

4 Joseph J. Schildkraut

The Catecholamine Hypothesis H.

Could we begin with where you were born and how you ended up going into medicine?

I was born in Brooklyn, New York, in 1934. A product of the public school system there, I went on to Harvard College in 1951, graduating in 1955. I was very naive about many things, coming out of Brooklyn. The first time I saw Boston was when I arrived there that September for my freshman year. It was a very different world from what I knew. A very exciting, very enchanting world and one that I came to be very comfortable with and grew, in fact, to love. I've not strayed far from Harvard ever since.

I ended up going into medicine more by evolution than by any design. I was always very interested in math and the sciences. There was no question when I went to college that I would be going into the areas of mathematics, science or conceivably philosophy. But, as I evolved through my college experiences, majoring in chemistry quite heavily, I began to toy with the question of whether I wanted to be a chemist or perhaps go into medicine. (Medicine was a more traditional field for kids from Brooklyn.) I was very strongly urged by the faculty in the chemistry department to consider becoming a graduate student there. On the other hand, Willard Van Orman Quine indicated that he might like to see me in the philosophy programme at Harvard, something that's always amused me, because this was on the basis of an introductory course.

But I decided on psychiatry in a rather interesting way, given the way my career evolved. In my junior year at Harvard, I took two courses in what was then the Department of Social Relations. They were basically on personality theory. I took these courses because friends of mine who were ahead of me in college had talked about how interesting they were. I'd hoped to have a fabled professor, Robert White, for the course on the abnormal personality. He'd written a textbook on this subject and he was somebody who was a magnet at Harvard. But, for whatever reason, in that year he decided that he was going to teach a course on the development of the normal personality. As a result, John Spiegel, who was brought in from the University of Chicago, taught the course on the abnormal personality. John Spiegel was a psychoanalyst and his course awakened my interest in the unconscious, in Freud, in psychodynamic theory.

I went on in the following term to take the normal personality course with Robert White, and that introduction to psychodynamic thinking and psycho-

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logical development led to my seriously considering becoming a psychiatrist. It was really in the course of making that decision that I made the decision to go into medicine. I went to medical school with plans to become a psychiatrist and a psychoanalyst. However, like most people that I know at medical school, I was on a kind of roller-coaster, changing interests each month or with each rotation. There were many things I found fascinating – various areas of internal medicine, renal physiology was a great interest. But it was my clinical experiences in psychiatry, during my clinical rotations at the Massachusetts Mental Health Center, that persuaded me to go into psychiatry.

Could I ask you about those experiences, because Mass Mental at the time was very famous as the home of an analytic approach? Who were the teachers there? Elvin Semrad is a famous name.

Well, some of us think it's still very famous and we are trying to keep it that way. Elvin Semrad was there at that time and he will come into the story during my residency. However, as a medical student, he was less prominent in my training and the key people for me were a number of patients, rather than any of the faculty. I found that my work with patients was fascinating, intriguing, compelling, that I enjoyed it and that I was kind of good at it. I really made the decision to become a psychiatrist because of a patient with schizophrenia, who I saw in my fourth year as a medical student. In those days, Mass Mental Health Center was geared towards student education as the first and foremost of its many activities. As a fourth year medical student, I had the opportunity to be treating this patient for the entire time I was on the rotation, with a resident in a more supervisory role. Vardo Ganz (the resident) and I fought like hell over this patient, because the person who was supervising me at the time had one set of ideas about treating the patient, while the resident and her supervisor had quite a different set of ideas. Surprisingly, the patient survived this conflict and actually improved, and the resident, who saw me as a mortal enemy at that time, has become a friend. But it was the experience with this patient, learning to see at first hand what psychosis was and what a psychotic patient was going through, suffering with and at times coming out of, that really locked me into psychiatry. After that experience, there was just no question in my mind that I wanted to be a psychiatrist, a psychiatrist following in what was then the tradition of Mass Mental Health Center, at that time, doing dynamic psychotherapy and ultimately training as a psychoanalyst.

With that decision made, I left medical school, going on to San Francisco for an internship in internal medicine. My reason for going to San Francisco was rather unconventional, at least in Harvard Medical School terms. Romantically intrigued by Jack Kerouac and the beat movement, I was lured by what was going on in San Francisco and I wanted to be out there. I also expected by then that I might be spending much of my professional career in Boston, if things went my way, and I wanted to be somewhere else for my internship year. The dean's office actually called me in when I submitted my rankings of internships rating University of California Hospital as number one over the Harvard

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L.C. E.R. Teaching Hospitals. The dean of students told me I had obviously made a mistake in my rankings. I said no I didn't think I had. And he replied 'The Boston City Hospital has let us know that they very much want you and surely you would not turn down a Harvard Teaching Hospital for the University of California in San Francisco'. I told him that I knew I'd done a good job in my rotation at Boston City Hospital and I had very fond feelings for them too, but I wanted to spend my year of internship in San Francisco doing something outside of Boston. He went on to tell me that I was jeopardizing my career and asked me to please rethink it. Nonetheless, I went to San Francisco. Several years later, when I was back in Boston, this dean met me in the street one day. He said, 'You know, I've got to confess something to you. When we talked about your internships, I'd never been to San Francisco. I have since then, and now I understand why you did it'.

E.R. L. During the internship in San Francisco, I was waiting for decisions on my applications for residency in psychiatry. Harvard, under Jack Ewalt, who was professor and chairman, played strictly by the rules, informing potential residents of their acceptance only on the official notification day. Other programmes let you know a little earlier. One of the programmes I was seriously considering if I didn't get into Mass Mental Health Center was the programme at Yale. Yale did let me know that they were prepared to accept me, but they wanted to have an answer by some time prior to the day I would hear from Massachusetts Mental Health Center. I contacted Jack Ewalt with my dilemma. He got back to me in writing, in a very typical Ewalt fashion, saying 'We cannot give you our decision until the agreed upon date but I must say that anybody with your record and with your accomplishments who would settle for anything less than his first choice ought to have his head examined'. So I turned down Yale and came back to Mass Mental Health Center on schedule. There, I began my first-year residency in psychiatry in what was Jack Ewalt's first hand-picked group of residents. He'd only recently come as professor and chairman. I mention this because it was a quite extraordinary class.

Who was there?

Of the first-year residents with me were Eric Kandel, Alan Hobson, George Vaillant, Judy Rapoport, Tony Kris, Ernie Hartmann, Paul Wender, among others. It was a class that was clearly very academically oriented.

Can you fill me in a bit more on Jack Ewalt?

Jack Ewalt was very eclectic in his approach to psychiatry. He came to Massachusetts to become Commissioner of the Department of Mental Health in the 1950s, at the time that Harry Solomon was then Superintendent of Mass Mental Health Center and Professor and Chairman at Harvard. Harvard had a 65 years of age retirement rule in effect back then and Harry Solomon had to retire. As was done in the Harvard/Boston circles in those days, there was an inside arrangement. Harry Solomon succeeded Jack Ewalt as Commissioner of Mental Health for the Commonwealth of Massachusetts and Jack Ewalt

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succeeded Harry Solomon as the Head of the Department of Psychiatry at Harvard and Superintendent at Mass Mental Health Center. Jack was a very interesting guy. Short fused, short tempered, he was known for his volcanic eruptions, straight talking. If he promised you something, you got it, and if he said no to you, you didn't do anything more than suck up the gut and walk out of his office or else you'd be thrown out of the office. I was very fond of him. Jack was really very supportive of broad-ranging academic issues. I don't think he was a psychoanalyst before coming to Massachusetts, but knowing that that was where the power was in Massachusetts' psychiatry at that time, I think he had a kind of instant psychoanalysis and a quick processing through the institute. So he had become a psychoanalyst by the time that I arrived at Mass Mental Health Center for my residency.

But, as you mentioned earlier, the key and revered figure at Mass Mental Health Center was Elvin Semrad, a compassionate, Buddha-like figure who was one of the most charismatic men that I've ever met. The only person I ever met who rivalled him in terms of insight and capacity to get to people was the Dalai Lama.

Do you know Semrad's background?

Well, he came from the midwest, became a psychoanalyst, and worked at Boston State Hospital before becoming Clinical Director of the Mass Mental Health Center. He was a roly-poly guy, with a very quizzical smile on his face, known for turning questions and issues back to the person he was speaking with. He spoke in enigmatic utterances that made one reflect on what was going on between the two of you. He had an uncanny capacity to communicate with very psychotic patients. He let them know that he was there for them, not to put them on show, not to support the resident who was treating them, but as he was with every person that he spoke to on a one to one basis, he was there with them. With a typical Semradian shrug or word, he would say 'Tell me about it' or 'I understand' and he was able to help the patient to talk and talk in a way that most of these patients hadn't talked for months or even years. Very often, there was a little bit of carry-over from these interviews. The patient might be stirred up in such a way that the ward staff had to take extra precautions because the patient's psychotic defences had been penetrated. Sometimes, the patient was able to carry over the Semradian interview into treatment with the resident. But most of these folks were really very sick people, who usually reverted back to their former selves. But he offered the opportunity for us to see what was going on inside the patient and to see that at least somebody was able to communicate with the patient, be there for the patient and get the patient to talk beyond psychosis.

I'd gone to Mass Mental Health Center because of an interest I had in schizophrenia, largely developed, I think, by my fascination with the drugs that were being used in those days – mescaline, marijuana, Aldous Huxley's experiences that I'd read about as a medical student. The whole question of psychosis was one that fascinated me. I felt confident when I came to Mass Mental Health

Center that I was going to become a dynamic psychotherapist, hopefully a psychoanalyst, and devote my career to studying schizophrenia.

But things don't always happen as one expects. I was very fortunate to have entered Mass Mental Health Center at the very time that the antidepressant drugs were becoming available. This was 1960. And, as you know, Mass Mental Health Center in those days was a largely psychoanalytic bastion, where these drugs were greeted with great scepticism by the faculty in general and by Elvin Semrad in particular. Elvin used to refer to the use of these drugs as taking a patient to a cocktail party. His theme for the first year of residency was to sit with patients, to learn to listen to your patients, to learn to bear the pain and help them bear the pain. Anything that got in the way of that, he felt, was in one way or another a form of resistance. At least that's what he taught. As I came to know him over the years, I found that there were many Elvins. There was the Elvin as he presented himself to medical students; the Elvin he presented to first-year residents was different from the Elvin who taught the second-year or third-year residents. He was far more complex, far more intellectual in a soft sense of the word, but in an informed and inquisitive sense, than he ever let on to the first-year residents.

Back then, one was made to feel by the ethos of Mass Mental Health Center that if you resorted to a psychoactive drug with one of your patients, be it an antidepressant or what were then termed the major tranquillizers, for example chlorpromazine, thioridazine, that you were giving up on psychotherapy. And so, in the early months of my residency, I found, in treating a number of patients, most of them depressed patients, that my therapeutic attempts were really not getting very far. These were patients who were sick and sick in a way that we don't see any more. As a first-year resident, it was a common experience to have to tube feed hospitalized depressed patients, who were actually starving themselves to death, who were considered cases of medical emergency and who were always at risk of having to be transferred to a general hospital if we couldn't properly provide nutrition at Mass Mental Health Center. We'd see the phenomenon of the agitated, depressed patients, who would pace up and down, wringing their hands, saying 'Oh my God. Oh my God. Oh my God. What have I done? Oh my God. Oh my God. Why did I do it? Why did I do it? Oh my God. Oh my God. Oh my God. Oh my God. Why did I do it? Oh my God'. This just went on ceaselessly, patients exhausting themselves, grossly psychotic.

At the time I began my residency, I had what I thought was the misfortune of being assigned initially to the electroconvulsive therapy (ECT) rotation. All first-year residents did a couple of months on this rotation. I, as the budding psychoanalyst, felt this was just going to get in the way of what I really wanted to be doing in psychiatry. But the ECT rotation gave me the opportunity to see these depressed, starving, near-dead, vegetating human beings, given a course of ECT, turn into vital, engaging people with charm and dignity and a personality that came alive. It was the most amazing therapeutic transformation that I'd seen in all of my experiences in medicine, far more dramatic than any kind

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of surgical procedure, far more dramatic than anything I'd seen done on a medical ward. Because these electroconvulsive treatments were transforming a patient who had really lost everything that we consider important about a human being back into an engaging, vital person.

Who was actually responsible for ECT within Mass Mental at the time? They must have felt slightly outside the mainstream.

Well, yes and no, because Mass Mental Health Center was never what it appeared to be. It really always was a very eclectic institution that supported people of very different persuasions and facilitated their communication and collaboration. There really wasn't an orthodox doctrine of psychiatry at Mass Mental Health Center. Semard taught and influenced the way he did, and he would chide you for doing things in a way that was different. But there was no animosity between the psychoanalytic faculty and members of the more eclectic faculty such as Milt Greenblatt, who, as Assistant Superintendent, was nominally responsible for the group of things that were coming to be called somatic treatments – including ECT and the psychopharmacology programme.

I say nominally responsible because psychopharmacology in those days hadn't permeated all of the hospital. There was a small psychopharmacology service and basically it was overseen by a psychologist, Al DiMascio, who had not yet obtained his PhD. Then there was the psychopharmacology nurse, a man named Carpenter, called Carp, and a group of residents who might come around on their twice-weekly psychopharmacology rounds, following those few patients who were being given drugs and making recommendations.

Well, anyway, getting back to my experiences attempting to treat severely depressed patients with psychotherapy alone, I had the frustrating sense that most residents did – my attempts at psychotherapy just weren't working, but if Elvin Semrad had been treating this patient, by now the patient would be better. Another problem I encountered in my first year was that I didn't understand some of the diagnostic language being used. For example, my supervisors would use the term psychotic depression and I never got it. Finally, towards the end of my first year, when I had enough confidence to think that maybe I hadn't got it because it couldn't be had, I went around to talk to my various supervisors, asking them to define for me this term 'psychotic depression'. I talked to about five supervisors and got five different definitions. One was the expected definition which we use today, which was a depressed patient who showed manifestations of psychosis as characterized by delusions and hallucinations. But other definitions included a depressed patient who has an ego that is psychotic; a depressed patient who is pre-psychotic and capable of having a psychotic decompensation; a patient who is clearly not thinking rationally because he wants to kill himself and that's a crazy thought, therefore psychotic. It was clear that this term was being bandied about in a vague and inconsistent way that made meaningful communication impossible. And it wasn't that I just didn't get it, it was that I got it all too well, but I got it differently from five different supervisors.

But, eventually, when treating my hospitalized, severely depressed patients, I felt that I had to resort to these antidepressant drugs. The range was pretty narrow in those days. We were talking about imipramine, the tricyclic antidepressant, and phenelzine, the monoamine oxidase inhibitor (MAOI). That was largely the antidepressant armamentarium. Doses were very different in those days. Imipramine was used very, very cautiously. Only hospitalized patients could get imipramine; it was considered so scary and so unusual. Fifty or → 75 mg per day was a standard dose. It was considered heroic to push up to 100 mg and I don't think anybody dared go above. One of the things I learned is that patients got better on these lower doses. It might take a little longer, but they did get better, and better in ways that my psychotherapeutic attempts could not accomplish. These drugs seemed like magic to me.

Coming out of Harvard, as a heavy chemistry concentrator, my imagination started to run wild. These drugs, these pharmacological agents, had to be working through some kind of biochemical processes. If we started learning about the pharmacology of these drugs, we might be able to find out about their biochemical mechanisms of action. And that might even help us to get some clues about the underlying biochemical pathophysiology of depressive disorders. All of this was going on without any loss of interest in psychodynamic psychotherapy. These concepts were not competitive in my head; still aren't. It was just another avenue that was opening.

Another thing that intrigued me was lithium. Lithium was not being used in the USA at that time, but Lester Grinspoon, who was my chief resident when I was a first-year resident, and I talked about the possibility of using lithium in manic patients and we went ahead and did it. You couldn't get lithium in the pharmacy in those days; it wasn't a drug. So we got it from a chemical supply house. I don't remember what salt of lithium we were using, but we had it put in gelatine capsules by a pharmacist. I was the front person of this operation, going around finding manic patients, talking to their clinical team, talking to the patients to see if they wanted to try lithium. We did know the history of lithium and of the lithium scare that occurred in US medicine, when it was used as a salt substitute with dire results some years previously. So we were very cautious and careful. It was too unusual a treatment to be used chronically at that time, but acutely I was able to see effects of lithium on mania. This enabled me to get exposed to manic-depressive illness in a way that was different from my cohort of residents, because I was seeing all the manic patients in the hospital. Again, the intrigue of manic-depressive oscillations was something that also captured my imagination. I could see biochemical oscillators of sorts in the brain.

All of this was going on during my first year of residency, when one day, walking back from the coffee shop at Mass Mental Health Center, Milt Greenblatt, who was an avuncular character, put an arm across my shoulder and said to me 'Young man, I have an offer that I think you might find appealing'. Dale Friend, an internist from the Brigham Hospital, ran something of a laboratory, and he and Milt Greenblatt had got themselves a grant to set up a

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depression research and treatment unit, which was going to take advantage of Dale Friend's capacity to measure vanillylmandelic acid (VMA) in his laboratory using a new method. In retrospect, it was a very crude procedure, but it was better than what had been used previously. The aim was to assay VMA while trying to give ~~X~~dopa to depressed patients.

Literally, we set up this depression research unit in a very small space at Mass Mental Health Center with only one toilet. In those days, unisex toilets had not yet been 'invented', and we were, therefore, restricted, to only one sex of patient on this unit. We opted for females, because depression was more common in women than in men. It was a small five or six bed unit. It came to be called Ward 1 because it was on the first floor. Coincidentally, it was just across from the office that I've had as a faculty member at Mass Mental Health Center continuously since 1967 when I returned from post-doctoral training at the National Institute for Mental Health (NIMH).

I was designated chief resident for the unit, which was an unusual title for a junior resident. Gerry Klerman, who had trained at Mass Mental Health Center and had been off working with Jonathan Cole at the NIMH Psychopharmacology Service Center, came back to Mass Mental to be the attending staff psychiatrist on this unit, and he and I largely ran the unit. In my second year, we had a couple of first-year residents who were also working with us early on. They were Dick Shader and George Heninger and they were my 'junior residents'. One of the projects that was going on in this unit was treating depressed patients with ~~dextro~~ levo-dopa not l-dopa because it was too expensive, but ~~dextro~~ levo-dopa, which was much more economical but, as we learned, ~~useless~~.

Another project was something that came out of Gerry Klerman's and my heads. This was taking advantage of this VMA assay that Dale Friend had, simply trying to see if the MAOI phenelzine would, in fact, cause a decrease of the deaminated metabolite of norepinephrine VMA. One assumed that it would and this was the hypothesis that we were studying in a double-blind, randomized, small trial. There was a placebo group, but there was also an interesting group, an active control or comparison group, a cohort of patients given imipramine, which we knew wasn't a MAOI. We weren't exactly sure what it was, but it was not a MAOI. Imipramine was given so that we would have a cohort of patients who we anticipated would improve, as with the patients on phenelzine. And we would be able to tease out whether the decrease in VMA that we hypothesized would occur with phenelzine was due to its being a MAOI or, maybe, if we saw a decrease of VMA in the imipramine group, it might just be a concomitant of clinical improvement.

The patients on this unit were carefully selected. I had the chance to see virtually all of the depressions that were coming through Mass Mental Health Center. There were many in those days, because depression was a disease treated in hospital, and I was able to select patients with what I thought was pure depression, no hints of any personality or character problems, no hints of what the English psychiatrists would call neuroticism. They were raising

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successful families and living productive lives; folks who suddenly became depressed and couldn't explain it. It came out of the blue, as it sometimes does. They got to the point of not only feeling depressed and dysfunctional, but literally being unable to function, and had to wind up in a hospital because it had become that serious. These were the patients I was able to select. It was really a hand-picked group of patients, who met Roland Kuhn's description of the imipramine responder.

These were people who did get better, and got better quite quickly, with the antidepressant drugs, albeit that we were using very low doses, so it might have taken 4 weeks instead of 3. I developed the hypothesis that if you could pick your patients very carefully, they would get better quite quickly with low doses of imipramine. That sort of patient is no longer seen by psychiatry and hasn't been for years. The results of this study, though, were surprising, because what we found was that there was a decrease in VMA in the depressed patients treated with phenelzine, as one would predict with the MAOI. There was no change in VMA in the placebo-treated group, which you'd also expect. But there was also a significant decrease in VMA in the imipramine-treated group, and this wasn't expected to happen.

Now, in science, when things happen that aren't expected to happen, they can be damnable frustrations or wonderful opportunities. I started to wonder why this occurred. The magnitude of the change with imipramine wasn't as great as with the MAOI, but it was substantial and clearly highly significant, even though we were dealing with six patients in each group. In starting to think about this finding and writing it up for publication, I found myself starting to dip into the existing neuropharmacological literature. I started to make myself conversant with what was known about neuropharmacology. Gerry Klerman had known Seymour Kety from his time down at NIH and one summer, thinking about our data and the work we were doing, we went down to visit Seymour on Cape Cod, where he was summering. That was my first introduction to Seymour Kety, who really was able to speak quite knowledgeably about the area of neuropharmacology. God knows, he had Julie Axelrod and Irv Kopin in his laboratories at the time and he's a very, very bright guy. He opened my eyes to a world that was out there and I started to delve avidly into the literature.

When we published our paper in 1964, I put forward the notion that imipramine, by acting on membranes, though it wasn't a MAOI, was probably preventing norepinephrine from gaining access to the mitochondrial monoamine oxidase and therefore causing a decrease in VMA. I entertained the hypothesis that perhaps imipramine was acting not only on the neuronal membrane, but perhaps also on the mitochondrial membrane. I made the prediction in that paper that patients treated with imipramine might be expected to show increases in norepinephrine and normetanephrine, a hypothesis that was actually confirmed fully by data that we have accumulated only in the past 10 years or so. But, getting back to the early 1960s, I became aware that there was a new world out there, a world of psychiatry informed by pharmacology.

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In that 1964 paper, the seeds of the catecholamine hypothesis were planted. It was for all intents and purposes stated there, but really stated in a kind of temperate discussion. I submitted the paper for publication in the *Journal of Psychiatric Research*, which was at that time edited by Seymour Kety. I submitted it with a long discussion section, letting my mind freely play out in speculative suggestions. Seymour's comments came back, and I remember them to this day: 'Good paper, interesting, small amount of new data, worthy of publication. Be glad to publish it if you write your discussion like a neuropharmacologist and not like a psychiatrist'. So, the discussion was cut right back, and much of what was left on the cutting room floor was resuscitated in the paper on 'The Catecholamine Hypothesis' when I wrote it.

I was scheduled to go to NIMH, after finishing my third year of residency at Mass Mental Health Center. Given my interest in psychodynamic psychiatry, I was scheduled to go down to what was then the Adult Psychiatry Branch that was headed by David Hamburg. David had interviewed me for this position while I was in my internship at the University of California. In those days, America was in the Korean War and physicians were subject to a draft, and spending time at NIMH was one of the ways of serving one's military obligations. So these positions at NIMH were coveted not only for their scientific value, but also by those of us who would prefer to be doing science than doing war.

Some time during my residency at Mass Mental Health Center, having got to know Seymour Kety, Seymour raised with me the possibility of whether I would consider switching from David Hamburg's branch to his. Actually, it turned out that David Hamburg had gone out to Stanford to become chairman there and Lyman Wynne had succeeded him at NIMH. I gave very serious thought to this and pretty much decided I wanted to do it. Lyman Wynne, being the concerned and careful mentor of people that he was, asked me to go to NIMH to talk to him about this decision before making it. He was sick with the most damnable flu the day I came down and was actually in bed, febrile. So our conversation took place in his bedroom, discussing the pros and cons. He really wanted to make sure that I was making my decision for the right reasons. The decision was made that day. I would go to Seymour's laboratory.

My career path was set, but not quite. I wanted to get the blessings of my mentors at Mass Mental Health Center as well. Milt Greenblatt, of course, thought this was a great move. I had aspirations of coming back to spend my career in academic psychiatry at Harvard at Mass Mental Health Center as a psychotherapist and research investigator. I talked to Jack Ewalt about making the switch and Jack said, 'sounds great to me. You're on to something very interesting. You want to pursue it, go-ahead. You'll just be even more valuable to us when you come back here'.

When the NIMH began, there was a wee bit of a hint that it was part of the public service, part of the government, and you couldn't expect good research to be done by the government. It has got to be done by places like Harvard and Yale. Had this all gone at this stage?

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It was in a transition. The National Institute of Health (NIH) and NIMH have to be distinguished. NIH and the various medical and surgical branches were far ahead of psychiatry. The NIH had already made its mark. NIMH was looked at with a bit of suspicion because, at least in terms of clinical research, it had not yet really done that much. For many years, Seymour Kety ran a research ward to study chronic schizophrenic patients. And this research ward had gone on for a long time and some interesting studies were done, including studies of the metabolism of epinephrine and norepinephrine. There was an interesting psychophysiological group and there was basic biochemistry that was being done by Lou Sokoloff and Jack Durell. Jack Durell, being a psychiatrist, was in Seymour's laboratory. Irv Kopin ~~was~~ there. There were interesting things going on, but it hadn't yet quite made its mark with respect to psychiatry. I'll get back to this.

But first I want to talk about Elvin Semrad again, because this was the person whose blessings I really wanted. I remember going to Elvin to tell him that I had decided to go to NIMH, but not to the psychodynamic branch run by Lyman Wynne, but to the Laboratory of Clinical Sciences run by Seymour Kety, the biological branch. I talked to him about the research that I had been doing, tried to give him some sense of the excitement that I felt, and I said 'So, what do you think of the idea Dr Semrad?'. I really meant pat me on my head, tell me I'm a good boy and give me your blessings. He looked at me, rubbed his cheek as he did and stroked his belly a little. He just looked at me and said, 'Who am I to tell a man what to do with his life?'. I became furious. My sense was, you damn son of a bitch, I asked you a simple question and you talk to me like a patient. I was furious. I took that fury with me to NIMH, where I came to understand in the process of working through my own feelings, that, in part, the essence of the residency at Mass Mental Health Center, which was the most coveted psychiatric residency in the country and maybe even the world, was the experience of Elvin Semrad's getting inside of you. He used to say to us, 'See what I do, learn from me, take what you feel is useful to you and throw away the rest'. Essentially, he became an introject for all of us. And part of the maturing experience was working through my feelings about Elvin Semrad because, in doing so, I did become my own man at NIMH. I understood why Elvin didn't answer that question. He wanted me to get inside my guts and for me to sort it out for myself. And the secret audience of one, for whom the catecholamine hypothesis was written, was Elvin Semrad. It was always subtitled in my head 'See, you son of a bitch, this is why I decided to do what I'm doing'. But with a great deal of affection, because by the time I'd got down to NIMH to work these things out, I had even greater respect for Elvin Semrad.

When I came to NIMH, my assignment from Seymour Kety was to take his ward, which had been used to house patients with chronic schizophrenia, some of whom had been there for many years, maybe more than a decade, which he felt had run its course, and turn that unit into an active treatment and research setting for studying depressive disorders. Essentially, to do what I'd done at Mass Mental Health Center. Friends of mine who had preceded me warned me

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about taking on that assignment, Dick Shader, in particular, saying that previous associates had come down there and tried to do this but couldn't. Somehow, I was able to do it. Something a Mass Mental Health Center residency gave you was that you saw everything in psychiatry in those days at Mass Mental Health Center and you really felt capable of handling anything that clinical psychiatry threw at you. That included patients coming in, in the middle of the night, with a gun in their pocket. But, with a great deal of difficulty and sad feelings on many peoples' parts – discharging patients with chronic schizophrenia from their home of 10 years was not fun – I was able to turn the unit round. We found some of the patients could actually be discharged out of hospital and they didn't have to go back to whatever state hospital they'd been in.

I started the depression research unit, in part, to take advantage of the catecholamine assays that were then being developed in Irv Kopin's laboratory, particularly the assay of normetanephrine, the O-methylated metabolite of norepinephrine. One of the things that my notion about imipramine predicted was that, with the decrease in VMA, one should also see some increase in normetanephrine. And, indeed, the first clinical study we did was just that: to try to replicate the findings with imipramine in a slightly different design. Here, we had a pre-treatment placebo, a drug treatment period and a post-treatment placebo with frequent clinical ratings. The Hamilton Depression Rating Scale was routinely used then. There were urine collections in a semi-metabolic ward situation. We were looking at VMA and normetanephrine in these 24-hour urines. What we found again was that there was a decrease in VMA during the period of treatment with imipramine. These were hospitalized patients in a very active treatment setting, and we learned that we could take them off their drugs and maintain their clinical response by social milieu interactions. When they were taken off their drug, their clinical improvements were maintained, but VMA went right back up. Clearly, it was in some way a pharmacological effect of the drug, not a consequence of its clinical treatment effect. The VMA decrease occurred very quickly. Normetanephrine, on the other hand, increased gradually over time. The normetanephrine increase appeared to be linked to the time of the onset of the clinical antidepressant effect. That spurred on my excitement.

I had clearly been bitten with the research bug. I'd seen something about this drug in the research I'd done at the Mass Mental Health Center. I had done a great deal of reading in neuropharmacology. My first year at NIMH added to this. What was a shock to me was to find that neuropharmacology and clinical psychiatry, although just literally one corridor away from each other at NIMH, did not talk to each other. So, somehow, I found myself uniquely in a position with each of my feet planted in a different world – in the world of neuropharmacology and in the world of clinical psychiatry. My identification had always been as a psychiatrist, but the other psychiatrists at NIMH really weren't into this stuff. They weren't thinking about it. I was preaching to anybody who wanted to listen, I was just so filled with the excitement of this.

That was the context in which I wrote the catecholamine hypothesis paper, because I realized then that there were potentials for psychiatry to get into the age of biological research that were being opened by these drugs, that the psychiatrists weren't recognizing because they didn't know what the neuropharmacologists were doing. Conversely, the neuropharmacologists had no idea about psychiatry.

Do you recall actually writing the paper? Where did you do it, at home, at work, where?

Well, as I said, that paper began being written in my residency at Mass Mental Health Center with that first paper. The seeds had been sown; even more, the plants were sprouting. My style has always been to write at home. I'm basically a night person, somebody who would work late into the night. There was a time when I really didn't get started on work until 10:00 or 11:00 at night. I still maintain those hours, but when I was younger and unmarried I was even on a more free-running schedule. The paper was written at home, probably in my first year at NIMH, that would have been 1963/64. As part of my sense that I had seen something that everybody should know about, I'd pass drafts of that paper out freely to anybody who was willing to read it. I'd learned from Gerry Klerman about sending out drafts, so I sent out drafts to people like Dave Hamburg and various others outside NIMH. Of course, Seymour Kety saw drafts; Jack Durell, who was my immediate mentor and senior psychiatrist on the unit, saw them. I gave drafts to Biff Bunney and John Davis and, as you'll see in their paper, they acknowledge this in the footnote.

As it turned out, the two papers came out close to the same time. It has to have been a tricky one to negotiate between all of you then.

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Let me just say that you'll see in their paper there is a credit line that thanks Joseph Schildkraut and Jack Durell for sharing with us their hypotheses and ideas. Anyway, ~~that~~ paper was circulating in house at the NIMH for close to a year as I was working on it. There was one major problem that I had with it. You'll note that the paper is entitled 'The catecholamine hypothesis of affective disorders: a review of supporting evidence'. I had done a very thorough review and a great deal of thinking about this and I was convinced, in terms of what I had read and was reading between the lines, that there was a real story here and that it could be put together in a logical and compelling way and I thought it could start the biological revolution in psychiatry. I also knew that I could kill it. Because there was so much in the literature, much of it that wasn't very good research, much of it that was controversial, much of it that could have been explained away, when I wrote the critical review that I originally did, I found myself essentially losing my story, because there were enough problems, negatives, controversial findings.

What were these?

One of them was that the neuropharmacological effects on catecholamines that occur with imipramine occur in animals after a single injection. Within half an

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hour you can see these. In patients, you very rapidly start seeing changes in VMA, but clinical effects take 3 weeks. That was clearly one of the things that could not be explained at that time. Then there was the question of cocaine, a drug that blocked uptake of norepinephrine and dopamine, but it apparently was not an antidepressant. Clearly, it did some things for mood – Freud was no fool. He took it for a good reason and wanted to give it to his fiancée to see her red rosy cheeks, but it did not seem to be an effective antidepressant. There was much that was controversial in the animal literature on what these drugs were doing. The field of neuropharmacology was a field that was discovering itself. It was first discovering how to do studies, how to do research, and there was a great deal in the literature that was very muddy.

I was anguishing over this because I'm a kind of anguishing guy. It's hard for me not to talk to both sides of an issue. I remember that Richard Green, a clinical associate who was working on the unit, looked at me one day and said, 'Look, you've got a story there'. He said 'You're going to kill it if you put in all of this stuff that your superego tells you you have to'. He said, 'Change your damn title – so it's not a critical review, it's a review of supporting evidence'. And I suddenly saw the light. That's what I wrote, a review of supporting evidence. I felt that this was a way that I was going to be able to bring the world of neuropharmacology and the world of clinical psychiatry together in a productive way, by giving them a paper that both sides might read and understand and be able to appreciate. I felt fairly confident that psychiatry was really at a watershed moment. And I know in your book *The Antidepressant Era* you see these things.

Oh, it was the critical paper, clearly.

But it was written with that purpose. I mean, I very much knew the potential of this paper and I knew that I was writing about more than catecholamines and depression. I was really writing about biological studies in psychiatry. That paper put forth the notion of what I subsequently came to call the 'pharmacological bridge'. The notion that pharmacology can become a bridge, linking neuroscience and clinical psychiatry. That was one of the things that I think that paper captured for the field and that was what these early studies had captured for me.

Why did you choose to send it to The American Journal of Psychiatry?

Well, that was, I thought, a very important venue for it. It is the journal that is most commonly read in psychiatry. It would have the widest distribution, and it would be communicating to psychiatrists. Just to jump ahead, the paper was published in 1965 in *The American Journal of Psychiatry*. By that time, I'd extended my stay at NIMH from the 2 years as a clinical associate doing clinical research to another 2 years working in Irv Kopin's laboratory as part of Seymour Kety's group. I wanted to get first-hand lab bench experience in catecholamine research because by that time I'd seen that this was going to be an important part of my future. I was working with my colleague and collaborator Saul

Schanberg – he and I worked together in Irv Kopin's laboratory, doing analogue studies in rat brain to what I'd done clinically, picking up on the kind of work that Jacques Glowinski had been doing in Julie Axelrod's lab so brilliantly at the same time that I was doing some of my clinical research.

I was working with Saul one day when there was a knock on the door and a towering figure came in and said 'Is there somebody named Schildkraut here?'. I came from my laboratory bench and said, 'I'm Schildkraut', and the person introduced himself. He said 'I'm Paul MacLean. I've just seen the paper that you published in *The American Journal of Psychiatry*. Young man, you don't know what you've done to yourself'. I figured the worst, because, you know, this hypothesis was a potentially controversial one, with not nearly enough data for me to feel confident about it. I'd made my own private deal that if I embarrassed myself scientifically, this would be the last paper that I would ever write. I'd accept it, go back to Boston and be a psychotherapist and a psychoanalyst. But MacLean went on, 'I have a prediction to make that, just as I found myself, having written about the limbic system, having to spend the rest of my career talking about it, you're going to spend the rest of your career defending this paper, because it is going to make a mark on the field. There will be many who will want to tear it apart. Good luck to you, young man, you've got a rough road ahead'. And he left.

That was very dramatic.

It was very dramatic, very booming and, needless to say, very flattering.

And also fairly prophetic?

Totally prophetic. But at that point I saw it as very flattering. I was certainly delighted to be in his company and to be put there by him. But that paper did have an impact on the field. From another side, too, because I remember at some time giving a seminar at NIMH, probably after one or two other things had been published. I was giving this seminar to a group of clinical psychiatrists, but a group of neuropharmacologists also showed up from NIMH and also from the Heart Institute. After I'd gone through this and talked about both the clinical side of my research and some of the basic studies we'd been doing showing that, in animal brain, we could demonstrate the shift in metabolism of norepinephrine produced by the tricyclic antidepressants with a decrease in deamination and increase in O-methylation, just as I had intuited from the clinical work, Sidney Udenfriend got up. He was noted for being very bright and sharp tongued and I was wondering what kind of criticism was going to be levelled at me. He said, 'Young man, this is fascinating. Why the hell haven't you published this stuff?'. I said that I had published it. He said 'Where? I said, Well, 'among other places, *The American Journal of Psychiatry*'. He looked at me and said, 'You don't expect me to read clinical journals, do you?'. So, I learned another lesson there, that it was important to present these works, at least for a time, in different forums. Actually, the catecholamine hypothesis paper was subsequently amplified and also written as an article in collaboration with Seymour Kety.

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Which went to Science.

Which went to *Science*. Seymour was invited to do a review of this. He was familiar with my work and asked me if I would collaborate with him, which was always a pleasure and a delight. The *Science* paper was the way it was read by neuropharmacologists. Clinical psychiatrists didn't read *Science* in those days. So it was published in the two forums. The catecholamine hypothesis paper is the most frequently cited paper ever published in *The American Journal of Psychiatry*, by a large enough margin that the folks who put out *Current Contents* have told us that they don't think there is any danger of it ever being surpassed.

I learned this in 1995, when the *Journal of Neuropsychiatry and Clinical Neurosciences* had selected it as one of their so-called 'classic articles in neuropsychiatry'. They began this new series in 1995 and in the first year they selected four papers that the editorial board felt had 'a significant impact on the intellectual history of neuropsychiatry' and 'were most influential in shaping their own professional development'. That's a good way to make you feel old. I was in the company of such people as James Papez, G. Moruzzi and H.W. Magoun, and Eliot Slater. I think I was the only one of those authors who was still alive in 1995.

Udenfriend was from the Brodie lab., which was very 5HT oriented in its thinking. How did they take this norepinephrine line when Brodie had put in years trying to sell 5HT?

Oh, yes, there was a kind of culture clash, if you will, competition between the Brodie lab. and the Kety lab. and, as you know, Julie Axelrod came from the Brodie lab. to the Kety lab. Kety was someone who let one do what one wanted, he just gave good scientists support and let them run with it. But, actually, the serotonin versus norepinephrine dichotomy was not a major issue for me. In the catecholamine hypothesis paper, I ended by saying that clearly this was a highly oversimplified reductionistic heuristic hypothesis and that the ultimate understanding of depressive disorders would have to take in many other factors and many other biological substances, including acetylcholine, serotonin, hormones, ionic changes – essentially what I said was, it's going to have to take in the whole biology of the brain, because depression is clearly a disorder of brain functioning.

A little while later, I used to refer to it as a neuroendocrinometabolic disorder. I never thought that depression was solely a catecholamine disorder. Knowing what I did about the interconnections between the serotonergic and the noradrenergic systems, I couldn't conceive of a way you could affect one without affecting the other. Nor did I have the notion that somehow norepinephrine just increased mood by turning up a mood amplifier. There were lots of things going on inside the neurones that we didn't even dream of in those days, but we knew they had to be of importance in mood regulation.

What you seem to be saying is that you didn't see it as a norepinephrine lesion paper – it was more the agents that are helpful act on the norepinephrine system. Would that be fair?

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Well, yes. It was really saying that one can put together a coherent story on the basis of what we then knew about a number of neuropharmacological agents that had clinical effects on mood and pharmacological effects on the biogenic amines, e.g. norepinephrine and serotonin. For example, reserpine, which could produce depression, depleted norepinephrine and serotonin; whereas the MAOI antidepressants relieved depression and increased levels of these monoamines, and imipramine, which also relieved depression, blocked the inactivation of these monoamines by inhibiting neuronal reuptake. Moreover, desipramine, which apparently didn't block serotonin reuptake but did block norepinephrine reuptake, was as effective an antidepressant drug as imipramine.

I saw the catecholamine hypothesis paper as having broader implications than the catecholamines alone. It was really talking about how these drugs were offering for the first time a way for us to do biochemical and biological research on depressive disorders that was hypothesis driven. The drugs could suggest hypotheses that we could start testing out in various ways.

Could I just push you a bit further on that point, in that it didn't only give people working within psychiatry a new language, it also gave the public a whole new language. Previously, they'd had this idea that you go along to see a psychiatrist and he or she will talk to you about your sex life; now they'll talk about lowered levels of some monoamine and this was a language that resonated with the public. Would you agree?

Yes. Part of what I was doing, of course, in treating patients was also educating them. In those days I would tell anybody who would listen. Who would be a better audience for this than people suffering from depression and their families? But I always found myself cringing when patients would say they didn't have a psychiatric disorder but a biochemical disorder or a biochemical disorder in the brain or a biochemical deficiency in the brain. Clearly, the pendulum has in many ways swung too far to the other side. But, yes, it was a way of talking about psychiatric disorders in an entirely new language and new dimension, a way for the public to talk about it, a way for psychiatrists to think about it. And that didn't mean throwing out psychodynamic psychiatry and all of the other aspects of psychiatry that are so important.

At one point, things were all psychoanalytic and psychodynamic and then this huge biological and pharmacological revolution occurred and there was a swing towards the biology of the psychiatric disorders and the use of drugs.

The catecholamine hypothesis of affective disorders has had a very beneficial effect in helping to decrease the stigma associated with psychiatric disorders, because they are now seen as they should be, as complex biopsychosocial, biomedical disorders, and patients are able to recognize that when they're depressed they have a disorder that reflects altered brain functioning, which somehow seems to be far more palatable than a disorder that is seen to reflect deficiencies in oneself or one's parenting or upbringing, and that has been all to the good. That has taken some of the stigma out of psychiatry. For somebody who was trained in psychodynamic psychiatry and who firmly believes in it, I don't think that way of thinking in itself necessarily brings any stigma.

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But so far as my history goes, I never gave up on my interest in psychoanalysis. In fact, I began my personal psychoanalysis in Boston during my residency. Once I saw that I was going to stay at NIMH for 4 years instead of 2, I resumed my analysis in the Washington area and it was actually in the course of my analysis that I made the decision that I was not going to pursue psychoanalytic training. That decision came out of my having to recognize that my day was finite, that I only had 24 hours in the day and that any time I took for psychoanalytic training I'd be taking away from the area of research that I was so committed to. It wasn't the way it was as a kid, where you don't have to give up something to take on something else, you just keep adding. I had to make a hard decision. Was I going to take time away from my research in neuropsychopharmacology? I had the good fortune of riding the crest of the kind of wave that comes along rarely – once in a lifetime. I couldn't let go of it. It was at that point that I decided that I would have to put the psychoanalytic training on the shelf, at least for this lifetime.

*A few years later, the NIMH then set up the collaborative programme to research mood disorders. This is the one that began with the Williamsburg Conference. That seems to have been a fairly important meeting – in a sense, DSM-III came out of it. That's the point at which people like Klerman met up with people from St Louis and things began to ~~take~~ **ROLL***

I was at it. The facts are a little different. I don't think Gerry Klerman was included at the beginning of that endeavour, in fact I think he was excluded. I was excluded too, although I'd been part of the conference. There was the sense of an in-group trying to put together a programme of research that was going to include nosology and epidemiology, some genetics and a biochemical component. This was largely, but not exclusively, orchestrated by Eli Robins and the folks from St Louis, to Eli's great credit. It was he who restarted the interest in descriptive psychiatry, going back to Kraepelin and purging from the psychiatric nosology the vague psychoanalytically derived language that made diagnoses so ambiguous, for example where psychotic depression could be defined in five different ways, as I found out as a resident. But I think that the programme that was set up there had the kind of problems that all of these very large mega programmes have.

This was in the late 1960s, when they aimed at setting up a 10–12-year programme, as it turned out. On the biological side, it was largely research that was based on 1967/8 science. You can't set up a project in a new field that's going to run for 10 years and be relevant at the end of that 10 years. They got themselves locked into this highly integrated system where they couldn't change assays, they couldn't change designs – it was just totally locked in. There was another problem. At one point, our laboratory and one of the 'collaborating laboratories,' a well known lab, were going to be doing a series of experiments. We had to standardize assays and what we found out during this process, where everything was done on a blind basis, was that our laboratory showed a very high correlation with the external reference laboratory, whereas the 'collaborating laboratory' did not. So, that's the problem they got into because they

were running assays in a long-term study without having the kinds of standardization required to maintain assays over time.

We were fortunate in that Paul Orsulak, the biochemist in charge of our laboratory, had ties to clinical pathology and brought into our system the quality control procedures that Brad Copland had introduced into clinical chemistry. Every assay had its own internal set of controls and standards that were run from assay to assay and if the standards from an assay didn't match, the assay was just thrown out.

I'm sure as you put the issues, it's quite right that they got locked in to trying to measure things that, clearly, by the time they had the results, weren't going to be the answer and that was unfortunate. But the point I was actually trying to hint at, and I'm not sure if you'd buy it, is this. The occasion to get the conference together was the catecholamine hypothesis. They were going to try to test it. The efforts to do that failed, but what came out of that was the research diagnostic criteria (RDC), which led on to DSM-III. So, in a sense, without the catecholamine hypothesis, maybe we wouldn't have had DSM-III. What do you think?

Well, that may be a little bit overstated. I'll thank you for the compliment, although I don't think that DSM-III or DSM-IV is the answer either. Now, one of the problems I've always had with the DSM diagnostic system is that it's a diagnostic system that was pulled together to achieve reliability in diagnosis, so that a diagnosis could be reliably made from one clinician to another clinician. They opted for reliability and they skirted around issues of validity. They came up with many things they could define reliably, but not necessarily things that always made a great deal of clinical sense. A lot of idiosyncrasies got built in and it certainly didn't necessarily make a hell of a lot of biological sense.

For example, the category major depressive disorder, which is one of the hallmarks of DSM-III, is such a heterogeneous hodgepodge that really the diagnosis itself almost tells you nothing. As the DSM-III and its various revisions were formulated, psychiatry was at a stage where some of the prototypic disorders were even then no longer being seen by psychiatrists. Take our own research on catecholamines and depression, which extended from the time I got back to the Mass Mental Health Center in 1967 till very recently. Early on, I was able, with a great deal of screening, to get prototypic patients. By the time we got into the latter part of the 1970s, for example, it was impossible to find a patient with a *bona fide* uncomplicated, bipolar, manic-depressive disorder, whom you could study under drug-free conditions. Why was that the case? Well, it's obvious. For a patient to have this diagnosis he or she had to have had a manic episode previously and a depressive episode, and those patients were on lithium. No investigator could justifiably take such a patient off lithium for the purposes of a study. So, virtually all of the studies that we did on patients with prototypic bipolar manic-depressive disorders under drug-free conditions were done in the late 1960s and early 1970s. And we found that that group of bipolar depressives had measures of catecholamine output and metabolism that were different from those in all other types of depressive disorders. That's a finding that was replicated very early on by other groups, but as time passed by it

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became increasingly hard to replicate these findings because you couldn't get those kinds of patients anymore.

We put out a series of papers called 'Towards a biochemical classification of depressive disorders'. (TBCDD). It stopped at X. And in number X, which is essentially a large-scale replication of a previously derived discriminant function equation that we had developed empirically based on catecholamines and their metabolites, we were able to show that the prototypic manic-depressive (bipolar I) depressions, without all of the character pathology that you see in so many patients with bipolar disorders, had very distinctive scores on this equation, reflecting low catecholamine output. Their scores were significantly different from all the other subgroups of depressions. Since so many investigators had been trying to study catecholamine metabolism in bipolar II depression, which I've always felt was quite a different disorder from bipolar I, in our paper 10th we specifically looked at the subgroup of bipolar II depressions. And we found that patients with bipolar II depression had catecholamine output that was not low like it was in bipolar I depressions. So, basically, other investigators were trying to do these studies of catecholamine output and metabolism in bipolar disorders at the time when they were getting a drift in the kind of patients that could be studied.

TBCDD: X

I can see that.

We changed our research over time because we had to study the kinds of patients that were available. The other way to go, and I've encouraged young investigators to do this, is to start looking for your patients in primary care settings. If you want to see fresh, untreated depressed patients, you've got to link up with primary care physicians, because they're the ones who are giving the first trials of antidepressant drugs. And the kinds of patients that we studied in our early studies are the ones that get better on fairly low-dose treatments and fairly promptly. They don't consult psychiatrists anymore; we never see them. A psychiatrist starts seeing depressions with secondary complications. Academic psychiatrists see depressions with tertiary complications. That limits the kind of research you can do in an academic institution if you're getting your cohort of patients there.

So, you were saying that out of Williamsburg came the DSM classification. As I say, I think it was important. It was important for political reasons, important for reasons of compensation in terms of health insurance, important in part so that investigators can at least talk to each other in a reliable way. But, I think, unfortunately, by putting aside the issue of validity, what it did was complicate life for the research psychiatrist and, I think, to a certain extent it might also have set back psychiatric thinking. Diagnostic entities, psychiatric illnesses became what DSM told you they were.

Actually, I tried to collaborate with Gerry Klerman when he came back to Boston after a period of being away. He got himself back into the collaborative depression study and eventually was largely running the diagnostic side of it. He and I used to engage in pitched battles over this very issue when we tried to

collaborate on research while he was at Mass General and I was at Mass Mental Health Center. He was focusing on reliability and I kept saying I'd rather be somewhat unreliable but picking cases that I feel have a biological validity to them.

In our research at the Massachusetts Mental Health Center, we evolved our own system for classifying depressive disorders, very different from the DSM system. Ours was not a forced choice system. If you're a clinician and you're treating patients, you've got to make a diagnosis that's going to bear on the treatment of the patient, so you've got to have a forced choice system. But, if you're a researcher, you have the luxury of designating patients as unclassifiable. The kind of system that we had meant that, first, the patient had to be depressed and meet a criterion score on the Hamilton Depression Rating Scale. Next, we excluded patients who had diagnoses of schizophrenia. Next, we identified patients with what we called 'schizophrenia-related depression'. These were patients who did not qualify for a diagnosis of schizophrenia, they didn't have schizophrenia, but they had characteristics of what I call chronic asocial, eccentric, bizarre behaviour. For example, the person who has never been psychotic but has led a rather isolated life, often not working, maybe having as their only friend a pet bird or a cat, someone who, at the age of 28, 30, 32, socializes only with parents, and then becomes depressed. The person has depression, but clearly also there is something else underlying it. Then psychotic depressions were identified in patients who did not have schizophrenia, and we called them 'schizoaffective'. We then identified the bipolar manic-depressive depressions.

This left a large unipolar residue. From that group we would try to extract the patients with unipolar endogenous depressions based on certain key criteria – the notion that we had of endogenous depressions was much more the European notion, a notion that might be called by some vital depressions, because you didn't have to have depressed mood. It was based on having a loss of vitality, anergia, anhedonia and psychic retardation. Another was that the depression did not readily change with ongoing interpersonal interactions or environmental events. It was a kind of a fixed-stuck disorder. Then we had another group called unipolar chronic characterological depressions. These were patients who had depressions with much more in the way of anxiety, self-pity, weeping and histrionics. A colleague of mine called them the 'weepy whiny wailey depressions', to contrast with the endogenous grouping that I still call the 'running out of gas depressions'.

Finally came a large grouping of unclassifiable depressions. Patients usually got in to this category because there was a hint of bipolarity but we couldn't make a diagnosis of mania or hypomania, or there was a whiff of a schizophrenia-related disorder but we couldn't make a diagnosis of a schizophrenia-related condition. Early on, when we were using this unclassifiable category, we might have had 5% or 10% of patients referred to us who wound up in it. But, as we were using this system into the 1970s and 1980s, over 50% were in this category, because there was a change in the kinds of patients that were referred to university settings.

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In a sense, pre-DSM-III, you were the darling of biological psychiatry, now you're moving in the opposite direction to DSM-III, you're going for what they're not going for, you're going for validity. When did you find yourself beginning to diverge from the mainstream?

Well, what mainstream? I always made very clear that there are differences in what diagnostic systems have to do – clinical diagnosis is for clinical purposes and treatment; research diagnosis may be to develop homogeneous groups. In teaching about diagnosis, I've always asked 'a diagnostic system to do what?'. It can't, in our present state of ignorance, do everything.

Just to recapitulate then, you produced the hypothesis that's turned the whole field around. In trying to see if it's actually true or not, your colleagues set up a process that, at least in part, contributed to DSM-III, but once DSM-III is actually produced, you've got a set of criteria, at least for depression, that really aren't friendly to the kind of research that you've been doing up till then.

Well, as I've said, diagnostic systems have to be developed for specific purposes. We have to develop diagnostic systems for specific tasks. And a diagnostic system developed for clinical purposes such as DSM essentially has to be a forced choice system, because clinicians in any field have to make their best-guess diagnosis in order to start treatment or develop a plan for treatment. You can't let the patient arrive in pain and say, 'I know there's something going on in your belly, but I don't know what it is, you're unclassifiable. Come back in a month and maybe we'll know a little better then'. It's the same in psychiatry. But for a research system you have the luxury of labelling patients unclassifiable.

Except an awful lot of the other people doing biological research were quite happy to run with the DSM system.

You see, the system we developed actually was developed before the RDC and before DSM. It was a system that was developed out of the heads of people experienced with depressive disorders, a group that I led. The system we developed was called the Clinical Inventory for the Diagnosis and Classification of Affective Disorders, affectionately known as CIDCAD. But this was a system that was developed for very specific purposes, *i.e.* to identify homogeneous subgroups of depressions.

I think for some, the issue of this system's reliability was in question because, quite frankly, we were too impatient and we were not prepared to do the kind of large-scale epidemiological reliability studies that you need to have for a diagnostic system that has widespread use. But, for our purposes, we knew we were internally reliable and we had a sense of a validity that was in part borne out by our biochemical measures. We were getting some kind of meaningful differences in these groupings. We tried to relate it to the RDC and, in fact, I think in the 10th paper, we show how patients break out on both the RDC and the CIDCAD, where we had enough data to do both of these. But the important thing about the CIDCAD was that it had an unclassifiable category and that was to keep our various diagnostic categories pure, because, for biological studies like ours, you cannot afford to have false-positive classifications.

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So, that's how that diagnostic system evolved. And what we found was that unipolar endogenous depressions were widely heterogeneous with respect to catecholamine metabolism. For example, a measure like MHPG was spread across a wider range in unipolar endogenous depressions than in control subjects. Values in patients with unipolar endogenous depressions were both lower and higher than in control subjects. The ones with very low values, we've often speculated, were really patients who had a bipolar manic-depressive diathesis who'd not yet had their first bipolar manic episode.

The ones with very high values, we speculated, might have receptor subsensitivity depressions. If there's not enough norepinephrine to be able to meet the needs of a subsensitive postsynaptic receptor, you can have a high output disorder in terms of what comes out of the presynaptic neurone. Even back in the catecholamine hypothesis paper, I discussed the notion that one of the ways of having a functional deficiency of catecholamines, and I kept using the term 'functional deficiency' because I knew it didn't necessarily mean you had to have absolutely low levels, was to have a subsensitive receptor so that, even with a high output, there could still be low functional activity. These were notions that were being thought about back in the mid-1960s and, as we went on in our studies of unipolar depressions, we did see this marked heterogeneity of norepinephrine output.

I might just say that a principal collaborator in the TBCDD series of papers was Alan Schatzberg, with both Jackie Samson and John Mooney playing very critical and long-standing roles – without them that series of papers would never have been done. I was first author of the first two papers in this series, but after that other people were the first authors and did a lot of the lead work. But that series of papers demonstrated that there were meaningful biochemical differences among subgroups of depressive disorders that could be defined clinically, albeit ~~imprecisely~~, and at the expense of having a large grouping of patients that remained unclassifiable. Some interesting data came out of the unclassifiable depressions as such, but not by mixing them up with the other diagnostic categories.

You mentioned earlier something about my being the darling of biological psychiatry. I found that comment a bit amusing because, though I know what you mean, that was never the way it was. It was rather as Paul MacLean told me it was going to be. From the outset, I was the whipping boy of biological psychiatry, at least with respect to the catecholamine hypothesis. A bit of that came out at the Williamsburg Conference. At some meeting or other, Eli Robins and I, about 25 years ago, wagered a nickel on this. I told him that all I ever claimed was that abnormalities in catecholamine metabolism were part of the pathophysiology of depression. I never thought it was a matter of aetiology, because you can't. But I was willing to bet him a nickel that, when the final word was written, catecholamines would be part of the pathophysiology. Of course, that's not fully resolved and Eli's gone to a place where I can't pay him or collect from him.

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But you still think there's a chance you're going to be collecting?

Yes. But I think that hypothesis was only a starting point for research. However, I'm not at all convinced that the brain that we have in here ~~[pointing to his head]~~ is smart enough to figure out the brain we have in here ~~[Again pointing to his head]~~. Hopefully, research will lead to a better capacity to diagnose and treat these disorders. But I speak as a psychiatrist not as a neuroscientist, or a neuropharmacologist. My identification always was as a psychiatrist. And I'm not sure that, for all that we're clearly going to be accomplishing with all the new tools and techniques, brain imaging and molecular neurobiology, we're ever going to be able to understand fully the function of the brain in that satisfying way of understanding like when one finishes a mathematical proof with QED. I've said that to medical students for years. I know I'm not going to be around when that answer is finally written. I'm not even sure that my children's children will be around, but it's an exciting venture. And I must say that the excitement that I felt in developing some of the insight I first had as a resident at Mass Mental Health Center very early on in my career has been most gratifying. I look back with a sense of the excitement that I felt in sometimes thinking to myself that maybe I was contributing at that point to a paradigm shift in psychiatry. I also thought that maybe I was just going to make a damn fool of myself and ruin my academic career.

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invited me 5 years in a row to give a guest lecture. The fact of similarities between the Slav languages was helpful. I even got to the point of knowing how to discuss issues in Serbo-Croatian.

I had a surprising experience 2 years ago in Israel, where, at a meeting in Beersheba, I gave my paper and then afterwards, I was asked from the floor if it would be possible for me to have the discussion in Russian. So many Russian-speaking Jews had emigrated to Israel that many of their discussions are now in Russian. Because of my experiences trying to sell our drugs in Russia, I was able to do this, and we had the discussion in Russian. It's funny the way history turns, isn't it? In many ways I prefer to look to the future, its only you who pulls me back to the past. But I am sure that, as they say, if you do not know the history, you are condemned to repeat it. On the other hand, you cannot trap people with the history.

I agree completely. You have to use history to show people ways to move forward, not to stop them doing things. My worry is that when we forget history we also forget about other developmental paths that we may need again in the future.

Yes. I still have the feeling that there are many more surprises to come in the future.

I expect great progress, not only because of molecular biology, genetics and genomics, but also due to a better integration of neurosciences with endocrinology and immunology. We have only one regulatory system and, historically, it is only due to different methods of study that there was a separation of neurophysiology, psychology, endocrinology and immunology. We have seen changes in immune state in anxiety and used levamisol to improve immune functions in pharmaco-resistant depression and in those patients in whom the immune functions improved, the depression was alleviated. We should study the mechanisms of binding neurotransmitters and drugs to receptors together with immunologists and allergologists. The problem of how to explain the origin of antibodies to antigens may shed light on the problem of how to explain the existence of binding sites to diazepam or imipramine. These drugs may not only act on immunity, they may also act differently according to the current immune functioning of the patient.

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