER, actually was the basis of a "syndrome" suitable for antidepressive treatment.

About a year later, the distinguished Belgian psychiatrist J. BOBON told me, "Your first publication is amazing, but even more amazing is the fact that it already contains 95% of everything essential there is to say about imipramine!" That statement is supported by the subsequent lack of new findings about imipramine (Tofranil) in the over 1,500 treatises that appeared over the next five years. After another five years, there were approximately 4,500 publications, not including the numerous treatises on derivatives of imipramine.[7]

Imipramine and the analog substances derived from it, along with neuroleptics and other psychiatric drugs, brought about an extraordinary surge in neuro-biochemical research. This had very interesting results, which have yet to be incorporated in clinical treatment. Of the new substances, the most interesting is maprotilin, for its very specific effect on catecholinergic synapses. The development of this substance by the CIBA company of Basel goes back to the first five years after the discovery of the antidepressive effect of imipramine. The company requested that I test one of a new group of substances. The substance was of little interest, but I proposed to combine the new ring system with the side chain of Tofranil and Largactil. The substance had to be synthetisized first, but it yielded Maprotilin (Ludiomil).

After the discovery of the imipramine effect, I was occupied with various problems:

1. An obvious relationship between the imipramine effect and that of opium demanded a clarification of whether the former would likewise

cause dependence or perhaps even addiction. My own experiments to that end yielded a negative result, which has not been contradicted in forty years.

2.Already prior to the publicizing of the Contergan catastrophe with the severe deformations that ensued at that time, I was concerned with the problem of possible drug-related detriment to the cells of propagation. Within the first experimental phase of one and a half years, a woman taking imipramine became pregnant during her recovery from depression. The treatment had to be continued during her pregnancy, too. Her child was born completely healthy. A later surfacing claim that imipramine could have a detrimental effect on the cells of propagation led to intensive testing that yielded a completely negative result.

3.Those who know how to look for the vital depressive disposition in the patient, who seldom talks about it spontaneously, find it not only in endogenous depressions, but also in many others, in physical and psychic symptoms of suffering patients for whose problems no sufficient cause can be determined. All of these patients benefit from antidepressive treatment. This is especially true for neuroses. Remedying the depressive components by means of antidepressants often leads to the complete disappearance of all other symptoms without a trace. In individual cases, an additional intensive but specifically tailored, and not simply psychoanalytic, psychotherapy is necessary. Whoever is neither willing nor able to look for vital-depressive symptoms in all of his or her patients, and who fundamentally ignores these symptoms when they are spontaneously mentioned by patients, often expends a great deal of time and resources performing psychotherapy until the depressive phase spontaneously abates. The therapist and patient then ascribe this outcome to the lavish therapy. This was already my view in 1958 in the USA, with which the prominent psychiatrist FRITZ A. FREYHAN completely concurred!

4.The side effects of antidepressive therapy are primarily neurovegetative. In many depressions of various genesis, similar symptoms arise. Among these are alternating sympathicotonic and vagotonic displacements of equilibrium. When a patient is given an antidepressant during a sympathicotonic phase, it is intensified, which then leads to disorders. The same medication at the same dosage in the vagotonic phase, which is to say, administered shortly after a meal, is tolerated without the least problem, and its effect on psychic symptoms is, moreover, even better. Something similar is true with regard to sleep disturbances for vagotonic phases. I gave a talk about this on October 16, 1959 in Graz entitled "Problems of the Practical Implementation of Treatment with Tofranil."[8]

5. As has already been mentioned, I was directed to problems of iron deficiency from two sides. A very competent lab assistant told me she could tell at a glance in the microscope of a discrete polymorph of a red blood

corpuscle whether a patient was being treated with imipramine. I inferred from that the possible relationship to iron which had already been suggested by the ENGELKE method for treating depression. Thus, I began very early to administer iron along with the imipramine treatment, and I ascertained a corresponding marked improvement in the results. Only much later, following new results in biochemical research, was I able to explain the effect. Iron and other trace elements play a role as necessary coferments in crucial steps in the formation and breakdown of essential transmitter substances. Disruption of this results in psychopathological phenomena. The effect of antidepressants is linked to the availability of carrier substances.

All of these research results have been made public. In conversations, lectures, and papers, I have continually referred to them. Everyone refuses, however, to take note of what I say, and it has been a long time since I have been invited to talks at psychopharmacological congresses. It is believed that my ideas have been surpassed, but this is not substantiated with experiments by those with this attitude, which experiments would provide instruction with regard to who is fooling himself.

IV. Resistance to the Classification of Antidepressants in Psychiatric Treatment Concepts

Opposition to drug treatment with antidepressants was announced very early on. The idea that psychiatric drugs would essentially proliferate a non-specific effect was at that time firmly anchored in the minds of many psychiatrists. Paired with that notion was the idea that depressions were fundamentally psychically triggered. An all powerful psychotherapy was called for to remedy depressions. Additionally, many psychiatrists and researchers did not have a clear idea of what depression actually is. It is imperative to provide specific examples of this involving authorities in the field.

Some time after confirmations of my findings were submitted, a university clinic professor known to me to be a good instructor and informed authority on psychopathology called me to him in order to make the "painful announcement" that everything I had written about imipramine was wrong. He had not read my publication, did not know what a vital depressive disposition was, and had used the medication only with severely psychotic depressed patients, for which cases I never recommended it as an isolated therapy.

The following episode provides further illustration. At the first international Congress of the Collegium in Rome, there was a meeting in September 1958 presided over by CORNELIO FAZIO, then a professor

of psychiatry in Genoa, later in Rome. At this meeting, seven speakers from various countries, including the United States and Canada, reported on their experiences with imipramine, the results of which were all positive. Among the listeners sat JEAN DELAY and, next to him, the director of his EEG-ward, G. VERDEAUX. Having been introduced by the latter, JEAN DELAY knew me for almost ten years. I was often at his clinic, had attended his consultations, and had held long discussions with him. When he heard about the new treatment discovered by me, he expressed his indignation that his clinic was unaware of the treatment, despite his personal relationship with me. VERDEAUX replied that DENIKER had been in possession of a large experimental quantity of the preparation for more than a year but had refused to use it. After the meeting, there was a discussion between DELAY and VERDEAUX, and the preparation was immediately put into use. That occurrence exemplifies the resistance to the acknowledgement of the existence of a specific medication for a defined psychopathological situation. The link between psychopharmacological effect and non-specific reaction of the organism was so firmly anchored in them that many psychiatrists were unable to believe in the possibility of a specific medication for depression.

ERNST ROTHLIN, who was a professor of pharmacology in Basel, director of the research division for the SANDOZ chemical company, and president of the first two congresses of the "International Collegium for Neuro-psychopharmacology" in Rome and Basel, wrote a treatise for the ten-year anniversary of the discovery of the first neuroleptic by DENIKER.[9] This highly-qualified researcher and authority outlines in detail the discovery of the first neuroleptic and places it in the context of subsequent literature. The discovery of the antidepressive effect of imipramine is only just mentioned in passing, without the corresponding reference to the literature. Its fundamental significance is not acknowledged. The author, Rothlin, had the corresponding publications at his disposal, we knew one another personally, and he presented me with a copy of his treatise.

Within the first five years following the discovery of the first antidepressants, world-wide conferences took place over psychopharmacology in general and antidepressants in particular. After preparations in Milan the previous year, the "Collegium of Internationale Neuro-psychopharmacologicum" was founded on September 2, 1957 in Zurich. Congresses were held from September 8-13 in 1958 in Rome; from September 4-7 in 1960 in Basel; and from September 2-5 in 1962 in Munich. The proceedings of all three events were published by the J.R. Geigy company of Basel, a production on which I collaborated and which at times bears the initials R.K. In the first set of proceedings is a contribution by

JAKOB WYRSCH on "Psyche and Psychopharmacological Agents," which still remains entirely current today.

Roland Kuhn and his wife, Verena

Between 1957 and 1962, I had a lot of opportunity--in conversations, at conferences, and from publications--to find out what people made of my discovery. No doubt there were some psychiatrists who employed in treatment ideas I had worked out regarding the vital depressive disposition. Many colleagues, however, did not know what it was and, above all, were incapable of bringing to light the often masked symptoms of depression in their patients. Patients do not usually talk about this of their own accord, and it is not at all easy to explain the nature of it to them. I then tried to shed some light on the subject with a publication, "Five years of drug treatment with iminodibenzyl derivatives for conditions of depression."[10] This was essentially unsuccessful. In 1960, there appeared on the horizon what today seems to me to be clouds of a coming disaster. M. HAMILTON published a treatise, "A Rating Scale for Depression."[11] Since that time, there has been a world-wide use of surveys, whose results are "exactly" tabulated with numbers, statistically evaluated, and represented in tables. People are fascinated by the scientific nature of this sort of activity and

overlook just how disproportionately slight such gains are in the treatment of patients. They are distancing themselves increasingly from everything I have said concerning the indication of drug treatment for depression. They consider the clarification of the vital symptoms superfluous, treat only severe cases, and often without sufficient pharmacological knowledge, and hand over to psychotherapists those patients who would most benefit from antidepressant therapy. As for my feelings regarding all of this, I believe I have made them clear!

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