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HEINZ LEHMANN AND PSYCHOPHARMACOLOGY

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INTRODUCTION

By introducing the first therapeutically effective antipsychotic and antidepressants drugs in North America, Lehmann played an important role in opening up the field of psychopharmacology in the 1950s. In recognition of his outstanding achievements in the new field, he was honored with the CINP-Pfizer Pioneers in Neuropsychopharmacology Award in 1998. (1). (Photo 1).

PERSONAL AND PROFESSIONAL BACKGROUND (1939-1953)

It would have been impossible to predict the major role Lehmann was to play in psychopharmacology. (Photo 2). He decided to become a psychiatrist after reading the work of Freud in his teens, and all through his professional carreer maintained that drugs are only adjuncts in the therapy of psychiatric patients. He also believed that therapy in psychiatry is incomplete if reduced to the treatment of illness, and that learning about the intrapsychic and interpersonal aspects of psychiatry, is an essential component of psychiatric training. (2, 3).

FIRST CLINICAL STUDIES

Lehmann became involved in psychopharmacology for purely pragmatic

considerations. He was looking for whatever means he could find to help his severly sick patients at the Verdun Protestant Hospital (VPH) in the late 1930s. (Photo 3).

The first clinical trial he conducted was with a pituitary extract (# 39. (4). This was followed by some "exotic therapies." The strangest among them was the injecting of sterilized oil of turpentine in the abdominal muscles of schizophrenic patients. It produced fever, and a huge sterile abscess which had to be lanced. (2, 4).

After reading about the therapeutic effect of nicotinic acid in patients with encephalopathy (5), Lehmann tried niacin with success in a 43 year old accountant who suffered from post-traumtic confusional state. (6). Encouraged by the results with nicotinic acid he made an attempt to develop a compound which contained niacin, a barbiturate, hyoscine and apomorphine, for the treatment of organic brain disease and senile disturbances (7), but did not succeed.

Lehmann also tried nitrous oxide inhalation in the treatment of depression, in vain. (8, 9).

From Lehmann's 19 publications between between 1939 and 1953 (Table 1) only six dealt with topics relevant to psychopharmacology: 3 dedicated to nicotinic acid (6, 7, 10) and 3

(from which 2 was coauthored by Bos) to nitrous oxide inhalation (8, 9, 11). (Photo 4). The topics of the other 13 papers ranged from Metrazol Convulsions in the Treatment of Mental Illness (12), his first paper (coauthored by Dancey), published in 1939, to The Administration, Scoring, and Percentile Standardization of the Verdun Projective Battery (13), his last paper (coauthored by Dorken) during the period, published in 1953.

TABLE 1

TOPICS HEL REPORTED ON	NUMBER OF PUBLICATIONS
Nicotinic Acid (1944, 1949, 1952)	3 (6, 7, 10)
Nitrous Oxide (1947, 1950, 1952)	3 (8, 9, 11)
Verdun Projective Battery (1952, 1953)	2 (13, 14)
Eosinophil Count/ACTH Response (1950, 1952)	2 (15, 16)
Iron Content in CSF (1951, 1952)	2 (17, 18)
Metrazol Convulsions (1939)	1 (12)
Nitritoid Crisis with Tryparsamide (1941)	1 (19)
Psychoses with Somatic Disease (1946)	1 (20)
Negative Afterimage Phenomenon (1950)	1 (21)
Stress Dynamics (1952)	1 (22)
Displaced Persons (1953)	1 (23)
Fingerpaintings (1953)	1 (24)
TOTAL	19

Topics of Heinz E. Lehmann's publications from 1939 to 1953 (inclusive).

INTRODUCTION OF PROTOTYPE PSYCHOTROPICS (1954-1958)

What followed during the next five years had already become psychiatric history in which Lehmann played a leading role.

In 1954 Lehmann was propelled into prominence by being the first in North America to publish findings of a replication study on the therapeutic effect of chlorpromazine, and one of the first in the world to successfully communicate the drug's antipsychotic (a term he coined) effect. (25, 26). Four years later in 1958, he was again first in North America to publish findings of a replication study on the therapeutic effect of imipramine, and one of the first in the world to successfully communicate its antidepressant effect. (25, 27).

Since the chain of events in those years can be read in numerous publications, including the Reader's Digest (28), Neuropsychopharmacology (4), and his interview with David Healy in The Psychopharmacologists (21), I will present here only the crucial steps, starting with a frequently quoted anecdote, to set the stage for the rapidly moving developments.

In 1952 during one of his "rounds" at VPH, Lehmann and a group of students were looking at two young schizophrenic patients who were gesturing excitedly toward the ceiling from where they were hearing frightening voices. Concerned about what he saw, one of the

students asked: "Will we ever get a pill to help these people?" Lehmann smiled and replied: unfortunately, it would never be as simple as "just a pill."

In less than a year (in 1953) of this incident, one Sunday morning Lehmann was reading (in French) some of the reprints of Delay and Deniker on chlorpromazine (CPZ), which were left with his secretary by a detail man from Rhone Poulenck. He was intrigued and skeptical about the peculiar sedating effect of CPZ described, but recognizing its importance, if correct, he decided to explore it himself. Hanrahan, the first resident he met the next day (Monday) was ready to join him in this research. To ascertain that THERE IS A UNIQUE DISSOCIATION between sedation and dopiness with impaired performance with CPZ, first, a single dose comparison between CPZ and secobarbital was conducted with 8 nurses. As soon as this was accomplished they moved ahead swiftly with a 4 to 6 weeks uncontrolled clinical trial with CPZ in 75 agitated, psychotic patients. The effect of the drug was spectacular. Already within days some of the patients had stopped hallucinating and by the time of termination many patients were free from psychotic symptoms. At the other end, within 2 to 3 months of starting the first patients on the new drug he recognised, that some patients developed side effects which looked like Parkinson's disease. Because Parkinsonism was known only in idiopathic form, Lehmann referred to these manifestations as drug-induced parkinsonian extrapyramidal symptoms.

The clinical trial was completed by August 1953, and the findings were published in the Archives of General Psychiatry in February 1954. (26). Shortly after, Lehmann published his findings and observations with CPZ also in the Nervenarzt in German. (29). The paper in the Archives was the first paper on CPZ in English. It had a tremendous impact. Lehmann was presented in 1957 with the prestigious Albert Lasker Award, considered America's leading prize for medical research. The document reads:

> "Dr. Heinz E. Lehmann, in a single scholarly paper in February 1954, with Dr.G.E. Hanrahan, brought the full practical significance of chlorpromazine to the attention of the Western Hemisphere after it had been left unnoted, except by certain small investigative groups for almost two years. In his first important publication on this subject,Dr.Lehmann was able to outline the clinical guidelines so clearly, describe the results so accurately and evaluate the dangers so frankly that with this paper alone, any other psychiatrist was in a position to apply this medication with confidence and safety..... The application of chlorpromazine together with that of reserpine, is generally credited with the sudden change of the over-all United State Mental Health Census which in 1955-56,

> fell by 7000, instead of the expected gain of over 10,000". (30).

In 1957 Lehmann co-chaired with Jean Delay the session on psychopharmacology organised by Nathan Kline at 2nd Congress of the World Psychiatric Association in Zurich. He could not attend the first public report of Roland Kuhn on the antidepressant effect of imipramine, but on his flight back to Canada he read Kuhn's paper which was just published. He was very impressed by his results. He contacted Geigy asking for a supply of imipramine, and as soon it arrived he embarked, in collaboration with 2 senior psychiatrists at VPH (Cahn and De Verteuile), on an eight weeks clinical trial with the drug in 84 patients. The study had several unique features. One of them was that it included a depression rating scale, which they devised, to be able to measure (quantitatively) depressive symptoms and their response to treatment. Another unique feature was that it started as an open trial which halfway through was converted into a placebo controlled double-blind study with 21 patients in each group. This unorthodox switch allowed to establish that after eight weeks of treatment 60 percent of the patients on the active drug were rated as recovered, or much improved. The paper was published in the Canadian Psychiatric Journal in 1958. (27). It was the first North American report with imipramine. It was also the first report which indicated that the response rate with imipramine is about 60 percent, i.e., about 2 in 3 depressed patients treated with the drug.

Lehmann's research in psychopharmacology between 1955 and 1958 was not restricted to CPZ and imipramine. He was also involved in studying the therapeutic effect of azacyclonol (with Linden and Cahn) in schizophrenia (31), perphenazine (with Cahn) in psychoses (32), and iproniazid, the first monoamine oxidase inhibitor antidepressant (with De Verteuile), in depression and apathy (33). It was also during this period that he developed his psychophysiological test battery with Csank (34, 35), Knight (36), and Prescott (37), and delineated with the employment of this battery, the performance profile of trifluoperazine (36), one of the many antipsychotic phenothiazines introduced subseqent to the introduction od CPZ in the mid-1950s.

MY EARLY YEARS WITH LEHMANN (1958-1960)

I met Lehmann for the first time at the VPH, on the 1st of July, 1958, on the first day of my first year residency. He took me, together with the other new residents, around the hospital that day and while walking through the wards, he pointed out a few patients posturing , some roaming around naked, and one happily fishing for his stool in the toilet bowl. When he talked about CPZ, he referred to it as a tranquilizer, which is something like an "antipsychotic," a term he coined later. By the time we parted from him, we understood that with the introduction of the new drugs, major changes for the better have taken place in hospitals like VPH.

In the Fall of 1958, a few months after I started my residency, the opportunity arose to assist Lehmann in a project with phencyclidine (Sernyl), an arylcyclohexamine. Sernyl was developed for general anesthesia and the question we had before us was whether its disinhibiting effect in low doses could be used in psychotherapy. Chemically induced abreactions, a form of psychotherapy, was still, a frequently employed treatment in the late 1950s. It was not, but in the course of the study we noted at a certain dose an accentuation of preexisting pathology, we referred to as "pathology specific" changes. Our findings with Sernyl were published in 1961 (38), and virtually forgotten by the time it was recognized in the early 1980s, that arylcyclohexylamines, such as phencyclidine, could selectively reduce the excitation of mammalian neurons induced by aspartate-like amino acids. The research which followed with excitatory neurotransmitters and N-metyl-D-aspartate (NMDA) revived interest in Sernyl. After well over 20 years , our findings with phancyclidine became relevant to neuropsychopharmacological research (39).

Between 1958 and 1960 I assisted Lehmann in many research projects, but will refer here only to one more: a series of studies on the effects of prototype psychotropics on "enzymological" and "biological" systems of which none was endowed with even a rudimentary central nervous system, e.g., dendelione which go to sleep night, oat seedlings (40). Lehmann talked about this project often, and in one of his last papers he wrote that it was his

".....somewhat irritated response to the ubiqitius animal experiments, all over the world, on drugs that worked on the human mind." (41). Be as it may when Lehmann presented the results of these studies at the Tenth Aniversary Symposium of the Galesburg State Research Hospital in 1960, in the discussion of his presentation Harold Himwich, the director of research of the hospital pointed out: "If there is a continuity in evolution, it is quite probable there is also continuity in development of psychological function. And I think that must have been one of the underlying ideas which led Dr. Lehmann to start his work." (42).

RESEARCH GRANTS (1960s and 1970s)

All through the 1940s and 50s most of Lehmann's work, including the research with chlorpromazine and imipramine was done without external support with the research operation folded into the ongoing service operations of VPH. This changed in 1961, when Lehmann received a major grant from the US Public Health Service to establish an early clinical drug evaluation unit for studying psychotropic drugs. As his Co-Principal Investigator I was responsible for the day to day operations of this unit. The grant from the US-PHS was renewed for many years and supplemented with another major grant for clinical studies with psychotropic drugs in the aged specifically. We also had another grant from the Canadian Medical Research Council for conditioning studies with psychotropic drugs. The findings from the numerous studies supported by these

grants are published in three books and over 200 journal (and book chapters) articles authored (coauthored) during the 1960s and 1970s, and four books edited (coedited). For three presentations based on these findings Lehmann received (shared) the McNeil Award of the Canadian Psychiatric Association in 1969, 1970 & 1973 (43, 44, 45).

During the 1960s and 70s, Lehmann contributed to the detection of the therapeutic effect and / or determination of the therapeutic efficacy and / or delineation of the therapeutic profile of about forty drugs currently in clinical use. He also contributed to the body of knowledge relevant to the adverse effects of some of these drugs, e.g., skin pigmentation with CPZ, cardiac conductance changes with thioridazine (Table 2). (45, 46, 47, 48, 49, 50).

TABLE 2

amitriptyline	amoxapine	carbamazepine
chlordiazepoxide	chlorpromazine	chlorprothixene
clomipramine	desipramine	diazepam
doxepine	ethclorvynol	fluphenazine
haloperidol	hydroxyzine	imipramine
levomepromazine	lithium	lorazepam
loxapine	maprotiline	meprobamate
mesoridazine	methyldopa	methylphenidate
nicotinic acid	nylidrine	pargyline

pericyazine	phenelzine	pimozide
pipotiazine	prochlorperazine	promazine
protriptyline	thioproperazine	thioridazine
thiothixene	trazodone	tranylcypromine
trimepramine		

Drugs HEL contributed to the detection of therapeutic effect/determination of therapeutic efficacy/delineation of therapeutic profile during the 1960s and 1970s. (43, 44, 45, 46, 47, 48).

During the same time period he was also involved with the development of a conflict avoidance test for studying the effects of psychoactive drugs and especially anxiolytics and antidepressants in human (49); a conditioning test procedure for the identification of predictors for the therapeutic effect of antidepressants and antipsychotics (50, 51); a conditioning test battery for the study of psychopathological mechanisms and pharmacological effects (52); and a set of pharmacological load tests which, with the employment of a modification of his Verdun Psychophysiological Test Battery, can provide orientation points in the selection of pharmacological treatment in psychogeriatric patients (53).

In the midst of all the ongoing projects during the 1960s and 70s, Lehmann still found time to explore whether the therapeutic effects of antipsychotic phenothiazines could be potentiated by nylidrine, a synthetic adrenaline analogue (54), and whether patients

refractory to the conventional treatments of depression would respond favorably to the combined administration of dexedrine and demerol (55). Similarly, he was always ready to be part of the clinical team testing new treatments based on avant-garde theories, e.g., beta-endorphin in schizophrenia and depression (56, 57), or baed on theories outside the main stream, e.g., diphosphopyridine nucleotide in schizophrenia (58).

Lehmann never found neuropharmacologic theories especially stimulating, but was always up to-date regardless how fast they changed. He preferred to refer to neuroleptics as antipsychotics which, at least for me sounds less committal of the relationship between affinity to the dopamine-D2 receptors and therapeutic effects. As one of the first clinical investigators of desipramine, he was well aware of the peccadillos of catecholamine theory, which set the stage for the development of theories regarding the action mechanism of antidepressants.(59). All through the years Lehmann published only a very few papers with biochemical measures. The last one appeared in the late 1970s. The title of it is: Clinical studies with maprotiline and the reversed catecholamine hypothesis of depression. (60).

THE FINAL YEARS (1970-1999)

During the 1980s Lehmann became increasingly concerned about the growing number of homeless mentally ill and since he thought that

his contributions were instrumental in clearing patients out of psychiatric wards he felt that it is important that he focus attention on the problems created by deinstitutionalization, forced by politicians to save money, without creating the necessary back-up services in the community.

During the 1990s from the many published meta-analyses he learned that none of the many antipsychotics is superior to his chlorpromazine in the treatment of shizophrenics, and that none of the many antdepressants is superior to his imipramine in the treatment of depressives. Furthermore, from the increasingly more accessible information on the norepinephrine (NE) and serotonin (5HT) reuptake blocking potencies of the different antidepressants, and dopamine-D2 and serotonin-5HT2A receptor affinities of the different antipsychotics he became aware that our neuropharmacological theories regarding the mechanism of action responsible for the antidepressant and antipsychotic effects of these drugs is tenuous.

In the light of this information Lehmann felt that psychiatric residents should be encouraged to return from basic science laboratories to the wards and spend their time with patients and, that at least some of the hundreds of million dollars spent on high-tech brain research should be spent on preventing emotional and mental problems by teaching parents how to bring up their children. He believed that by doing that we would see a 20- to 30-

per-cent decline in emotional and mental problems.

CLOSING REMARKS

By December 1998 Heinz was very ill. Nevertheless he attended, the annual meeting of the American College of Neuropsychopharmacology in Puerto Rico, an organization he was the president of in the mid-1960s.

Although visibly week, Heinz attended the sessions he was interested in and enjoyed talking about whatever he learned. The only thing he complained about was that he couldn't sleep. He told me that there is a real need for a hypnotic which would make people like him sleep. Walking around the Poster Session he carefully reviewed every poster which dealt with insomnia and / or sleep, and brought to the attention of the exhibitors the need for a different kind of hypnotic from the ones available.

In the next three months we talked regularly on the phone and whenever we spoke, he always brough to my attention the need for a different kind of hypnotic from the ones available. One night, just a few days before he was readmitted to the hospital for the last time, he sounded different when I called. He told me that finally he had had a good sleep after taking a small dose of olanzepine. In his usual way, as I heard it from him many times, he added, one should look into this matter, because surely there are many OTHER

PEOPLE with similar problems who need help.

TABLE 2