

THE CATECHOLAMINE HYPOTHESIS

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Could we begin with where you were born and how come 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 came to decide 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 these courses were. I'd hoped to have a fabled professor, Robert White, for the course on the abnormal personality. He'd written a text book 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 psychological 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 Centre, 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 around a patient with schizophrenia, who I saw in my fourth year as a medical student. In those days Mass Mental Health Centre 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 Centre, 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 with 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 where I rated University of California Hospital as number one over the Harvard Teaching Hospitals, the Dean of students called me into his office. He 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 jeopardising 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.

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 programs let you know a little earlier. One of the programs I was seriously considering if I didn't get into Mass Mental Health Centre was the program 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 Centre. 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 Centre on schedule. There I began my first year residency in psychiatry in what was Jack Ewalt's first self 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, there 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 50s at the time that Harry Solomon was then Superintendent of Mass Mental Health Centre and Professor and Chairman at Harvard. Harvard had a 65 year 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 succeeded Harry Solomon as the Head of the Department of Psychiatry at Harvard and Superintendent at Mass Mental Health Centre. 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 an instant psychoanalysis and a quick processing through the Institute. So he became a psychoanalyst by the time that I'd arrived at Mass Mental Health Centre for my residency.

But as you mentioned earlier, the key and revered figure at Mass Mental Health Centre 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 Centre. 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 did 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 carryover from these interviews. The patient might be stirred up in 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 have the patient talk beyond psychosis.

I'd gone to Mass Mental Health Centre 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 Centre 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 Centre at the very time that the antidepressant drugs were becoming available. This was 1960. And as you know Mass Mental Health Centre 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 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 Centre that if you resorted to a psychoactive drug with one of your patients, be it an antidepressant or what were then termed the major tranquillisers 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 hospitalised 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 Centre. We'd see the phenomenon of the agitated depressed patient, 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 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 electro convulsive therapy 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 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 main stream.

Well yes and no. Because Mass Mental Health Centre 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 Centre. 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 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 electro-convulsive treatments 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 gotten, I went around to talk to my various supervisors asking them to define for me this term "psychotic depression". I talked to about 5 supervisors and got 5 different definitions. One was the expected definition which we use today which was a depressed patient who showed manifestations of psychosis as characterised 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 the patient 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 5 different supervisors.

But eventually when treating my hospitalised 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. That was largely the antidepressant armamentarium. Doses were very different in those days. Imipramine was used very, very cautiously. Only hospitalised patients could get imipramine, it was considered so scary and so unusual. Fifty or 75mgs per day was a standard dose. It was considered heroic to push up to 100mgs 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 US 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 up 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 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 kind of 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 Centre, 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 gotten themselves a grant to set up a depression research and treatment unit, that 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 Dopa to depressed patients.

Literally we set up this depression research unit in a very small space at Mass Mental Health Centre 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 5 or 6 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 Centre continuously since 1967 when I returned from post doctoral training at the 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 Centre, and had been off working with Jonathan Cole, at the NIMH Psychopharmacology Service Centre, 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 included 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 d,l-dopa not l-dopa because it was too expensive, but dl-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 monoamine-oxidase inhibitor, 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 randomised 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 monoamine-oxidase inhibitor. We weren't exactly sure what it was but it was not a monoamine-oxidase inhibitor. 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 hypothesised would occur with phenelzine was due to its being a monoamine-oxidase inhibitor 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 Centre. 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 characterological type problems. No hints of what the English psychiatrists would call neuroticism. They were raising 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 who 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 now. 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 anymore 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 monoamine-oxidase inhibitor. 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 6 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 avidly delve 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 monoamine-oxidase inhibitor, was likely 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 actually 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 accumulated only in the past ten 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.

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 way 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 Centre. 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 to those of us who would prefer to be doing science than doing war.

Somewhere during my residency at Mass Mental Health Centre, having gotten 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, 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, had me come down 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 Centre as well. Milt Greenblatt, of course, thought this was a great move. I had aspirations of coming back to spending my career in academic psychiatry at Harvard at Mass Mental Health Centre 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 as it was part of the public service, part of the government and you couldn't expect good research to be done by the government. This has got to be done by places like Harvard and Yale. Had this all gone at this stage?

It was in a transition. 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 Centre, 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. And 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. And it was always sub-titled 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 gotten 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, that 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 Centre. Friends of mine who had preceded me, warned me 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 Centre residency gave you was that you saw everything in psychiatry in those days at Mass Mental Health Centre and you really felt capable 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 homes of 10 years was not fun, I was able to turn the unit round. Some of the patients we found 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 hospitalised patients in a very active treatment milieu 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, we found 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 Centre. 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 realised 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 recognising 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 Centre 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 to work until 10 or 11 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 63/64. 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 of NIMH. Of course Seymour Kety saw drafts, Jack Durell who was my immediate mentor and senior psychiatrist on the unit saw it. 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.

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 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 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. To just 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 two years as a Clinical Associate doing Clinical Research to another two 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 says "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, I predict that 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 but 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 written also as an article in collaboration with Seymour Kety.

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.

Wow.

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. Moruzzii 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 neuristic 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 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?

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, eg. norepinephrine and serotonin. For example, reserpine, which could produce depression depleted norepinephrine and serotonin; whereas the monoamine oxidase inhibitor 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 wee 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 one 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 recognise 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.

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 recognise 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 program to research mood disorders. This is the one that began with the Williamsburg conference. That because 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 and all met up with people from St Louis and things began to role..

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 program 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 5 different ways as I found out as a resident. But I think that the program that was set up there had the kind of problems that all of these very large mega programs have.

This was in the late 60s, where they aimed at setting up a 10/12 year program as it turned out. On the biological side it was largely research that was based on 1967 / 68 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 standardise 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 standardisation 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 this. The efforts to do that failed but what came out of that was the RDC which led on to DSM III. So in a sense without the catecholamine hypothesis, maybe we wouldn't have had DSMIII. 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 DSMIII or DSMIV 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 done from one clinician to another clinician. They opted for a 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 Centre 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 70s 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 they'd had to have a manic episode previously and a depressive episode and those patients were on Lithium. No investigator could justifiably take such a patient off of 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 60s and early 70s. 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 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, in paper X 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.

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 know you were saying that out of Williamsburg came the DSM Classification. As I say, I think 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 Gerry 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 Centre. 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.

We evolved our own system in our research at the Massachusetts Mental Health Centre, 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 was one that at the first cut 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, socialises only with parents, and then becomes depressed. The person has depression but clearly also there is something else underlying. The next cut identified psychotic depressions in patients that did not have schizophrenia and we called them "schizoaffective". At the next cut 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, psychic retardation were hallmarks. 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 that category. But as we were using this system into the 70s and 80s over 50% were in this category, because there was a change in the kinds of patients that were referred to university settings.

In a sense pre DSM-III, you're 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 its 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, ie 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 TBCD. X 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 can not afford to have false positive classifications.

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 sub-sensitivity 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 sub-sensitive 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 have never 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 sub-groups 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 on something about my being the darling of biological psychiatry. I found that comment a little 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 little 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 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.

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 (pointing to the head) that we have in here is smart enough to figure out the brain we have in here. (Again pointing to the 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, I'm not sure we're ever going to be able to fully understand the function of the brain in that satisfying way of understanding like one does 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'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 Centre 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.