SPECIAL LECTURE

Before They Called It Psychopharmacology*

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BEFORE THEY CALLED IT PSYCHOPHARMACOLOGY

It is a great privilege and honor to be here today, giving the second annual lecture on the history of psychopharmacology. My friend Frank Ayd did such an admirable job with his lecture last year, on the early history, that I have had a hard problem finding gaps to fill. What I have finally chosen to do is to trace for you some of the early history, complete with anecdotes, which preceded our modern notions of psychology and pharmacology and then to tell you something of my own experiences and findings in the psychiatric world of the 1940s and 1950s, a world that was remarkably different and simplistic compared to today. I also intend to give you a subjective "oral history" of my own stumbling attempts to make some sense out of the vague and somewhat chaotic potpourri of ideas and pharmacologic approaches to psychiatric problems a half century ago.

HISTORY OF THE TERM PSYCHOPHARMACOLOGY

The term psychopharmacology was first suggested in the year 1548. It was a renaissance term used by Reinhard Lorichius in his "Psychopharmakon, hoc est Medicina animae" (Wolman 1977). Almost 400 years later, in 1920, we find the first use of the full term psychopharmacology by D. Macht, a pharmacologist working at Johns Hopkins, who called the domain of psychopharmacology "certainly very meager." Macht conducted pharmacologic experiments with opium narcotics and coal tar analgesics on reaction time, tapping speed, etc., much as Kraepelin as early as 1883 had done in Wundt's laboratory with alcohol and caffeine, calling it then Pharmacopsychologie (Macht 1920).

W. Freeman, in 1931, wrote a more general paper in the Journal of the American Medical Association on what he called psychochemistry, and in 1935 Thorner wrote the first paper resembling our modern concept of the term with "Psychopharmacology of Sodium Amytal in Catatonia." I will discuss this paper in more detail later. After a careful search of the modern literature, I came to the conclusion that official general use of the term psychopharmacology in publications dates only to 1960, following a paper by Ross and Cole entitled "Psychopharmacology," when also psychopharmacology appears for the first time as a free-standing item in the Cumulated Index Medicus. So, the period I will concentrate on will be pre-1960 (Freeman 1931; Thorner 1935; Ross and Cole 1960).

HISTORY OF PSYCHOPHARMACOTHERAPY

Let us make a distinction between psychopharmacotherapy and psychopharmacology. The former is a clinical discipline, based mainly on empirical observations, and the latter is a scientific discipline that is founded on systematic research. In the beginning, the achievements of the clinical psychopharmacotherapy ran ahead of those of scientific psychopharmacology. However, during the last 20 years or so, academic psychopharmacology and neuropsychopharmacology, with its sudden brilliant outbursts of new discoveries, sophisticated theories, and complex instrumentation seems to have outrun the success of clinical psychopharmacotherapy.

On Figure 1 I have tried to represent graphically the successive milestones of modern psychopharma-

* This special lecture was presented at the 30th Annual Meeting of the American College of Neuropsychopharmacology in San Juan, Puerto Rico, December 10, 1991.

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Received February 26, 1992; accepted February 28, 1992.

Published by Elsevier Science Publishing Co., Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/93/$6.00

cotherapeutics (Lehmann 1985) over the last 140 years. The time course is charted on the horizontal axis and the ordinate is divided into increments from one to ten, according to arbitrarily chosen values of the historical significance of the various discoveries. The year 1840 was chosen as the beginning, because it was then that the first major breakthrough occurred with the discovery of general anesthesia. With nitrous oxide, ether, and chloroform, pain was conquered completely for the first time, at least for periods of time. In 1848, Morton successfully performed the first ether anesthesia during a major surgical operation at the Massachusetts General Hospital. The new medical technology of general anesthesia, in turn, enabled surgery to make its own rapid progress. Further milestones in man's fight against pain were the discovery in 1894 of cocaine by Koller and Sigmund Freud and the introduction of the all-purpose analgesic, acetylsalicylic acid, Aspirin, by Dreser in 1899.

Freud also was aware of the stimulating effects of cocaine on the central nervous system. He used the drug frequently himself and wrote to his fiancée how the boredom at certain evening parties in Paris was relieved by the pleasant action of cocaine (Freud 1960). He also wrote that cocaine lifted him almost instantaneously out of a depression. However, it soon became clear to him that cocaine was neither a harmless stimulant nor, as he had believed at first, a cure for patients who were addicted to morphine, but had addicting and dangerous properties of its own. He abandoned its use and from then on disliked and mistrusted psychoactive drugs. However, he also predicted that many of the psychologic symptoms that at his time could only be treated with psychoanalysis would some day be treated with hormones or other chemical substances (Freud 1964).

The first phase of psychopharmacotherapy, which had concentrated on the conquest of pain, was followed by a phase that focused on insomnia. In 1857, Locock introduced the bromides into therapy. They were initially used as anticonvulsants, but later became the first medical tranquilizers. For many years they were prescribed for insomnia and anxiety. However, they were not very effective and also highly toxic. Interestingly, their anticonvulsant action was suspected by Locock because potassium bromide was first known to reduce sexual libido. Since epilepsy, during much of the 19th century, was believed to be caused by excessive masturbation, it seemed to follow that bromides, by reducing sexual impulses, should also reduce epileptic seizures. One of many examples that a theory that makes no sense may, nevertheless, still lead to the desired results.

In 1868, chloralhydrate was introduced into medical practice as a hypnotic and it proved to be so excellently suited for this purpose that today, more than a century later, it is still considered one of our best hypnotics. Incidentally, chloralhydrate provides another historical example of the right result having been generated by a wrong theory. Liebreich, who introduced chloralhydrate as a hypnotic, had done so on the notion that the drug would be metabolized in the body to chloroform and thus put the patient to sleep. Chemically, this makes no sense, nevertheless, the drug works. That is, of course, all that really matters in psychopharmacotherapy; why it works is a question for the psychopharmacologists.

In 1903, Fischer and von Mering synthesized Veronal as a hypnotic barbiturate. It was, together with many barbiturate derivatives, to reign supreme for more than a generation as the remedy for insomnia. Today we rarely prescribe barbiturates since we are better informed about their high toxicity and addictive potential. But in the first third of our century the many varieties of barbiturates, long-acting, intermediate, short- acting, ultrashort-acting ones were, besides chloralhydrate, the only respectable psychopharmacotherapeutic agents.

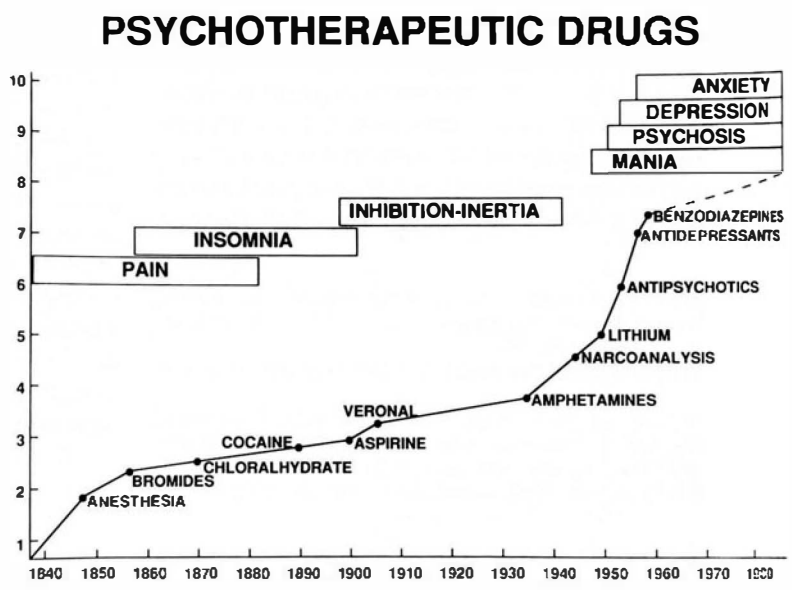


Figure 1. Successive milestones of modern psychopharmacotherapeutics.

In 1935, the next pharmacologic attack on the psychologic foes of humanity was made on inhibition, inertia when Prinzmetal and Bloomberg introduced the amphetamines. These powerful stimulants have often some euphorizing effects, and there were high hopes, for a little while, that a general cure for depression had been found. It soon became evident that the therapeutic uses of amphetamines and amphetamine-like drugs were quite limited, although their abuses abound.

For a brief period, during and after World War II, narcoanalysis was much in vogue as a psychiatric treatment modality. This technique involved the intravenous injection of a short-acting barbiturate, producing disinhibition, which elicited otherwise suppressed information and intense emotional responses from the patient, a so-called cathartic abreaction, as an adjunct to psychotherapy. Although this procedure is used to a much lesser extent today, it still has considerable value, possibly as a chemical way to induce or reinforce positive transference.

At about that time, too, Cade in Australia discovered the antimanic effects of lithium. Although lithium turned out to be the first truly disease-specific treatment for a psychiatric functional disorder, its importance was not fully recognized for another 15 or 20 years, perhaps because our psychopharmacologic and neurochemical understanding of the affective disorders was still very limited at that time.

In the early 1950s came the most dramatic breakthrough in psychopharmacotherapy since the advent of anesthesia more than a century before. Delay and Deniker reported from France that a newly synthesized drug, chlorpromazine, produced a dramatic state of sedation in animals and humans and also showed unexpected therapeutic benefits in psychiatric patients. In fact, chlorpromazine had a reliable suppressant action on psychotic syndromes, more specifically on such cognitive and perceptual symptoms as thought disorder, hallucinations, and delusions.

Then in rapid succession came the antidepressants, when Kline reported on the monoamine oxidase (MAO) inhibitors and, almost simultaneously, Kuhn on the tricyclics. We had some ideas how the MAO inhibitors worked but, at first, no notion of the action mechanisms of the tricyclics or, for that matter, of the antipsychotic action mechanism of the phenothiazines, at least not for several years.

Finally, in 1960, Randall reported on the "taming" action of chlordiazepoxide (Librium) and thus introduced the benzodiazepines, the first low toxicity minor tranquilizers for the treatment of anxiety.

PSYCHOPHARMACOLOGY: HISTORICAL REVIEW

The early history of psychopharmacology started with several significant achievements in organic chemistry, e.g., the analytic isolation of morphine from opium by Serturner in 1803, the production of chloralhydrate by Liebig in 1832 (almost 40 years before Liebreich introduced this compound into therapeutics), and the synthesis of barbituric acid in 1864 by von Baeyer, also about 40 years before its clinical use by Fischer and von Mering (Fig. 2).

This chemical phase of building the foundations of psychopharmacology stretched over most of the 19th century. It was followed by the first elementary experiments in psychopharmacology conducted by no other than Kraepelin, the father of modern psychiatry who investigated, in Wundt's laboratory, the effects of various psychotropic drugs including caffeine and alcohol on simple mental functions.

There was very little further activity in this field until

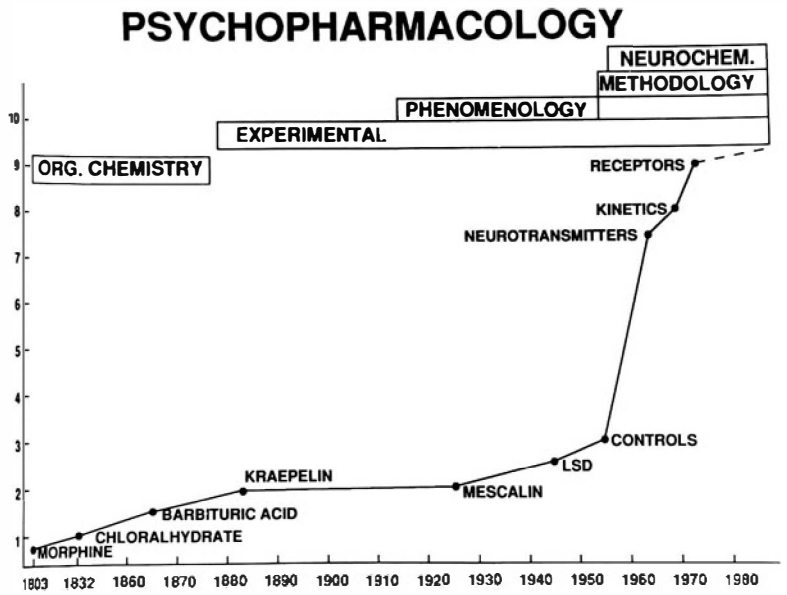


Figure 2. Successive milestones of modern psychopharmacology.

the 1920s and 1930s when, at the University of Heidelberg, and later at the Maudsley Clinic in London, well-designed experiments with the hallucinogenic mescalin were carried out. Lewin had by then published his basic book on hallucinogens, "Phantastica," and there was a great deal of interest in the new and strange mental phenomena that these drugs elicited (Lewin 1931). These studies in phenomenology were crowned by Hofmann's accidental discovery of D-lysergic acid diethylamide (LSD) and its striking effects in 1943. D-lysergic acid diethylamide was a substance that, in extremely small amounts, could experimentally produce psychotic states in normal volunteers. The psychotomimetic action of LSD gave a tremendous incentive to neurophysiologists and neurochemists to study its action mechanisms in the hope that they could offer valuable clues to the causes of schizophrenia.

The most powerful impetus to psychopharmacology occurred a few years later with the discovery of the antipsychotic effects of the phenothiazines and other antipsychotic drugs. For the first time in psychiatry, there were now drugs with reliable therapeutic effects in psychotic states. One immediate consequence was the almost explosive development of the methodology of clinical trials to assure the best possible control of such trials.

Once set into motion, psychopharmacology did not stop again. The clinical discovery of the antidepressants only a few years after the antipsychotics led psychopharmacologists to the elucidation of the role of neurotransmitters in the brain. That, in turn, provided fertile hypotheses on the causes of depression, the action mechanisms of antidepressants, and the action mechanism of antipsychotic drugs. All this was followed by a host of new findings in the fields of neurochemistry, neuroendocrinology, and neurophysiology, many of which also had an important impact on psychopharmacology.

PSYCHIATRY IN THE 1940s

At the brink of World War II I parachuted from Europe into the new world of North American psychiatry. Let me sketch for you the picture of psychiatry in the early 1940s. We had Kraepelin's and Bleuler's guides to the diagnosis of the major psychoses, manic depressive disorder, and schizophrenia. We had only two theories to explain the rest of the psychiatric illnesses, the neuroses and personality disorders: Freud's psychoanalysis and Pavlov's and Skinner's theories and findings on conditioning and learning.

Our two major therapies were insulin-induced hypoglycemic coma and electroconvulsive shock therapies (ECTs) for schizophrenia and affective disorders; and, we had psychoanalysis and some derivative psychotherapy for the treatment of the neuroses. Paraldehyde and the barbiturates were about our only means to quell agitation and violence in addition to physical seclusion and restraint. The trouble with the shock therapies was that they often worked dramatically for a few weeks or months and then the patients, 70% to 80% of them, relapsed and had to be rehospitalized and treated again with questionable results. The treatments were very invasive, cumbersome, and often dangerous. The outlook then was that 60% to 70% of all schizophrenic patients would, once hospitalized, never live in the community again. Most clinical psychiatric research was carried out with stopwatches, Rorschach cards, and personality inventories.

Our pharmacopoeia contained, in addition to paraldehyde and barbiturates, hyoscine-apomorphine, an injectable mixture that was used at the Douglas Hospital in Montreal where I was working then. It was given subcutaneously or intramuscularly and was one of the most effective antiexcitement drugs that I know, even today. The traditional combination for that purpose was hyoscine-morphine. Why had they chosen apomorphine at my hospital instead of morphine? I really don't know. It certainly was not done in anticipation of the dopamine theory of schizophrenia. Hyoscine-apomorphine was an inky looking substance that worked within 10 to 15 minutes. The hyoscine usually counteracted the nausea that might be produced by the apomorphine, but not always. If an excited patient became nauseated, this would have a powerfully synergistic sedative effect. Anyone who has ever been badly seasick knows that nausea is utterly incompatible with agitation or violent behavior.

For the treatment of depression we routinely used oral tincture opii or injections of the then newly introduced hematoporphyrine. The latter substance was supposed to photosensitize the organism and thus reduce the depression, an interesting forerunner of light therapy for seasonal affective disorder. However, hematoporphyrine didn't work. Finally, besides ECT, we had a number of vitamins and hormones that we employed with hope, but without success, in what was then called involutional melancholia.

THE PREVAILING "ZEITGEIST" IN THE 1940s

In the 1940s mental illness was generally viewed as a hopeless stigma to be treated in hospitals with a variety of unspecific shock treatments. The scientific paradigm surrounding schizophrenia was hypoxia of the brain, and possibly the whole organism, as expressed succinctly by Freeman in 1931, "a generalized inherent tendency to . . . deficient oxidative processes" (Free-

man 1931). Quastel, in 1939, wrote, "in vivo there is much greater O_2 uptake in brain than in vitro (slice or mince) . . . accurate estimates of the oxygen uptake by brain . . . in vivo are urgently required" (Quastel 1939). Himwich et al. in 1939 published a paper in *Science* on "Cerebral metabolism during fever." About that time too, Himwich introduced pure nitrogen inhalation therapy into the treatment of psychoses as an attempt to stimulate, by temporary suffocation, a rebound of increased oxygen uptake in the brain. It was not effective (Himwich et al. 1939; Alexander and Himwich 1939).

Some advanced research in neuroanatomy was carried out at our hospital then that would be impossible to repeat today. Randomly selected psychotic patients had brain biopsies done by a neurosurgeon that revealed some disorder of the oligodendroglia in schizophrenia (Elvidge and Reed 1938). (Remember that in those days there was no such thing as institutional review boards.) We also did many air encephalograms on various patients, clearly as a fishing expedition, although we knew since Jacobi's and Winkler's work in 1921 that schizophrenic patients tended to have enlarged ventricles, either as a genetic or a progressive feature (Jacobi and Winkler 1927). We had one of the first electroencephalograph (EEG) machines in mental hospitals with Herb Jasper as our consultant. Several years before my arrival, a research study on manganese treatment of schizophrenia had been performed at the hospital. This treatment had been first proposed by Reiter and Bisgaard in Denmark, because Walbum had observed that small doses of manganese would prevent bacterial infections in animals. They reported 50% improvement in their schizophrenia patients. Our results showed that of 100 schizophrenia patients 36% of treated patients were discharged within a year compared to 18% of untreated. Improvement was partly measured by weight gain and reduction of the sedimentation rate. It is interesting to note that manganese, in toxic doses, is one of the few substances that may produce extrapyramidal symptoms (Reiter 1929; Walbum 1925; Reed 1929).

My first personal involvement with psychopharmacology came when Collip, the Nobel Laureate of insulin fame, gave me a new pituitary extract that he had produced and asked me to observe its effects on a few schizophrenia patients. I gave the extract, #47, as an oral medication to one of my acute schizophrenia patients and soon learned a lesson about placebo effects, coincidences, and confounding variables. On the 5th day of treatment my patient changed dramatically for the better, not only in behavior and insight but also on a quantitative association test. However, the improvement lasted for only 2 days, and a little later I learned that the #47 pituitary extract had a strong alcohol content.

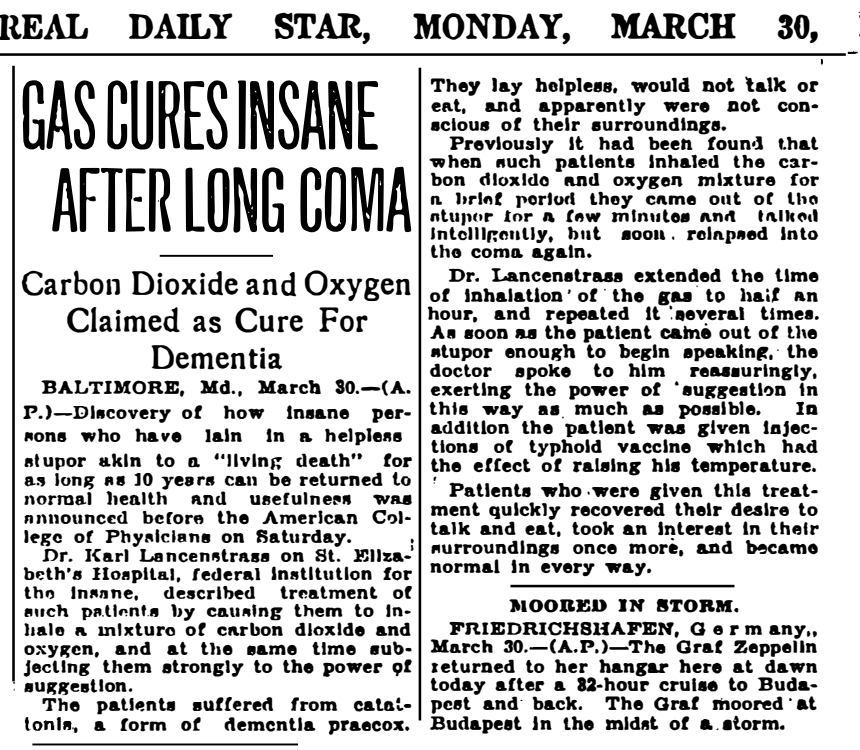
In 1929, Loevenhart et al. had reported that amazing cerebral stimulation was occurring in catatonic patients who were exposed to carbon dioxide inhalation for several minutes (Loevenhart 1929). Five years later, Hinsie et al., inspired by this finding, undertook a large and sophisticated study on the effects of oxygen and carbon dioxide on catatonic symptoms. The investigators placed 18 schizophrenic patients in a specially prepared dormitory for 2½ months. The dormitory was carefully sealed to maintain a 50% oxygen atmosphere, and some of the patients were also treated with periodic short-lasting inhalations of carbon dioxide. The researchers concluded that not the oxygen but the carbon dioxide had temporary therapeutic effects. Two of the patients had complete remissions. Although the authors had employed simple statistics in their study, they eschewed its use when they arrived at this delightfully expressed nonconclusion, "it can neither be affirmed nor denied that there was any relationship between treatment and the clinical condition . . . two facts are known; the patients received treatment and they became well." It should be noted that the carbon dioxide treatment was so aversive that one chronically mute patient promised he would speak if he would be spared another treatment (Hinsie et al. 1934). See Figure 3.

Thorner who in 1935 had introduced the term "psychopharmacology," reported on an interesting study of sodium amytal in catatonic patients. He observed that catatonic uncommunicative patients would begin to talk and communicate quite freely when they were injected with a sodium amytal solution that, according to a term used by Gullotta, "decatonized" them. Thorner explains this phenomenon on the basis of Sherrington's hierarchy of cerebral functions: the "super-inhibited," catatonic brain is partially disinhibited and remains in that more normal state for several minutes or hours (Thorner 1935; Gullotta 1932).

In the same year in which Thorner's paper appeared, another somewhat enigmatic paper was published about apomorphine in the experimental inhibition of catatonia. I could not locate this paper, so I do not know why the author chose apomorphine instead of carbon dioxide or a barbiturate for his experiments (Martinengo 1935). Not much research at that time focused on the affective disorders, although the possible roles of cholesterol and carbohydrate metabolism were highlighted.

PERSONAL RESEARCH

One of my first systematic investigations, using a neuropsychopharmacological tool, i.e., intravenous pentobarbital, was a study of yawning. Why yawning? For no better reason than that yawning, particularly



THE MONTREAL DAILY STAR, MONDAY, MARCH 30, 1931

GAS CURES INSANE AFTER LONG COMA

Carbon Dioxide and Oxygen Claimed as Cure For Dementia

BALTIMORE, Md., March 30.—(A. P.)—Discovery of how insane persons who have lain in a helpless stupor akin to a "living death" for as long as 10 years can be returned to normal health and usefulness was announced before the American College of Physicians on Saturday.

Dr. Karl Lancenstrass on St. Elizabeth's Hospital, federal institution for the insane, described treatment of such patients by causing them to inhale a mixture of carbon dioxide and oxygen, and at the same time subjecting them strongly to the power of suggestion.

The patients suffered from catatonia, a form of dementia praecox. They lay helpless, would not talk or eat, and apparently were not conscious of their surroundings.

Previously it had been found that when such patients inhaled the carbon dioxide and oxygen mixture for a brief period they came out of the stupor for a few minutes and talked intelligently, but soon relapsed into the coma again.

Dr. Lancenstrass extended the time of inhalation of the gas to half an hour, and repeated it several times. As soon as the patient came out of the stupor enough to begin speaking, the doctor spoke to him reassuringly, exerting the power of suggestion in this way as much as possible. In addition the patient was given injections of typhoid vaccine which had the effect of raising his temperature.

Patients who were given this treatment quickly recovered their desire to talk and eat, took an interest in their surroundings once more, and became normal in every way.

MOORED IN STORM.

FRIEDRICHSHAFEN, Germany,, March 30.—(A.P.)—The Graf Zeppelin returned to her hangar here at dawn today after a 32-hour cruise to Budapest and back. The Graf moored at Budapest in the midst of a storm.

Figure 3. Report in a Montreal newspaper on inhalation of carbon dioxide-oxygen combined with fever treatment and psychotherapy of schizophrenic patients at St. Elizabeth Hospital in Washington D.C.

noisy yawning, has always been very irritating to me. In the psychiatric mode, I asked myself "why" I was so irritated by it and decided to attack the question scientifically. I would have preferred to use sodium amytal to induce yawning, but our limited resources at the hospital forced me to use the less expensive pentobarbital, which I had to weigh myself, then sterilize. I also had to buy my own slide rule and first textbook on statistics, in order to analyze the results of drug-induced yawning. In one patient the drug produced the unusual side effect of a dislocated jaw. That was quickly repaired. I found among other things that many psychiatric patients, particularly those with schizophrenia, yawned less frequently than people in stores, buses, or parties where I made my control counts. However, patients with organic mental disorders yawned more frequently than the controls. I reviewed all of the then-known physiology of yawning in humans and animals and introduced some existential speculations on the meaning of yawning as a homeostatic and ideomotor reflex. At that time the paper was rejected by two psychiatric journals as being "too philosophical." More than 20 years later I was asked by an editor of *The Menninger Bulletin* to submit it and it was finally published. In recent years, it has elicited a new round of interest because of the observation that yawning occurs with dopaminergic stimulation (Lehmann 1979).

Nicotinic acid had been reported by Sydenstricker to be therapeutic in various organic syndromes. I published a case report confirming this and then went on to develop, for a pharmaceutical company, a new hypnotic containing nicotinic acid, a barbiturate, scopolamine, and apomorphine. The idea was to support cerebral metabolism with the niacin during the barbiturate- and scopolamine-induced sleep and to produce vomiting with the apomorphine in case of accidental or suicidal overdosing. There is no need to tell you that this medication was not on the market for very long (Sydenstricker and Cleckley 1941; Lehmann 1944; Lehmann 1949).

Because nitrous oxide often produced euphoria, I tried N_2O inhalation as a treatment for depression. That did not work. But N_2O inhalation, which we used for up to 2 minutes in 100% anoxia-producing concentration, did have the effect of frequently producing vivid dreams that could be reported after wakening. Some papers on the adjunctive use of this intervention with psychotherapy were published. When I personally underwent this treatment for 2 minutes while my EEG was recorded, I had what I still think was the most significant dream of my life. But, alas, as I sat up after awakening to tell my coworker about this extremely important dream, it vanished from my memory before I could report it (Lehmann 1947). See Figure 4 for results.

Placebo as a methodological instrument was, of course, discussed and used long before the clinical trials in psychopharmacology. As early as 1912 Hollingworth, who had been commissioned by the Coca Cola Co. to study the effects of caffeine on human performance, wrote that any good investigation of this kind should use placebos (Hollingsworth 1912). In order to put the placebo to an extreme clinical test I chose three of our mute and most deteriorated schizophrenic patients in one of the back wards and treated them with a saline solution, taken from a mysteriously labeled bottle, and injected, in very small quantities, intracutaneously. The nurses and the patients were told that the substance was a new experimental hormone that I wanted to test. The injection site on the skin was painted with mercurochrome that left an impressive red stain. I repeated these injections four times within 2 weeks. In the 3rd week two of the patients who had been mute for a long time started talking and asking rational questions. That convinced me of the power of the placebo.

I then started, together with a psychologist, a study of the "placebo proneness" of various test procedures. We found, among other things, that the Word Fluency Test was less prone to be influenced by placebo than simple reaction time and that timed tests were less resistant to placebo effects than tests concerned with accuracy of performance (Lehmann and Knight 1961).

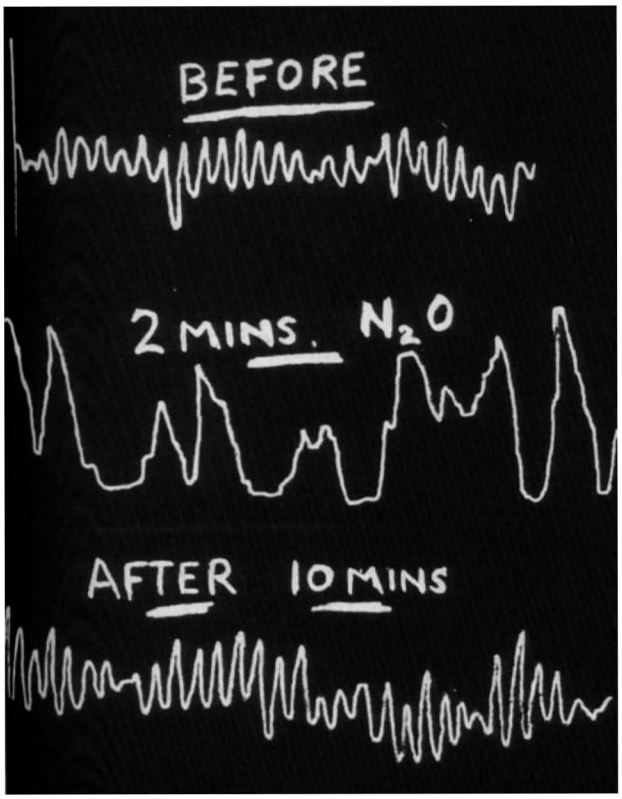


Figure 4. Author's encephalogram before, after 2 minutes of 100% nitrous oxide inhalation, and 10 minutes after termination of inhalation.

Not many clinical rating scales existed at the time, so we produced several of our own at the hospital, among others; a rating scale for patients who were receiving a lobotomy, a rating scale for psychotic patients, a projective rating scale and a depression rating scale, some of which were published (Lehmann and Dorken 1952; Lehmann et al. 1958). Somehow I always had reservations, and I still have, about rating scales that depend on value-tinged clinical judgement rather than on judgement-free pointer readings. Consequently, we developed various methods for the evaluation of psychoactive drug effects that were based on psychologic performance tests (Lehmann and Csank 1957).

One ambitious attempt at a psycho-cognitive-behavioral-biological-physiognomic profile of a patient's expression of psychopathology consisted of a chart that contained the patient's photograph, word-association test, Rorschach test, freely chosen drawing, and glucose tolerance test, all taken on the same day at the beginning and at the end of a treatment intervention. In the 1940's, there was interest in variations of glucose tolerance as a biological marker during depressive states. Figure 5 shows a bipolar depressed patient with all these factors registered. Figure 6 shows the same patient's psychopathologic profile, now hypomanic, 3 weeks later, following a course of six ECT treatments.

When the first modern antipsychotic substances appeared on the scene, I referred to them as "phrenotropic agents," because I held the peculiar notion that the term "psycho" should be used only for unique self-reflecting phenomena in humans. I still remember how puzzled Conan Kornetsky and his colleagues looked some 30 years ago, when they had invited me for a lecture in Boston and I said that I did not consider the term "experimental psychology" appropriate when applied to animals. The controversy Chomsky versus Skinner was just evolving then. To demonstrate what I thought of the anthropomorphic practice of translating behavioral effects of drugs in animals into human psychology I set up a project of testing psychoactive drugs in "biological systems of low complexity," so low that they even lacked a central nervous system. Working already with Tom Ban and having enlisted a multidisciplinary team of coworkers, including a botanist, we tested a Hela-cell culture, a firefly-derived luciferin-luciferase enzyme system, the feeding reflex of hydra, and the opening and closing behavior of dandelions with a variety of sedating and stimulating drugs. The most human-like responses were observed in the dandelions. An experiment performed on them after random selection and age matching under double-blind placebo-controlled conditions showed unequivocally

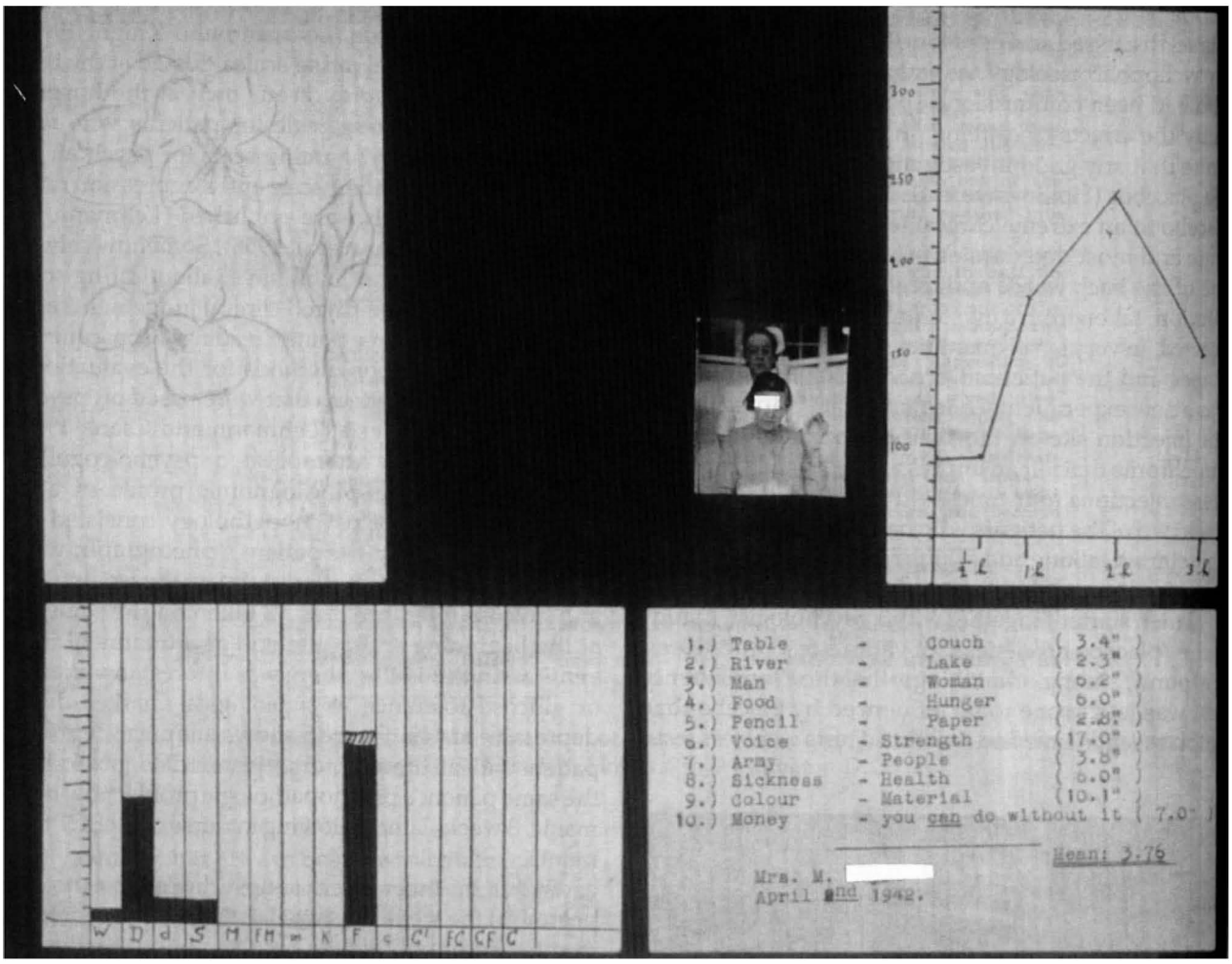


Figure 5. Chart containing a bipolar depressed patient's photograph, and, from left to right, freely chosen drawing performed on request, Rorschach test scores, word association test scores, and glucose tolerance results. For further explanation see text.

that over a 24-hour period, the stimulating drugs amphetamine and LSD produced equal or increased opening of the inflorescences during the 2nd day when compared to the controls, and secobarbital and chlorpromazine kept the flowers as tightly closed during the next day-light period as they had been during the night when they were normally "sleeping" (Lehmann et al. 1962). See Figure 7.

One more story of my work, still before 1960, but already during the dawn of full-fledged psychopharmacology: a study of conflict-induced behavior in human subjects under the influence of different psychoactive drugs. Our subjects received money rewards for the length of time they kept a button depressed; but after certain signals there was a risk that they might be receiving electric shocks through the button. They clearly kept the button depressed for longer periods of time and earned more money under the influence of meprobamate, chlordiazepoxide, and secobarbital than under the effects of antipsychotic drugs. No doubt human subjects reacted like animals in this situation (Lehmann 1968). See Figure 8.

THE NEW DRUGS

I remember a group of students making hospital rounds with me in 1952 in Montreal. We were looking at two young schizophrenic patients gesturing excitedly toward the ceiling from where they were hearing frightening voices. One of the students asked afterwards, "Will we ever get a pill to help these people?" I smiled patronizingly and replied that, unfortunately, it would never be as simple as "just a pill."

Not more than a year later I read one Sunday morning some medical literature that a pharmaceutical detail man had left with my secretary, saying: "This is about some new drug that is so good that these papers

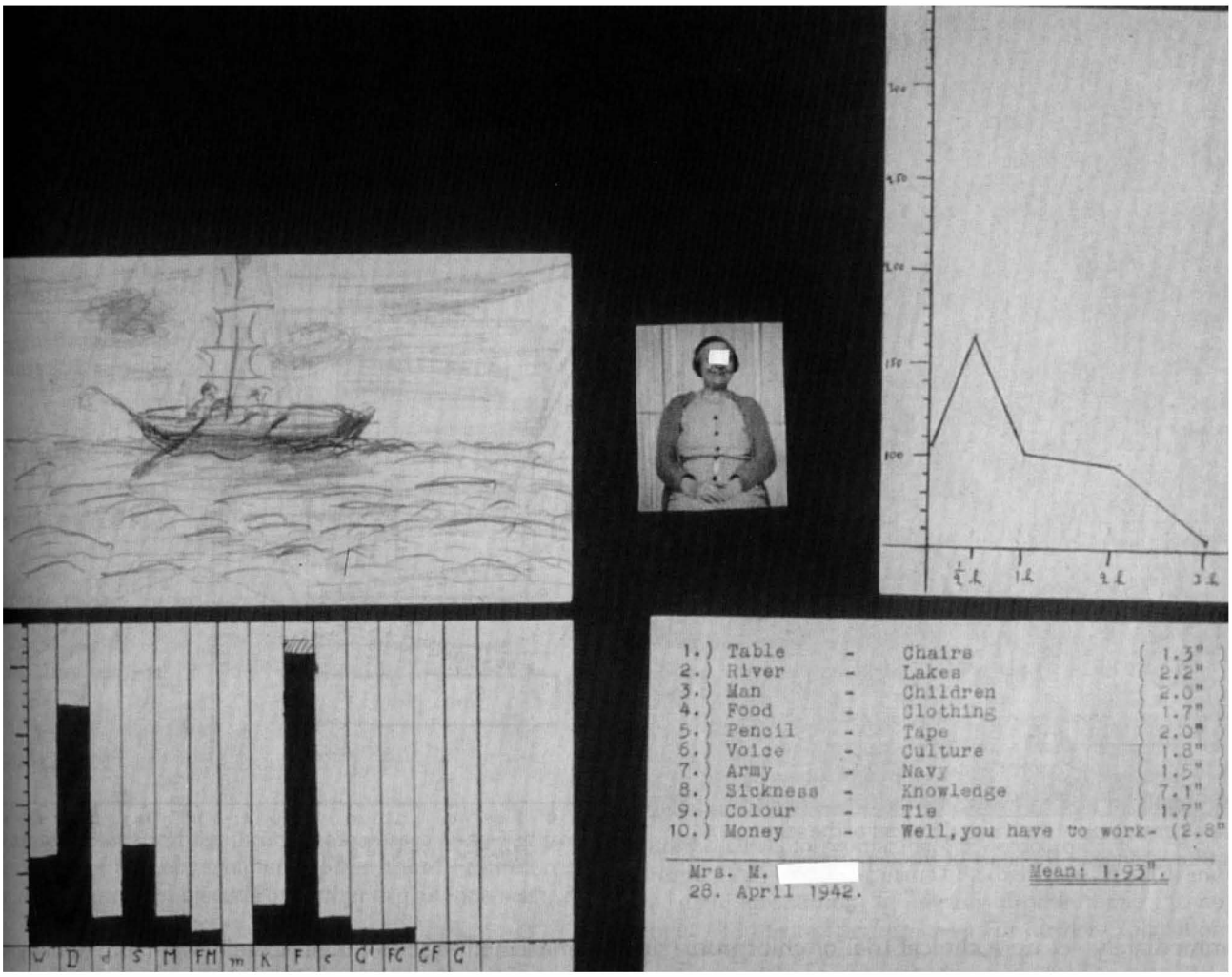


Figure 6. Psychopathologic profile of same patient shown in Figure 5, now hypomanic, after 3 weeks following six ECT treatments.

will sell it." He was referring, I thought, rather arrogantly, to a few French publications about chlorpromazine, a substance that was supposed to produce peculiar sedating effects in states of clinical excitement like a "chemical lobotomy."

I was intrigued but very skeptical. In order to establish whether the sedative action of chlorpromazine was really qualitatively different from that of the traditional hypnotics I set up an experiment that is worth describing here briefly, as an illustration of the almost unbelievably naive way in which clinical research could still proceed only 38 years ago. I asked eight nurses to volunteer for the experiment that consisted in performing a few tests, i.e., reaction time, tapping speed, digit span forward and digit-symbol-substitution before and 1 hour after receiving an oral dose of secobarbital and, on another day, before and 1 hour after an oral dose of chlorpromazine that was about equivalent to the secobarbital in its drowsiness-inducing effects. I then recorded roughly drawn scores of improved performance, no change and decreased performance. For the secobarbital condition, I thought I needed only three subjects, since the results were so conspicuously different from those under chlorpromazine. My evaluation of the results was made by inspection of these graphs with no attempt at statistical tests, of course, and I never confirmed my impression by a duplication of the experiment. In the tests some of my subjects performed actually better under the influence of chlorpromazine in a psychomotor and a cognitive test, but none of the three subjects on any test did so under secobarbital. These results convinced me that chlorpromazine did indeed induce a new kind of sedation that seemed to be dissociated from the "dopiness," the impaired performance that, we thought at that time, was an inherent component of all drug-induced somnolence. See Figure 9.

Armed with my new pharmacodynamic insight I

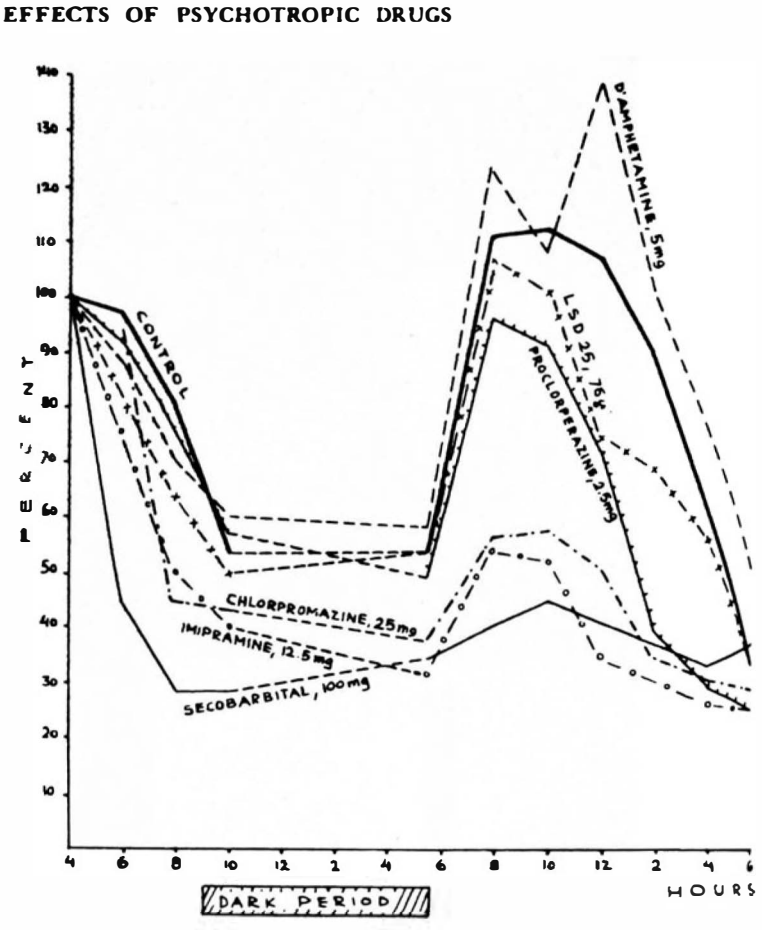


Figure 7. Sleep movements of excised dandelion inflorescences in different drug solutions. The mean diameter of the inflorescences for each drug condition at each time interval is expressed as a percentage of the mean diameter of the same inflorescence at the start of the experiment.

immediately set up a clinical trial of chlorpromazine with some psychotic patients, most of them schizophrenic. Within days, some of the patients had stopped hallucinating and within 2 weeks a few were in remission and ready to leave the hospital. I assumed we were seeing a series of flukes, perhaps resulting from an extremely strange chance selection in the sample. It seemed almost as improbable as winning one million dollars twice in a lottery.

Much as I wanted to believe what I was seeing, I didn't for a long time. Even in my correspondence with other clinicians in the United States working with the phenothiazines neither I, nor they, dared to attribute specific antipsychotic effects to these drugs. We thought it might be a new modification of some sedating and inhibiting action, but we did not label the drugs antipsychotic. In 1956, when I was addressing the Canadian Medical Association, I introduced the term "antipsychotic" apologetically, and more as a metaphor than a designation.

It did not cross our minds that the new drugs might help the chronic back-ward patients, those who had not responded to insulin coma and ECT. However, we put a number of these "hopeless" patients on chlorpromazine for its symptomatic sedative effect and to our amazement, some of them actually went into remission. Again, it took us at least 2 years to accept the fact that at least some chronic schizophrenia patients were improving, even remitting, with phenothiazines.

Now we wondered: might there be such a thing as long-term, perhaps indefinite, protective maintenance treatment, a real secondary prevention of major mental illness? It seemed too much of a long shot that these patients might be protected against recurrences by continued administration of the new drug. There was no choice but to try it; and, to our amazement and delight, it worked.

Two or three months after we had started patients on chlorpromazine, I remember standing on the ward with a neurologist colleague and watching three patients who walked with a shuffling gait, did not swing their arms, and had mask-like faces. We wondered about these peculiar side effects that looked very much like Parkinson's disease. But nobody had ever been able to produce Parkinsonism experimentally with any substance in animals or humans. The disease was known only in its idiopathic form. Yet here, for the first time, were drug-induced parkinsonian, extrapyramidal symptoms. Other investigators had made the same discovery and it became clear: clinicians had done inciden-

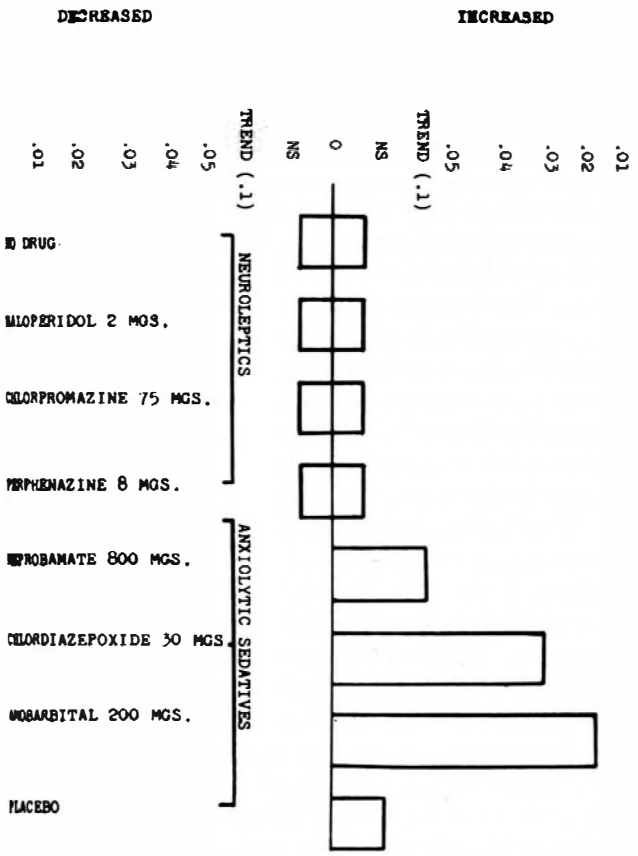


Figure 8. Statistical significance of increased and decreased length of time of keeping button depressed under conflict conditions in human subjects. For further explanation see text.

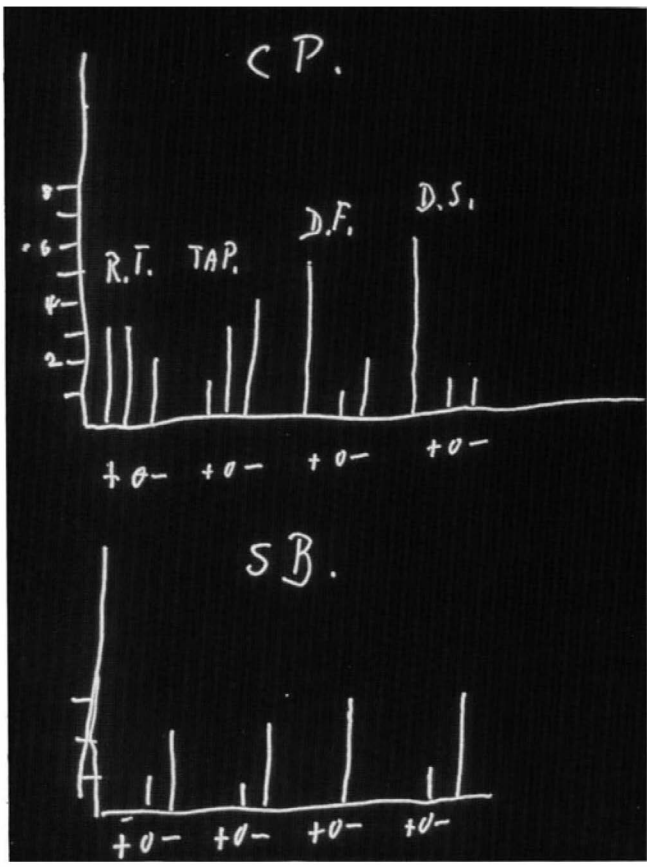


Figure 9. CP: chlorpromazine; SB: secobarbital; R.T.: reaction time; TAP: tapping speed; D.F.: digit span forward; and D.S.: digit substitution. +: improved performance. 0: no change. −: impaired performance. For further explanation see text.

tally what experimental neuroscientists had not been able to do until then.

An avalanche of new psychotropic drugs soon started to appear. It was evident that our primitive early open-trial procedure of chlorpromazine would be utterly inadequate to test all these new drugs in any valid fashion. Our first trial with chlorpromazine had been conducted with 75 psychotic patients simultaneously, using no written protocol, no stated criteria for selecting the patients, no placebo or other controls, no government permission (not required then), and, it seems incredible today, no informed consent from the patients or their families who were all happy about the treatment. We also had no financial assistance from the pharmaceutical company, no grant from the government, or any private agency. The work was simply folded into our clinical routines. Clearly, a new methodology had to be devised, which soon grew into considerable complexity involving careful design of every study, random selection, diagnostic criteria, placebo control, and sophisticated statistical evaluations.

Many of us veterans balked at the placebo requirement, feeling that our clinical savvy qualified us to detect placebo effects without having them concretely introduced. We also disliked being compelled to permit outside statisticians to infiltrate our cliquish clinical enclaves.

Medical ethics was not an important special discipline at the time. We had only the Hippocratic oath to guide us. Virtually nobody was looking over our shoulders. Then the thalidomide disaster obliged governments all over the world to become involved in the regulation of clinical drug trials.

The United States Food and Drug Administration required informed consent, to the point when patients had to be told that they might be getting either a placebo or an active new drug. Many of us thought then that this spelled doom for any future clinical drug trials. Fortunately, and to our surprise, we were wrong. Even under the new rules, many patients did consent to participation in placebo-controlled trials.

Epistemologically speaking, psychiatry now had the cart before the horse. For the first time in history, we had drugs that suppressed hallucinations and delusions, drugs that could bring some chronic psychotic patients back to remission, drugs that could prevent

psychotic relapses and, in addition to these quasi-miracles, drugs that could produce parkinsonian symptoms. Could all this be explained by the simple paradigm of deficient oxidative processes in the brain? No way. The action mechanisms of the new drugs were a mystery in the early 1950s.

In the absence of a solid pharmacologic explanation of their action mechanisms I had some theories of my own in the early days of the antipsychotic drugs. Maybe the healing process of a psychosis was undertaken by the patient's own psyche reorganizing itself, if it could only be freed from the disruptive interference of excessive affects by a drug not grossly interfering with cognitive processes? Viewed in this way, some of the rapid remissions produced by chlorpromazine may be called self-recoveries, simply but powerfully aided by the drug. Seeing their action from this angle, I even proposed to call the drugs psychotostatic rather than antipsychotic (Lehmann 1956).

There seemed to be no need to abandon the psychoanalytic perspective altogether now that the existence of a physical substrate of schizophrenia had at last been established. Maybe the psychotic defenses of splitting, withdrawal, and decathexis were replaced under pharmacotherapy by a movement toward external objects. Antipsychotic drugs do not induce disinhibition like anxiolytic sedatives; instead, they have selective inhibitory effects. Unlike anxiolytics that enforce defenses like regression, denial, and projection, chlorpromazine seemed to facilitate the operation of more constructive defense mechanisms, such as isolation, rationalization, and sublimation, allowing the patient's ego to work through to a better adaptation to the reality principle (Lehmann 1966).

Now that we had effective drugs for the treatment of schizophrenia, it was only natural to anticipate the discovery of antidepressant drugs in the near future. In the plane on my return from the 1957 World Psychiatric Congress in Zurich I read Kuhn's paper on his results with imipramine. Back in Canada I phoned Geigy, the pharmaceutical company that had produced imipramine and asked for samples; however, the Canadian Branch of Geigy had never heard of the drug. Admitting some embarrassment, they provided me with clinical samples flown in from Switzerland within a week and we started our first clinical trials with depressed patients. At about the same time, Nate Kline developed his successful antidepressant treatment with an MAO inhibitor.

In contrast to the antipsychotic drugs whose probable mechanism of action was not proposed until 1963 by Carlsson and Lindquist, an explanation for the mode of action of the antidepressants was offered almost as soon as their clinical efficacy was discovered. Now the therapeutic focus no longer was on unspecific coma, convulsion, or fever nor on deficient oxygen metabolism, but on the processes involving specific neurotransmitters in the brain. What puzzled clinicians and neuroscientists at that time, and to some extent even now, was the long delay between the onset of antidepressant therapy and its effects. Still imbued with the old physiologic concepts prevailing at the time, I thought that the brain-blood barrier might delay the therapeutic action of imipramine and conducted a clinical trial with pyrexia induced by a series of typhoid toxin injections. This method, which was reported in a publication, seemed to be successful in depressions that had resisted treatment with imipramine for more than 3 weeks; it also seemed to shorten the time between the beginning of therapy and its effects. I have not repeated the trial and, to my knowledge, nobody else has either. But perhaps somebody should (Lehmann 1960).

The first opening for a theoretical understanding of the action mechanisms of the new antidepressants came with the discovery, at the National Institute of Mental Health, that reserpine, another antipsychotic drug that sometimes induced depression, depleted presynaptic neurons of their biogenic amines, more specifically noradrenaline and serotonin. This led to the theory that a deficiency of biogenic amines might be a factor in the etiology of depressive disorders. The action mechanism of the antipsychotics was not understood until several years later when Carlsson and Lindquist reported, in 1963, that all substances with antipsychotic action shared the common property of blocking dopaminergic neurons (Carlsson and Lindquist 1963). The role of these amines as neurotransmitters was a novel revolutionary concept and introduced a new paradigm into psychiatry. In this way the antipsychotic and antidepressant drugs served as a "Rosetta stone" for the hieroglyphs of severe psychopathology and opened new avenues for the development of modern neuroscience.

The 6th decade of our century had arrived and with it the spectacular development of the neurosciences and the official science of psychopharmacology.

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