The Clinical Discovery of Imipramine

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The major classes of psychotropic drugs were introduced in an extraordinary decade of discovery between the late 1940s and late 1950s. In the present climate of pessimism about the absence of new drug development, it may be instructive to look back at the research methods used during that era. The study that identified the first antidepressant is a case in point. It was conducted by Roland Kuhn, a Swiss psychiatrist working in a remote psychiatric hospital. Kuhn, like the other pioneering researchers of his day, was given access to new drug entities, and the method he used to discover their clinical effects was open-minded, exploratory, comprehensive, clinical observation. The paper that reported the results of his study has not been available in English, but because of its historical significance and because Kuhn's achievement stands in such contrast to the present impasse in drug development, the authors thought that it might be informative to read about his discovery in his own words. Accordingly, one of the authors (M.R.) translated the paper into English, and they now present excerpts of that translation with the intent of encouraging reevaluation of contemporary approaches to drug discovery.

By today's clinical research standards, Kuhn's method of unfettered, exploratory, clinical observation was substandard, haphazard, even messy. Yet it produced a major breakthrough—the discovery that a drug can alleviate depression—that has had a lasting impact on the treatment of depression and on the development of antidepressant drugs. Kuhn's experience might usefully inform our strategies of drug development.

Am J Psychiatry 2015; 172:426–429; doi: 10.1176/appi.ajp.2015.14101336

In a climate of pessimism regarding present-day drug development, it may be instructive to look back at the research methods of 60 years ago, when a generation of groundbreaking psychotropic drugs was discovered. The study that identified the first antidepressant is a case in point (1). In 1955, Roland Kuhn, a 43-year-old Swiss psychiatrist, examined the antidepressant effects of an unknown Geigy compound designated G22355. Kuhn worked in a psychiatric hospital in the small, remote Swiss village of Münsterlingen. He was trained in psychodynamic psychiatry and had a scientific interest in existential psychoanalysis. At the same time, he had been caught up in the excitement surrounding the discovery, several years previously, of the antipsychotic effects of chlorpromazine. Drug companies, including Geigy, were collaborating with hospital-based psychiatrists like Kuhn to come up with other compounds that would have the antipsychotic effects of chlorpromazine. Working closely with Geigy scientists, Kuhn had tried a number of compounds bearing structural similarity to chlorpromazine in patients with schizophrenia. None of these compounds had much of an effect on psychotic symptoms. But Kuhn noted that although one of these compounds, G22355, did not reliably improve psychotic symptoms, some of the schizophrenia patients became hypomanic from it. Furthermore, G22355 seemed to alleviate depression in the few schizophrenia patients who had prominent depressive symptoms. With the encouragement and support of Geigy, Kuhn then undertook a study of the antidepressant effects of G22355.

It is noteworthy that Kuhn trusted his initial observations and pursued this study despite the fact that in the prevailing psychiatric culture the idea that a drug alone could cure depression was implausible and despite his psychoanalytic perspective on psychopathology and its treatment.

Kuhn gave G22355, later named imipramine, to about 100 depressed patients and reported the results in a paper published in the August 31, 1957, issue of the *Swiss Medical Weekly* (1). The following week, he presented his results at The Second International Congress of Psychiatry in Zurich. There were about a dozen people in the audience who, in general, seemed oblivious to the fact that the quiet-spoken, dignified man at the podium was bringing them groundbreaking news (2, 3).

Kuhn's original paper appeared in German. In its six pages, he provided, with notable thoroughness and accuracy, almost all the essential information about imipramine, including its clinical effects, the type of depression it most benefits, its delayed onset of action, and its anticholinergic and other side effects. He wrote nothing about his method for assessing patients, but in reminiscing about this study 40 years later, he pointed out that he eschewed rating scales, relying instead on close and frequent (sometimes daily) observation of his patients and that he also paid close attention to the comments of nursing staff (3, 4).

Kuhn begins by discussing the absence of satisfactory treatments for depression and then points out that the only treatments that are at all effective are shock therapy for endogenous depression and psychotherapy for "psychoreactive depression":

> "The disadvantages of shock therapy are well known. Psychoorganic symptoms are observed, particularly if seizures are frequently induced. It is common that a good effect is only seen with initial treatment and that this therapy becomes less effective in the course of frequent recurrences. Furthermore, some patients do not respond at all to electroshocks. Psychotherapy for mostly reactive depression can be very tedious and difficult, and is not always successful. Biological, pathophysiological and psychopathological experiences seem to suggest experiments regarding the influence of pharmacological treatment on depressive states of various geneses. Up to the present time, none of the recommended medications have gained acceptance. Amphetamines and similar agents sometimes have some influence on certain types of depression. Most of the time, the effect is insignificant and temporary or absent. Addiction is also a common problem…. Therefore, waiting until the depression subsides is in many cases, even today, the only available option." (1)

Kuhn then points out that research is needed in order to find better treatments but that the type of research required is confronted with "significant basic problems":

> "[T]he diagnostic evaluation of patients with depressive states is not always easy. Errors are common, and the assessment of treatment results is difficult for these reasons alone. In many cases, a combination of endogenous, organic and reactive-psychogenetic factors may further complicate the conditions for pharmacological research. These diseases cannot be induced experimentally, and all studies have to be performed with diseases in humans. The reports of these sick persons are the basis for an evaluation of the effects. In addition, spontaneous courses of the disease and the influence of the environment and interpersonal relationships must be taken into consideration." (1)

Kuhn describes the results of treating several hundred patients with G22355. He used doses and frequency of administration similar to what was used with chlorpromazine. Daily oral doses usually ranged from 75 mg to 150 mg, but if that range was insufficient, patients received from 200 mg to 250 mg. About 200 patients had schizophrenia, and about 100 had predominantly depressive symptoms. In his paper, he focuses on the 40 depressed patients who responded well to G22355. The heart of his discovery consisted of two paragraphs on the influence of G22355 on depressive symptoms:

> "Symptoms of depressive mood that are obvious when observing the patient's appearance often improve significantly under treatment with G22355. The facial expression loses rigidity, modulation and expression abilities return. The patients become livelier, the depressive whispering becomes louder, patients become more communicative, and moaning and whining can no longer be heard. If the patient was discontented, querulous or irritated, he changes into a friendly, content and amenable person. Hypochondriac and neurasthenic complaints are no longer dominant or disappear completely. Patients who had great difficulties in getting up in the morning, get out of bed early with their own initiative, at the same time as other patients. They initiate relationships with other people, start conversations, participate in the daily life of the clinic, write letters, and are again interested in their family matters. They start working spontaneously, get their work done, and the slowness in their life is replaced by a normal vitality. With these improvements, the patients become popular in the ward. Their mood and behavior appear to be balanced. Several times, family members were fascinated and told the physician that the patient had not been in such a good condition for a long time.
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> Most of the time, the patients notice the change, report it, are, of course, very joyous about it and talk about a miraculous cure. The feelings of heaviness, tiredness, weakness, depression, inner tension, rigidity and restlessness subside. The patients feel free again, inhibition of thoughts and activities disappears, thoughts and activities return. A sad, depressed, desperate and fearful mood turns into a neutral unburdened or somewhat cheerful mood with the feeling of healing and increasing strength. Feelings of guilt, delusions of impoverishment or culpability simply disappear or lose their affective importance, move into a distance, and the patient becomes indifferent and unconcerned with respect to these feelings. It happened that a pronounced suicidal intent of a patient suddenly disappeared! If sleep was disturbed by depressive symptoms, it normalizes quickly without sleep-inducing medications, even in cases who did not respond to common hypnotic agents. Nightmares, sometimes occurring in depressive people, with blood, dead bodies, terrible accidents, and gruesome atrocities, frequently accompanied by terrible fear, no longer occur under the treatment. Morning moodiness and other daytime fluctuations of the depressive state are no longer observed. If the patient had no appetite, his appetite returns. Sometimes, constipation due to depression improves." (1)

The report then provides information on the particulars: onset of action, proportion of patients improved, suicide risk, and, notably, the type of depression most likely to improve with G22355:

> "In some patients, the effect of G22355 on depressive states occurred suddenly after 2–3 days of treatment, and was fully pronounced from the beginning so that it seemed that the depression disappeared completely. Frequently, however, the change occurred only after 1–4 weeks, sometimes after several weeks.
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> Our experience is based on 40 successfully treated patients with predominantly depressive states. How many patients with similar disorders had no or only a partial response? Our numbers are too small to provide statistics. The problems of evaluation are also very complicated. We can say with certainty that not all depressive states respond to G22355. Sometimes, the drug had no effect whatsoever. With all possible caution, we estimate that one fifth to one fourth of all cases diagnosed with common diagnostic measures did not respond to treatment. In about one fourth to one half of the cases, *full remission* was achieved. In all other cases, G22355 induced significant improvement but no *full remission.*
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> If improvement occurs slowly, the dangers are similar to those during spontaneous subsidence of depression. *Self-endangerment* increases with decreasing inhibitions. The suicide of a depressed schizophrenic patient in the restroom of one of our closed wards was probably the result of such an effect.
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> Based on our experience, we recognized certain patterns that suggest that the drug has *particularly good effects* in patients

> with certain conditions. First and foremost, this is the case in patients with *typical endogenous depression*, including depression in menopause." (1)

Although Kuhn identified endogenous depression as the type of depression most likely to improve with G22355, he recognized that reactive depressions might also improve and addressed the complex relationship between psychotherapy and drug treatment:

> "Even more difficult to predict is the response to G22355 in patients with reactive-depressive states. We have treated various cases with dysthymia due to an actual reason. For example, an old woman was depressed after the death of her husband, a young woman had depression after a criminal abortion under difficult circumstances, and in a middle-aged woman, severe disability for many years due to paralyses caused by poliomyelitis, was associated with depressive mood. In these and other cases, we were impressed to see that very difficult, burdensome situations lost their significance to a great extent under treatment with G22355, although the circumstances did not change.
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> In some cases, we had the impression that actual reasons for a depressive mood or neurotic development in childhood prevented the full effect of G22355 or were responsible for quick recurrences after discontinuation of the drug. Of course, the psychological problems may be discussed in long-term psychotherapies. In the course of psychotherapy, the drug may be useful if mood disturbances or anxiety occur unexpectedly. We also observed changes in the effectiveness in relation to the course of psychotherapy. In a patient with a physical disability who underwent psychotherapy for many years and achieved only slight alleviation of severe depressive symptoms (despite solving numerous problems in his life and detecting relations of symptoms with his childhood), G22355 improved his mood disturbance significantly within a week." (1)

In the rest of the paper, Kuhn summarizes his assessment of the effects of G22355. He describes the effects of G22355 in patients who had depressive symptoms in association with epilepsy, cerebral atrophy, and schizophrenia. He observed that these comorbid depressions were less likely to improve with G22355. He also depicts the results of G22355 in patients with "pure schizophrenia." Whereas G22355 sometimes improved mood in these patients, it had little effect on psychotic symptoms.

He concludes with a detailed description of the side effects of G22355, including its anticholinergic effects, the results of ophthalmologic examinations (no evidence of eye damage), and a table depicting blood counts before and during treatment (no changes except for a slight increase in eosinophils).

By today's standards, Kuhn's study was extraordinarily flawed. There was no control group, no standardized rating scale, and no statistical analysis, and except for blood counts, only the most rudimentary bit of quantification was incorporated. Perhaps most damning of all, Kuhn based his description of imipramine's antidepressant effects solely on the patients who responded well. Yet, this study produced a major breakthrough—the discovery that a drug could alleviate depression—that has had a lasting impact on the treatment of depression and on the development of antidepressant drugs. And in this single study, Kuhn managed to describe in detail most of the essential information about imipramine.

Kuhn's method was open-minded, comprehensive, clinical observation in response to the opportunity that he had to study a series of compounds synthesized by Geigy's medicinal chemists, based on the structure of chlorpromazine, in their efforts to improve antipsychotic efficacy. Kuhn believed that in order to fully appreciate a potential psychotropic drug's usefulness, it needed to be tried in a wide range of patients. Accordingly, he tried imipramine in a broad sample of depressed patients and in patients with some other conditions as well. This approach allowed him to make the prescient observation that imipramine was most effective in the endogenous type of depression and to recognize its ineffectiveness in schizophrenia.

The patients in Kuhn's study were severely ill; most were inpatients. The severity of their illnesses left room for substantial, unambiguous improvement. If Kuhn's study sample had been the sort of mildly and moderately depressed patients who are the typical participants in the clinical trials of today, the impact of imipramine would have been far less obvious.

Current research methods certainly have their advantages. Placebo control groups and randomization to treatment arms are now essential elements of clinical research, and rightly so. Moreover, the standardized diagnostic procedures and rating instruments of today make it easier for a study to be replicated than would have been the case in Kuhn's day. But the current methods sometimes come at the expense of overlooking significant and sometimes unexpected clinical changes. Exploratory research of the kind that Kuhn and others of his era did has taken a backseat to large numbers of patients, measurement consistency, and complex statistics, which can reveal small treatment effects, suggesting that a treatment is effective, even when that treatment does not offer meaningful improvement. And it is not clear whether the sorts of rating instruments used today, reliable as they might be, best capture what is going on with patients.

Jonathan Cole, one of the fathers of psychopharmacology, said, "... if you're working with a drug in 100 patients and a few of them haven't said, 'Wow, do I feel better,' then you probably haven't missed anything and it probably isn't going to turn out better than placebo" (5). Kuhn's paper has not been available in English, but because of its historical significance and because his description of patients includes the experience described by Cole, we thought it might be informative to read about his discovery in his own words. Thus, one of us (M.R.) translated his paper into English, and we have presented our colleagues, readers of the *Journal*, with salient excerpts of that translation, with the intent of helping to rethink our strategies of drug discovery. The increased regulatory environment for research, in efforts to protect human subjects, and the decreased inpatient length of stay for psychiatric illnesses, in efforts to lower costs, have obliterated the

opportunity that Dr. Kuhn so successfully exploited. Reviving Kuhn's experience might help leaders in industry, regulation, and psychiatry rethink how opportunities for drug discovery might also be revived.

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The authors thank Christine E. Ryan, Ph.D., for help with this manuscript.

The authors report no financial relationships with commercial interests.

Received Oct. 26, 2014; revision received Jan. 16, 2015; accepted Jan. 20, 2015.

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