Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Lehmann Collection 2

William E. Bunney's interview of Heinz E. Lehmann*

HEINZ E. LEHMANN

Interviewed by William E. Bunney, Jr.

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WB: I'm William Bunney, Professor of Psychiatry and Human Behavior, University of California, Irvine, and I will be interviewing Dr. Heinz Lehmann,* Professor Emeritus of Psychiatry, McGill University, Montreal, and Deputy Commissioner for Research for the Office of Mental Health in the State of New York. We're going to go through a series of question, about Dr. Lehmann's career and I wonder if you'd start by telling us a little bit about your training.

HL: My training was in Germany. I went to school there, the Gymnasium, and then to some various universities as it was the fashion then in Germany. You went to as many universities for your medical study as your father could afford to send you, so I studied in Freiburg; I studied in Marburg; I studied in Freiburg again, then in Vienna, and finally graduated from Berlin University. But it didn't go that easily, because when I was about twelve I felt what I can now diagnose as depression, which lasted for almost a year. In those days, children didn't have depression, so that wasn't diagnosed and nobody knew what to do about it, and my main symptom was that I couldn't work. I couldn't concentrate at all, and I couldn't do any homework. Now, when you're twelve years old and in the Gymnasium and you're supposed to learn Greek and Latin and mathematics, that didn't go very well. So my teachers told my parents that they had to take me out, that I just

* Heinz Edgar Lehmann was born in Berlin, Germany in 1911 and received his MD from the University of Berlin in 1935. He took a post in 1937at the Verdun Protestant Hospital in a suburb of Montreal, Canada, and stayed there for the rest of his career. In 1948 he joined the department of psychiatry of McGill University, and became professor emeritus in 1981. Lehmann died in 1999.

would never be able to get through high school, and I just wasn't made for it and I should learn a trade. Well, my mother didn't believe it and used her good judgment and got me a tutor. The tutor came every day. He was a student, and he did my homework with me, and much of the time for me, actually. He was interested in psychology and he saw that obviously I couldn't do it; I couldn't concentrate, so he would do the homework for me. That went on for about six months and I got out of my depression. And so, I did get through the Gymnasium. I got through the universities, and then I had to leave Germany in the late '30s, because of Hitler, and came to Montreal, Canada. I worked in a mental hospital there, the Douglas Hospital, then, called Verdun Protestant Hospital, and I didn't have the time to get any postgraduate training. I've always been interested in psychiatry. In fact, before I started medicine at the university I told my father, who was a surgeon that I would become a psychiatrist. Now, back in the early 1930s, that was certainly something you didn't go into. There was practically no really good diagnosis, except Kraepelinian. The only therapy was psychoanalysis. But, anyway, I insisted on it, probably because I had gotten through the depression, and my tutor, who got me out of the depression and did my homework with me, was interested in psychology as a student, and he had given me all of Freud's works that had been written until then, all of which I read. By the time I was fourteen, I had read all of Freud's work. That got me interested in psychiatry before I started medicine, and I stuck with it. Everybody said, "you will change your mind about that," but I didn't. But then I didn't have any postgraduate training in psychiatry. There was no time for it. The War started when I started working in the hospital in Montreal, in the mental hospital, and there weren't many people left. I was one of the few, so I didn't have time and I didn't have the money for postgraduate training, so I never got any. I didn't get certified, and later when this came up I said, "Well, I certainly didn't have the time to go for the examinations now, and anyway, I wasn't so sure that the examiners would know more than I would, so I didn't bother." Eventually, they sent it to me by mail, the certification, I didn't even ask for it. So now, I'm a certified psychiatrist, without any postgraduate training. Well, what was the training? I learned it the right way, I think, by just working from 8:30 in the morning until about 12:30 at night. I had up to six hundred patients during the War, and there were only two or three doctors left in the hospital. We didn't have interns; we didn't have residents. I had one trained nurse. The others were untrained attendants, and up to six hundred patients. So I did learn a lot, because I spent my time with the patients.

WB: You taught yourself.

HL: I taught myself and the patients taught me.

WB: Did you read during that time, too?

HL: Yes, I did read. That's what I did after 11:00 o'clock at night or 10:00 o'clock at night in the hospital library. I courted my wife, who was a nurse there, and word got around to her that I probably was a heroin addict, because nobody else would walk around the hospital library at 3:00 o'clock in the morning. So, I did read a lot, and I saw a lot of patients and I learned quite a bit, of course. I was convinced that there was quite a bit of difference between what we then called neuroses and psychoses, and I was convinced that psychoses, such as schizophrenia and the affective disorders, had some sort of a very strong physical component, and that wasn't necessarily so for the neuroses.

WB: How did the whole area of drugs come up? How did you get involved?

HL: Because I was convinced that there was a physical substrate for the psychoses, so I tried very large doses of caffeine. I came up with the notion that manic depressive swings may have something to do with acidity and alkalinity and pH, so I gave my patients very large doses of ammonium sulfate or sodium carbonate, in order to alter their pH. I was always hoping and dreaming about some drug that eventually would do something to psychosis. Well, then what happened is, that in 1953 – my wife is French Canadian, so we speak French at home – I read a French article by Delay and Deniker on chlorpromazine, on their first experience with chlorpromazine in 1952, and that intrigued me very much. I couldn't believe that psychotic symptoms such as hallucinations and delusions could be affected by a simple pill. But, anyway, I tried it. Of course by the late 1930s, early '40s, we already had shock treatments. I had been treating patients with insulin coma therapy, hypoglycemic coma, and with Metrazol (pentylenetetrazol) therapy before we had electroconvulsive therapy, and these treatments worked fine for a few weeks or a few months. But then, of course, the patients relapsed, as we know now, about seventy percent of them, and then we didn't know what to do. We applied the same shock treatments again, and the second time they usually didn't work as well.

WB: Didn't you have a role in the first use of chlorpromazine?

HL: In 1953, I read about this pill, and, so, we got samples from Rhône-Poulenc, who made the chlorpromazine. I read the articles one Sunday, I remember, and the next day, Monday, the first resident I met – by that time, in the '50s, we did have residents – I asked, "Do you want to try this fancy new drug? It seems to be incredible, what they claim for it." And he said yes, so we set up a

clinical trial in, I think, seventy-two patients. We got it all arranged in about a week or two, because we didn't need any permission. I didn't even ask the director of the hospital. Certainly, there were no ….

WB: No Institutional Review Boards (IRBs).

HL: No IRBs, no informed consents, no Food and Drug Administration (FDA) regulations, nothing; also no money whatsoever. So we had to kind of fold these seventy-two patients into our regular routine. I didn't even have the heart to ask the hospital for a secretary. So I made my own cards out for each patient. Well, it worked remarkably well, because after two weeks, two or three of my acute schizophrenic patients were practically symptom-free, and that, I'd never seen or heard about before.

WB: That had to be an exciting week.

HL: Oh, yes. We started our study in May, and in August, we had finished, simultaneously, all seventy-two patients, and we had written the paper. I remember writing in the paper that these were the drug's 'unique effects,' and my boss, another psychiatrist, said in a short note in the manuscript, "don't ever say anything is unique," nothing is unique. But this one was and I insisted on keeping it. At the time, of course, there was no other way to describe it. At first, so, my co-worker and I thought that what we saw was a fluke, and perhaps some sort of mistake.

WB: Who else in the field was studying chlorpromazine at that point in time?

HL: Well, there was Nate Kline. He had started reserpine, which didn't last very long, but it also was an antipsychotic drug. And then I remember Frank Ayd, and I think, Douglas Goldman. I don't think anyone in Canada had worked on it.

WB: Did Fritz Freyhan study it, did he?

HL: Fritz Freyhan, of course. Now, Fritz Freyhan coined the term target symptoms, and that's fine. We did have target symptoms, typical psychotic symptoms like delusions, hallucinations, formal thought disorder. I think for a while he thought, like many others, that the drugs were anti-schizophrenic, but from the beginning that seemed to be very unlikely, almost impossible. But, we did find that it worked in psychotic manics, even in psychotic depressed patients, as well as in schizophrenics.

WB: You found that out fairly early.

HL: In our first seventy-two patients, we had about twelve different illnesses; a few manic patients where it worked miraculously well, of course, and a few depressed patients, and even a few organic psychoses, where it didn't work very well.

WB: So you had the whole story in those seventy-two patients, almost?

HL: Almost.

WB: In the first paper?

HL: Yes, and then in the next two or three months, before Christmas of that year, we tried it in a few anxious patients, and found out that definitely the drug wasn't an anxiolytic, so we really had the whole story.

WB: Now, in Europe, who was working with the drug at that point?

HL: In Europe, they worked with it primarily in France.

WB: The French, primarily?

HL: Delay, Deniker, and two or three others. Deniker came over to Montreal to visit us from Paris, and we had some jaundice cases, which the French hadn't seen. I haven't seen them since either. Possibly it was sub-clinical hepatitis. From then on, of course, there has been a never-ending chain of new drugs, such as Stelazine (trifluoperazine) ….

WB: What hospital were you in when you did the seventy-two cases?

HL: The same hospital I'm still teaching in. It was the Douglas Hospital that was called then the Verdun Protestant Hospital. I'm still teaching students there every Monday, so that's quite a long time. They have now a research center there. At the time, it was one of those big, well, snake pits, really. It's very nice to see what, over a lifetime, can happen with a snake pit becoming a good research center. Well, that is how I got into psychopharmacology, but really it was realizing a dream. I had hoped there would be a drug for those patients. I'd been looking for it, hoping to find it eventually. From then on, Tom Ban joined me. He had just come from Hungary and for the next ten or fifteen years, we did a lot of clinical trials. There's hardly any drug between 1952 and 1970 that we didn't do clinical trials with.

WB: Well, tell me some of the most interesting findings in those clinical trials.

HL: Of course, nothing can match the unbelievable thing that there was a drug, chlorpromazine, first time in history, that could in two weeks wipe out hallucinations and delusions. After we had really believed that was so, which took a year or so or more, nothing else could really….

WB: Anti-climactic.

HL: Everything else was anti-climactic, yes. But, then, I remember a funny story. I went in ’57 to Zurich to the international psychiatric meeting, and there on the way back from Zurich to Montreal on the plane, I read Kuhn’s first paper on imipramine, which he had given at the meeting in Zurich. I wasn’t there; apparently he had about only twelve people in the audience. I read the paper he had written in German on the way back that there is possibly now a drug for depression. I immediately called Geigy when I arrived in Montreal, and their branch in Montreal hadn’t heard of this; although their company had worked with it, obviously, for more than a year. Well, they felt a little embarrassed, but got me the drug from Europe, and, then we did one of the first trials with imipramine in Canada, and probably North America, and found that it worked, too. But that wasn’t so surprising. I had told the various drug representatives, after we had antipsychotics, it shouldn’t be so difficult to find an antidepressant, because it’s likely that there’s a metabolic disturbance in affective disorder as in schizophrenia.

WB: Do you think we’re going to find drugs for the twenty to thirty percent schizophrenics and twenty percent or fifteen percent depressed patients that don’t respond to anything; do you think we’re going to find a drug for them?

HL: I think so, not one drug, but probably a half dozen, and we’ll learn how to make diagnoses based on the substrates involved in depression and schizophrenia, probably. That’s where the new imaging technology will help us, probably. So far, we can’t make any diagnosis with it, but we may be able to distinguish substrates. So far all our diagnoses are based on phenomenology, just the way Kraepelin did it, but we will probably be able to find certain traits with endocrinological measures, molecular research or functional imaging that will allow us to make distinctions between various depressives and various schizophrenics.

WB: Do you remember where your first paper on Thorazine was published?

HL: It was in the *Archives*, the *Archives of Neurology and Psychiatry*. It wasn’t easy to get it published. We sent it in August and since I hadn’t heard anything by December, it seemed that something was fishy. So I wrote them that I wanted the paper back, and “I’ll get it to somewhere else.” Then, they immediately published it. It came out in March of the next year. I think what happened is that we were in Canada, and the Americans that were working with it, I think Winkelman, wanted to be the first one out. His paper came a month later. He had worked with chlorpromazine in neurotic patients.

WB: The usual story.

HL: Yes.

WB: Who was the editor of the *Archives* then? Do you remember?

HL: No, that, I don't remember.

WB: Was it Grinker?

HL: No, it wasn't him.

WB: It was before him?

HL: It was before Grinker.

WB: Well, you've worked on a lot of different hypotheses and tested a lot of different drugs and had a lot of different theories. Are there any that particularly come to your mind?

HL: No, what I would like now is to find methods to determine sub-clinical minor stress. I'm thinking of that, particularly, because I have a notion that many aging people suffer from subclinical – to them probably unknown – chronic stress that actually kills their hippocampal cells. I think Ewing has shown, and several others have shown it too. In California, there's a group showing that corticosteroids produce atrophy of hippocampal cells, and a chronic stress condition would of course produce a chronic outflow of corticosteroids. I think a lot of elderly people suffer from chronic stress conditions without knowing it. Now, if we could, well, test, for instance, their saliva for corticosteroids, their electrolytes for corticosteroid receptors, we would possibly be capable of finding in a lot of people, who would never know about it, and the doctors don't know about it, that they are chronically stressed. If they are chronically stressed, then one would have to find out why, and probably with psychotherapy; they could be helped to get over this change in their lifestyle or whatever it is. There's a lot of undiscovered chronic stress. Some people have suggested that post-traumatic stress might be due to an outflow of corticosteroids.

WB: Going back to your first major study with chlorpromazine, did you present it at a meeting before it was published? Do you remember?

HL: No, I didn't. I presented it a year later at the American Psychiatric annual meeting.

WB: After it was published?

HL: After it was published. And I was very much surprised when people clapped and applauded when I went up to the podium. I never expected it and didn't know why and that was the first time….

WB: That was the first time you presented it?

HL: That I presented it.

WB: And, they, obviously, knew about it?

HL: They knew, because they read the paper.

WB: Right, right.

HL: But, I didn't realize that it had caused the impact.

WB: You didn't know the impact.

HL: I didn't know the impact.

WB: What do you think was the biggest contribution that you've made?

HL: To psychiatry?

WB: Psychiatry.

HL: Psychiatry needed a big contribution to show that the psychoanalysts were wrong. Up to the early 1950s, the teaching in most American universities was that it is simplistic to believe that there's any kind of organic substrate to schizophrenia; that most psychoses, except the organic ones, could only be treated with psychoanalysis and that any other treatment than psychoanalysis was anachronistic and just simplistic. We had to show that there was a physical cause, a physical substrate, physical pathophysiology for the major mental disorders. And the only way to show this, and therefore, to help patients to get the right kind of integrated treatment, was by proving that with a pill you could remove hallucinations. Having shown that, the analysts had to admit that there was a physical cause, and we could begin to use the biopsychosocial model that we have now. I think that was the main contribution I made.

WB: Just go to the various positions you've had.

HL: Well, as a refugee from Germany and untrained psychiatrist; I was a Junior Psychiatrist at the Verdun Protestant Hospital the hospital I'm still working at once a week, and then I became Senior Psychiatrist there, then Clinical Director, and I stayed there for thirty five years, full time. Incidentally, I don't know any other psychiatrists who stayed that long, full time, with a mental hospital, so I think I have credibility in knowing my schizophrenic patients. I became Director of Research and Education at that hospital, and then I became Chairman of Psychiatry at McGill University. I didn't want to, because I didn't want to have anything to do with administration. I hated anything that had to do with administration. I thought it was just a waste of time; so when they asked me whether I would take the chairmanship, which was open, I still remember, I told the dean I needed it like a hole in my head. Well, he didn't like that, so he insisted then, and finally, eventually, I took it on. I took it on because the department was almost falling apart at that time.

That was in 1970 at the time of the Quiet Revolution in Quebec. There was a lot of unrest and a lot of psychiatrists and university teachers were leaving, so I thought, well, I'd better take it over, because I was from there and I knew about holding things together, anyway. So I took on the chairmanship. Then later, after I had finally left the full time hospital job, I took on, originally for about a year, the job that I still have now, since 1980, as Deputy Commissioner for Research for the New York State Office of Mental Health. I have no license in the state, so obviously, I'm not practicing there. It's all administration, the one thing that I've hated all my life and kept away from, but I thought, well, at that age, then, after sixty-five, it was about time to learn a little about it, and, so, that's when I came on.

WB: What does that involve?

HL: Well, I have a budget of some thirty-six or thirty-seven million dollars a year on paper, but it actually involves being responsible for the administration of two major research institutes, one of which happens to be the Nathan Kline Institute, and actually for all the research that is going on in the state of New York. I have to sign off on all of the research protocols. I have to make sure that every IRB is working all right. I have to deal with all the political inside fighting about the various jobs in the various hospitals and research institutes. I have to fight about budgets and try to outwit people, get around and manipulate; you know, I do the things that administrators have to do. But, since I'm there only two days a week in Albany, and I live in Montreal, I live, really, in two worlds. The Canadian world is very different. I don't know what the Americans are going to do with their health care, but in Canada, of course, there's no problem. But it's interesting to have a position that all my life I never dreamt about, and in another country, in another political world, altogether.

WB: And it's a very responsible position.

HL: It's a very responsible position. Well, I had the experience, obviously. It's interesting, I think, that I know more researchers in the States than in Canada. Some of the Americans took quicker to developments, and I was more in communication with American researchers than with Canadian researchers.

WB: Let me ask you, since this is the ACNP, what was your involvement in the beginning with the ACNP? You were one of the founding members.

HL: Yes, again, against my wishes. I remember quite a few of the people that I knew quite well asked me to join them in founding the ACNP, the American College, and we had had meetings, and I said, "well, that's fine, but leave me out of it." I said, "I had no time, definitely no time, and

I hate institutions, anyway, and I don't want to have anything to do with it." Then, I think it was Malitz who told me, "Well, we'll draft you," and I said, "I don't know what you mean." He said, "You don't know what drafting is?" So he explained to me what drafting is, and so anyway, they got me into it, and, I finally became one of the founders. Eventually, they drafted me again for being a president. I think it was in 1964. Again, I didn't want to, and I said, "I don't know anything about the procedures of running it." Anyway, I got into it, and as I was doing it, I was learning it. Now I'm very glad that we have an ACNP. In fact, it's very difficult to imagine that we didn't at any time.

WB: Looking back on your life, were there key turning points?

HL: No, really not, except that I had to leave Germany, which I didn't like at the time. I made one big decision within the first three weeks after arriving here, never to have a car. I kept this promise to myself. I think that helped me; otherwise I wouldn't be alive anymore. I was driving in Germany as a student. Otherwise, my life has become, really, remarkably the way I wanted it to go, step by step by step, no great crises, no great surprises. One of the surprises was chlorpromazine, but that wasn't such a surprise. My father, as a surgeon, told me "it's ridiculous to want to go into psychiatry," which was ridiculous at the time. I thought, well, perhaps I can do something about it if he knows so little about it. So, you know, that wasn't planned.

WB: Okay, well, maybe one last question: as you look to the future, now, of our field, what do you see as the challenges?

HL: After we had the serendipitous discovery of the drugs for the affective disorders and for the psychoses, we didn't know what they were, so we challenged the neuroscientists: "Now, you've got to find out why the antipsychotics work, why the antidepressants work." They found out first why the antidepressants work, and another five years later, why the antipsychotics work, and, from then on, neuroscience took off. Before that, we had a lot of anatomy but we did not learn very much more about what goes on in the brain. And now, neuroscientists are far ahead. We clinicians set them going, and they are very successful; they have left us behind. I don't think we have enough communication, and perhaps the focus isn't right. It's difficult for me to see the focus of the neuroscientists and molecular biologists. Well, there is a C-fos and N-RAS, and that works on a receptor on the cell wall, which then enables certain chemicals to get into the cell, which enables something else to help in the cell. You don't even have an aggregate of neurons anymore. It's all

within one cell and, from the neurons to the brain and from the brain to the behavior and from the behavior to the human being, there's a gap.

WB: The gaps.

HL: Huge gaps, so we have to find a way to communicate and to get a general focus, which is the same for research and clinicians.

WB: Okay. I've been interviewing Heinz Lehmann, who has been and is one of the pioneers in the field of neuropsychopharmacology. He's past president of the American College of Neuropsychopharmacology, and clearly, one of the greatest neuropsychopharmacologists that ever lived. I enjoyed interviewing you.

HL: Thank you. I think you exaggerated a little.

WB: No, I'm not exaggerating. Are there any other things you'd like to add? We can always go back and dub it in if you want.

HL: No, I also want to make the point of having had this long-lasting depression which was so disabling at twelve years of age that the experts said that I would never make it. I got over it and have been doing fairly well for quite a long time without any drug therapy or any definite structured psychotherapy.

WB: Have you had subsequents?

HL: Subclinical ones.

WB: Subclinical ones?

HL: I had one or two, that's all. I never had to stop working. Once I took a drug, for a short time. For me that indicates that the prognosis is not as bad as recent follow up studies have shown.

WB: Right. There are many stories of educators who've told people they can't do it, and fortunately, a parent said, "but you can do it" and stuck with it.

HL: And the therapy of my tutor, doing the work for me, the homework, you know, which was considered to be horrible, his bibliotherapy of giving me all of Freud's stuff to read, when I was thirteen, apparently worked.

*Heinz E; Lehmann's interview by William E. Bunney was first published in Volume One (Starting Up, edited by Edward Shorter) of an Oral History of Neuropsychopharmacology, The First Fifty Years Peer Interviews (edited by Thomas A. Ban. Brentwood: American College of Neuropsychopharmacology, pp. 81-90).

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