

## ROSS BALDESSARINI

### **Can we begin with where you were born and when?**

Yes I was born in 1937 in a small town in Western Massachusetts called North Adams.

### **During school did you have any hunch that you'd ultimately go into medicine and on to psychiatry?**

I had a pretty good idea by the time I was in High School I wanted to do something scientific but exactly what was not clear. I was more interested in chemistry and physics in those days. That shifted a little bit toward the end of college.

### **What were the influences on you at the time?**

I had a very little understanding of why or where the idea of doing something scientific came from. I ended up in High School though doing a number of summer jobs in industrial laboratories. I spent one summer working on designing and testing memory components for of all things juke boxes. The technology is actually the same kind of memory devices they were using in computers at that time - this was in the early 50s. I liked that very much and then I had a chance after that to begin working in industrial chemistry labs. For a while I thought I might want to become an industrial organic chemist. I did that for several years from the end of High School through college. In fact one summer very memorably I lived through an industrial merger and saw 50% of the scientists out on the street without any warning from one day to the next. That left an indelible mark. My conclusion was there must be a more secure way to make a living. Boy did I make a mistake. Academic medicine has been anything but secure. But that was my thinking at the time.

### **I guess at that point in time it was more secure.**

Yes certainly through the 60s and early 70s things were a little bit more predictable. If you worked hard and got into a decent department you could usually stick with them. Now it's not so secure.

### **No it's clearly changed. After you moved into medicine, why did you move back toward psychiatry? This has to have looked very far from chemistry..**

Well I started in medical school not really knowing what medical school was all about. I had very little family experience with higher education. Nobody had gone to graduate school and nobody was in a learned profession. To me medical school was a surprise because I thought it was going to be an extension of senior year in college which was mostly about having tea in professors houses and thinking great thoughts and doing that kind of thing. I found that medical school was really a lot more like trade school. And you had to kind of get into step, learn what you were told to learn and not ask too many questions. Be thoughtful but not provocative. That was difficult. It was not a mould that I easily fitted into.

I was on the verge of heading towards a PhD in chemistry as an alternative. The thing that turned me around was that I was taking a physiology course

with Vernon Mountcastle at John's Hopkins at the time. He had a tradition of requiring students who were willing and interested in putting themselves through the exercise for extra credit to do a little research paper reviewing some part of the field. I remember sitting through many of these at the end of semesters and watching the professor dose off in the middle of them. I did one on the reticular activating system. I really knew nothing about neurobiology and neurophysiology at the time and I found it very interesting, very exciting. The most remarkable thing was that Mountcastle stayed awake and when the thing was over he said you seem to be very interested in the stuff would you like to come and work in my lab for a summer.

I did that. I actually spent a summer plus some free periods and put together an entire academic year and worked on the auditory system of the cat. Did some single unit recording and tried to work out some of the frequency coding based on neuronal response rates. It was enormously fascinating. I enjoyed it very much but I learned from that that I'm not cut out for that kind of quantitative very precise mathematically oriented neuroscience.

By luck around that time Seymour Ketty came up to Hopkins from the NIH to take over the Chair in Psychiatry. I heard him lecture a couple of times and he had this I think in retrospect a little bit strange but very stimulating view of the future of psychiatry as a neuroscience based increasingly pharmacologic science. That sounded a lot like chemistry to me so I thought maybe that would fit better. As it turned out he felt like a fish out of water after a year at Hopkins. He had no clinical training and went back to the NIH. But felt obligated in some way and said would you like to come and spend some time at the NIH and see what's going on in this new form of neuroscience. And I jumped at the chance and again between a summer and a couple of free quarters I spent the equivalent of an academic year there.

I worked with Irv Kopin and a little bit with Julie Axelrod. It was an amazing experience. There were so many people who are well known now who were post-docs or students who were hanging out in that environment. It was an incredible time, full of new ideas and energy and enthusiasm. All things were possible and while most of the ideas were way premature and wrong headed it was an exciting time. I came back for a formal two year post-doc, after I did a year of medicine in Boston. The people there included Les Iversen and Jacques Glowinski, Goran Sedvall, Dick Wurtman and Sol Snider. It was a who's who of neuroscience as it turned out. I didn't know it at the time. But it sure was exciting.

So I got caught up in this vision of the new neuroscience as it might possibly relate to neurology and psychiatry. Then I had another fateful encounter with Joel Elkes who was just moving from Saint E's, up to take the chair at Hopkins. I had been toying on the idea of doing something clinical and I was on the fence between neurology and medicine and what to do. I'd actually looked at departments of psychiatry around the country. I did two grand tours of the leading departments and I came back shaking my head thinking there's such a disparity between what goes on out in the field and what people at the NIH were thinking about as the future.

### **What was going on out in the field?**

It was very old fashioned traditional clinical practice of the 1950s, early 60s variety. It was very psychodynamic. Drugs were just beginning to be thought about a little bit but not used routinely. Accepted with great reluctance and a lot of ambivalence. At best toward the middle of the 60s I think the analysts thought that you know maybe if it helped people to get a control on their thinking and behaviour and emotions a little bit, they might get more out of their therapy and in that way drugs might be some use. That was the style of thinking. I was very sceptical about getting involved in it. It just seemed so foreign. I went to Kety who said why don't you go and talk to Joel Elkes because he's going to Hopkins and he has our point of view.

I remember spending an amazing afternoon with Joel in his garden outside of Washington. He showed me his paintings and his rose garden and his vision of the future. They were all beautiful. He said why don't you come and take a look at what's going on at Hopkins. I ended up applying and got in there as a resident. I found out since that time that his vision was lovely and attractive and wonderful but very premature.

### **In what sense?**

Psychiatry even at Hopkins was still very much in the mode of what was going on in the rest of the country in the 1950s, early 60s. It was a little descriptive, with some more willingness to try the new treatments but it was very dynamic in its theoretical base. And yet when I started working closely with very disturbed patients I found I really enjoyed it. It felt natural, it felt right, it felt comfortable, it felt like something I really wanted to do. So it stuck and I've been doing it ever since.

### **Clinically who else was there in Hopkins at the time? Fritz Freyhan had been linked to it at one point.**

That was before my time. Jerry Frank was a major influence. Joe Stephens was a schizophrenia research person who I ended up doing a project with on one of the first American studies on Lithium when I was a resident. The people who were there were people I really learned an enormous amount of the art from. These people were gifted clinicians, many of them analytically trained but enormously sensitive, gifted clinicians and very intuitive about working with disturbed patients. The clinical staff were marvellous and wonderful teachers.

### **Where was the clinical base?**

It was at John's Hopkins hospital. They had their own wards. There were some chronic and some acute patients at the old Henry Phipps Psychiatric Institute. This was founded by Adolph Meyer back around 1900. It was one of the early experiments in this country of what they call the psychopathic institute model. The same thinking and modelling was done in institutes in New York, Chicago, Denver and elsewhere.

### **What's the model?**

The model was to try to create a psychiatric clinic or institute within a General Hospital in a University Medical Centre to try to bring academic and research activities into the mix in a way that had not been possible previously with institutions that were really very separate. A lot of the public mental hospitals were really quite separate places, far away from academic centre. And even though there were some wonderful things done there in the old days this move was an attempt to amalgamate and bring closer what was going on in academic medicine and research to the bedside so they could move back and forth. In fact the way the Phipps' building was designed it was a literal architectural expression of that idea - you had a clinical unit and then a set of labs and then another clinical unit and the idea was that people would have to talk to each other in the hallway. This aimed at trying to get some cross fertilisation between clinical and research people. And it worked pretty well.

**In terms of the treatment of patients, had drug treatments begun to take hold as first line treatments at this point?**

Well I worked there from 66 to 69. By the mid 60s the neuroleptic drugs had an established and accepted place although they were misunderstood as to what they were and were not good for. I think initially people saw them as specific anti-schizophrenic agents but that was back in an era when schizophrenia in this country didn't mean very much. Any kind of psychotic or in some centres severe mental illness got called schizophrenia. The antidepressants were just beginning to come into vogue by that time. There was still a lot of ambivalence about whether a drug could treat something so obviously psychological. This was a very hard sell. There was a lot of scepticism about that in this country.

I remember Gerry Klerman having to write very tough review articles, putting a mass of evidence together before anybody would begin to take the idea seriously. By the late 60s we were beginning to accept lithium clinically, even though it hadn't quite been licenced in this country. So we had basically the neuroleptics, the early antidepressants and lithium and some sedative anxiolytic drugs and that was about it. But while the drugs were beginning to be accepted at an empirical level the idea that they were tuning in on something biologically important about the illnesses was far from anybody's mind. In that era that was a very concept for American psychiatrists to get their heads around.

**Why?**

think it was because of the psychodynamic view of the world that fundamentally these illnesses were psychologically determined and based. The idea that a medical intervention might tune in on something biologically important. It was just too far away.

**Why if the analysts were going to make a fuss about any biological treatment, didn't they do so about the treatment of people who were anxious being treated with the minor tranquillisers? This was really going to take away their business. But they didn't make a fuss about this, it was about things like schizophrenia, the psychoses and the major mood disorders.**

It's an interesting question. I was chatting with Uhli Uhlenluth in the hallway on the way to the last session today. We were talking about how historically and even still now, the anxiety disorders are perceived as different in this country as a minor, not core, not central to the field group of disorders. Now that's totally wrongheaded. They are turning out to be some of the most common, often devastating, relatively treatable, most interesting disorders that we have. And they may be amongst the first to yield to genetic and biologic understanding. But there was something about, at least in that era, major mental illness hospital level of psychopathology that academic department chairman thought was the core of our field - psychotic depression and schizophrenia were the real diseases that psychiatrists knew about. It probably grows out of an institutional tradition in this country. American psychiatry from the very founding of the APA has always been a very institution oriented field and there's been a vast difference between institutional and academic psychiatry which have had a tight bond and private practice, primary care, office based psychiatry which was something needed and tolerated but a little bit peripheral to academic and institutional concerns.

### **From Hopkins you moved to Boston.**

At that point I had a lucky break. Seymour Kety got restless once again. He wanted to try it again but get it right - being a professor of psychiatry in a leading department. This time he did it cleverly because he went with Leon Eisenberg who is another great teacher of mine at Hopkins. Leon was meant to deal with the more clinical side of the department and Seymour was to be the scientific head of the department in Mass General. They went up in 68, I came in 69. We started from scratch, designed and built labs from scratch and invented new methodologies, and really got a lot of dirty fingernails for several years just getting things set up and organised, getting methods going.

### **When you moved up, as I understand it through the 60s Boston had been very analytically oriented with Elvin Semrad and people like that.**

Well Semrad was across town in Mass Mental Health Centre. There's a geography in Boston psychiatry that gets very complicated. Mass Mental at the time was I think the leading training centre, some people would argue, in the country. One of the leading ones anyway in the country. It was very analytic. They attempted to apply psychoanalytic insights into working with very disturbed patients. Semrad was that kind of person. He was a very charismatic man. He was a gifted interviewer of very disturbed patients and could get himself into their heads and he had a way of communicating his empathic understanding of the patients to anyone listening in. He was a very influential teacher.

That kind of model was a very influential one in academic psychiatry in this country for many years. Many leading academic psychiatrists came out of that tradition and out of that program. Mass General had always been somewhat eccentric and different. It had a mixture of analytically oriented people who were mainly interested in psychosomatic medicine as it turns out. So these were people who were working with the most medical part of psychiatry and yet trying to understand medical illnesses and reactions to them from a psychological developmental perspective. Then in addition there were people

like Stanley Cobb who came out of more or a then neuroscience, neuroanatomy, descriptive neurology tradition. He was a very important scientific progenitor of that department. That tradition and the general hospital staying in the middle of medicine tradition made it fairly comfortable to bring in people like Eisenberg and Kety and have a more biologically reunified look at the field, something that goes back to pre-analytic European descriptive roots.

**Just on that score there was a man lurking around the Boston scene called Mandel Cohen.**

Yes and he's still around as a matter, a very elderly man who's still active. I remember when I first went to Mass General one of my most memorable experiences was going to Grand Rounds in the etherdome where ether was first used for surgery - an antique medical amphitheatre. And there was this elderly man who at the end of every lecture would stand up and pontificate giving his point of view on what the speaker had just spoken about. I didn't know who he was and after a few Grand Rounds I asked who was this guy. It was Mandel Cohen. He was more a part of the department of neurology even though he was a traditionally trained psychiatrist but I think he had a lot of neurological background. He was one of these bridging people between the fields. There was a lot of that that back in the 1930s, 40s and 50s.

**I understand that when he used to talk about his work he'd begin by saying that he was there during the 1930s and 40s and then this plague of locusts came over from Europe - which was the analysts. But in a sense people like Sam Guze and Eli Robbins and that line of thinking can be traced back to him. He brought in the operational criteria that idea very early on.**

In some ways, that's true. I remember one of the first times that I had a chance to really talk in some detail with Robbins. I was visiting to give a talk or something in Washington University in St Louis in the early 70s. I sort of vaguely knew who he was and where he came from and what his ideas were. I knew they were different from most of the departments that I'd worked in. I had lunch with him and spent an afternoon chatting with him. I hadn't appreciated that he had trained in Boston. He said he got out of Boston just in time. His mind was just about to be destroyed by this kind of fuzzy thinking.

As it turns out, he was ahead of his time or renewing old times from a European tradition, kept it alive. I subsequently went back to visit a number of times and I have a number of good friends in that department. It was not until well into the 1980s that they were widely accepted. Back in the early 70s they really felt like an endangered species. The whole department - I won't say it was paranoid - but it had a flavour of having a wall or moat around the outside of the department; we have our point of view and then there's all those people thinking in a fuzzy or confused way outside. But eventually their ideas got into the DSM.

**Okay at this point in time in the early 1970s, to people like you how aware were you of this neo-Kraepelinian group as they later were called. There were a few people like Klerman and Bob Spitzer and the St Louis group. Were you really aware of them as an axis or not?**

Yes but I viewed them as prophets without followers basically. I thought they were bright interesting people who were trying to be more clear headed, logical and objective but were very much out of the mainstream of things. And if I had had to bet money on how it would turn out I would have bet against them.

**Absolutely, it was an amazing political coup wasn't it?**

It was indeed and I suspect the key to it was getting APA to take it on and make it an officially acceptable point.

**In the early 1970s, after you'd gone up to Harvard, what did you do?**

What I started with was basically a couple of things. When I worked at the NIH as a medical student I spent that year working on the idea that transmethylation of monoamines might have something to do with psychotic pathophysiology. I worked on a lot of assay techniques for the methyl donors and for methionine itself and modified these radio-enzymatic assays so you can measure the enzymes activities, the substrates and the methyl donor. I extended it a little bit later to be able to measure the adenosyl transferase that activates methionine. This concept came from Julie Axelrod's work I guess, starting with his catechol-o-methyl-transferase assay techniques. We were able to get hold of radio-actively labelled s-adenosyl methionine and with that tool we were able to parlay the technology into assaying all kinds of things from it.

That was great fun and that theme continued a little bit in Boston because I adapted the assay for histamine. We developed a histamine methyl-transferase assay to measure histamine. A little bit later, right around the time when I left MGH to go out to McLean there was a very interesting encounter with the Research Director of a small company in Milan called Bioresearch. They've been bought out by BASF in the meantime. But this fellow Georgio Stromentanolli was a very clever biochemist. He took a sabbatical from the company and came to work with me because we had this shared interest in methylation.

His company was developing s-adenosyl methionine as a possible tonic. It's hard to describe what it was supposed to be good for. You have to be a southern European to grasp the concept and it helps to be Italian to understand it. It has something to do with making livers healthier, happier, better. There's a whole tradition of southern European liver tonic pharmacology that I don't think is understood or appreciated anywhere else in the world.

**Just on that score before we go any further one of the things that you will have a feel for perhaps is how for example the French have a way of thinking about mental illnesses that in the English speaking world we just don't have. They understand that these drugs may act to the anti-impulsive agents in a way that we don't. For the English speaking world mental illness is very cognitive. The English in particular don't have feelings – they're even happy to admit it. Do you think the fact that**

**psychiatry has become English speaking has meant we have lost out on some concepts?**

I don't know enough about far Eastern and Asian mainland and South American psychiatry to know whether we are missing important things there, but I know from the American perspective, having had a number of European colleagues in the department over the years, that we've missed out enormously on the Anglo-German axis on descriptive psychiatry and psychopathology, and on a more philosophical southern European tradition. None of those traditions have really penetrated American psychiatry.

**Or even English psychiatry.**

But you have that descriptive objective tradition that we foresook for a long time. But even in that tradition we've done something I would say a little mischievous from a world view. We've technified the whole nosology into a checklist and you can get a computer algorithm to do it for you now. And I think we've squeezed an awful lot of the juice out of the field by doing that. The blood and the subtleties of psychopathology are lost in that process. And it creates a level of disdain for all the complexities and the subtleties.

A lot of American, especially academic, psychiatrists like nice neat diagnoses and nice neat numbers for their papers and that carries over into their teaching style and their bedside style. They tend to see things a lot more crisp and syndromised than I think human reality supports. I've learned a lot about this by spending time with European colleagues and I think that it would be nice if we could re-capture some of the rich descriptive side of psychopathology before it's lost.

There is an analogous problem that we talk about a lot at home which is that in neurology an enormously clever generation of descriptive knee tapping what's my lesion kind of neurologists are fast disappearing. We have now a group of molecular technocrats and brain scanners. Tapping on knees and ferreting out from signs and symptoms doesn't amount to much anymore. I think the same thing can happen in psychiatry. I think we can get too technically oriented and too empirical and lose sight of the real complexity and mysteriousness of most of the conditions that we are dealing with.

**Okay lets come back to liver tonics.**

Ah liver tonics. Just to put a fine point on Stromenthanol coming into the lab, we then designed a critical experiment that destroyed the whole line of thinking. The idea of the methylation theory was that if you gave psychotic people a bunch of amino acids to see if you could provoke something, the only one that really did anything replicable was methionine. This was the least likely. I think people were betting on tryptophan, and tyrosine and phenylalanine and things like that because they were going to lead to amines.

In fact the very first clinical project that I got involved with was a replication study of just this. When Kety was at Hopkins he worked with a fellow named Lee Park on a very well designed controlled trial of a methionine loading experiment. In fact going out to one of the state hospitals and helping them do ratings on patients was the experience that may have done more than any

other clinical experience to turn me toward being really interested in psychiatry. Because without using any formal rating scales I think I was able to figure out who got what in about 99% of the cases. I don't know how I did it - it was just purely intuitive. They were not floridly psychotic, they were not grossly obviously different, but there was something different about the people who were taking methionine. It was a very interesting experience to pick up on.

But anyway the theory was that if you loaded with methionine, as the s-adenosyl methionine transferase process was not saturated, you will therefore make more methyl derivatives. So you'd make methyltryptamines and methylated phenethylamines and so on, compounds that were known to be psychotomimetic in man and so on. Well the critical experiment that Stromenthanoli and I did was this. We actually worked out an assay for n,n dimethyltryptamine, starting with precursors in animals under normal conditions and loading them with methionine. And what we found was that we could raise s-adenosyl methionine easily but the process of n-methylation could not be pushed. And what we figured out in vitro is that many methyl transferases are saturated with cofactors and can't be pushed. The endogenous of s-adenosyl methionine is enough. If you deplete it you will slow the process down but loading up and pushing it has no effect because you're saturated already. It took until the late 70s before we got that all figured out, but by that time the field had moved on and nobody cared.

**This is what happens, fields move on.**

But it was nice to have a kind of a fine point on it. Anyway in the meantime in the early 70s what I did was a continuation of another line of work that I got involved in with Irv Kopin, when I went back to NIH after my internship. I was trying very hard to figure out a way of studying the release process of monoamines from nerve terminals. I spent I think about a year and a half of a two year fellowship working on methods that were absolutely doomed to failure. We were doing things like vascular perfusions of cat spinal cord segments, trying to catch the monoamines coming out of and assaying them by fluorimetric methods. These were laborious techniques. The surgery alone was a crusher. It never worked.

Finally, I don't know where Irv got the idea, but he was aware of Henry Mclwain's work in England and knew that you could keep slices of brain going pretty well in vitro if you oxygenised and gave them a Krebs Ringar medium to live in and so on. And he said you know maybe since we know that nerve terminals can take up exogenous radio actively labelled monoamines, which is the kind of work that Glowinski and Les Iversen were doing with Julie Axelrod at the time, the thought was maybe we could get slices to do the same. Maybe you could load up your nerve endings with radio active material and wash it clean and then stimulate the slices in an electrical field and maybe something will happen. And it did. It worked the first time. It worked amazingly easily and within six months, the remaining time on my failing post-doctoral time everything came together. We actually did the first work showing in vitro release of superfused lysates, of releasing with electrical fields, with drugs, with potassium depolarisation and all that kind of stuff.

So that line of work I carried over from the NIH in a very peculiar way. One of the postdocs with me in Kopin's lab was a surgeon of all things, a fellow named Joseph Fisher. He is now the Chairman out at the University of Cincinnati in Surgery. But for some reason he was one of these strange Boston trained surgeons who was very interested in a metabolic understanding of surgical conditions. He was an absolutely wonderful technical surgeon. In fact, he and I worked together on some of these spinal cord perfusion technologies, but even though we'd get the surgery to work the rest was a bummer. Anyway one of the things that Joe was very interested in when he was at Mass General was the problem of hepatic encephalopathy, liver failure, alcoholism and problems of which I'd seen too much of when I was an intern at Boston City. Every other person was an alcoholic with terminal cirrhosis and bleeding varices and all kinds of horrible psychiatric problems. Now when Fisher was working with Irv Kopin they were working together on what we ended up calling false transmitters and the idea that they could displace the real thing. You could load up nerve terminals with tyramine or octopamine and things like that and some of these, particularly octopamine, in the norepinephrine nerve terminals would not only be taken up but they would compete for the release sites and could give you a proportional reduction in physiologic effect postsynaptically.

One of the marvellous things about working on the metabolic problems in hepatic encephalopathy was that you can't miss because everything is wrong. Everything you measure is abnormal. Among the things that we got involved in was looking at the pattern of amino acids and amine metabolism and so on. Joe he worked at it on the clinical side and I worked at it in animal modelling and in vitro modelling and what we tried to do was to extend these ideas from Kopin's work. Our idea was that in hepatic encephalopathy there may be a problem of an excess of aromatic amino acids going on to form tyramine and tryptamine and octopamine and a whole group of derivatives. What I ended up doing was spending several years trying to work out the molecular rules of the game. What did it have to look like to be taken up, to be stored in vesicles, to be released on depolarisation and so on.

We worked out a whole metabolic theory about hepatic encephalopathy, that it may be in part reflecting brain accumulation of bogus amine derivatives with an excess of poorly metabolised amino acids. I saw a review on this in that literature about two or three years ago where they listed some of the still contemporary theories and our theory was listed as one of those things that had a lot of evidence supporting it, that was never really disproven. The frosting on the cake was that Fisher actually went ahead with a treatment. He knew in part from working collaboratively with Dick Wurtman, who was across the river at MIT, that you could change the proportion of aromatic amino acids available to the blood brain barrier, if you reduced aromatics and increased neutral aliphatics - they would compete for the same transporter. Fisher actually designed a therapeutic intervention where he would make intravenous hyperalimentary fluid cocktails where instead of the normal distribution of amino acids he would reduce the aromatics and increase the aliphatics and he actually pulled people out of coma by doing that. It was not a terribly

practical clinical thing because the liver was still going down hill and people were bleeding and dying but it did work and it was one of the supports for the theory that may be there's something to this.

**It's also an interesting to have a man who ends up being a surgeon kind of producing a treatment for a medical problem.**

Yes, but that's not a rare tradition in Boston surgery. One of the earliest and most illustrious people in that tradition is Francis Moore who just retired a few years back. He was again a GI surgeon with a lot of interest in metabolic consequences of disorders. So Joe Fisher wasn't a totally unique guy. So that was where things were until I began getting interested in antipsychotic drugs, psychotic illness, what do neuroleptic drugs do to the dopamine system and that's where all the tardive dyskinesia story comes.

**Well just to open it up a bit. I've had stories from Frank Ayd during the last few days how he was called by Schering Plough who produced perphenazine to look at the problem when Arbild Faurbye first reported it. He went to have a look at the patients and he wasn't sure what was going on. There was scepticism by people like Bill Wilkelman, who had been one of the first people to use chlorpromazine in this country, who famously brought into a case conference some lady who seemed to have the classic mouth movements and a whole range of people were asked to say what she had and they all said ah she's got tardive dyskinesia and he asked her to leave the room and she went out and came in a few minutes later and she was cured. What had happened was that she had removed her teeth. There's another story about Degkowitz, a German, who was quite big on all this, who at the 1966 CINP meeting tried to show US psychiatrists the problem. He took people around a ward at St E's and showed them an African-American who appeared to have the condition. He said look here it is it's obvious. But when one of the nursing staff asked the guy to take out his chewing gum the syndrome cleared up. It became a big issue didn't it? It took a while for people to recognise it was there, then it became a huge hot political issue. Can you take me through this because you were fairly centrally involved.**

Yes. Just to make a final point about Dr Winkelman he was actually I think the first American psychiatrist to use chlorpromazine. This was around the time that Heinz Lehmann was doing it in Canada. This was the middle 50s. He was a most remarkable man - one of those old fashioned analytically trained American psychiatrists and yet he recognised a bargain when he saw it.

The TD story is an interesting one and I think in America it has involved the medico-legal scene more than the medical scene. What I've learned about TD over the years is that it's something I wouldn't wish on my worst enemy but it's a it's really more of a medico-legal problem and a liability problem than it is a truly disabling clinical syndrome in many cases. Sometimes in young males with dystonic forms of it it can be quite disabling. In the average sort of older person, it's some mouth movements a bit of finger dyskinesia and things like that and something can be done about it in many cases.

In the United States there were a number of very successful malpractice actions that were brought and they followed a very peculiar pattern. In reading a number of these cases in some detail what I read into them is fairly broad spectrum I wouldn't even call it malpractice. Neuroleptic drugs were just being used as your basic tranquilliser to keep people quiet and in line and so on. These were people who were being seen for maybe five seconds on rounds by a not very well trained guy who maybe came through one afternoon a month or something like that. They just didn't pick up on these things. And when the syndrome began to get into the literature and into public consciousness malpractice lawyers had a field day.

**When did that begin to happen?**

Oh middle to late 70s it was becoming quite a hot topic in this country. That fuelled the fire of professional interest. The APA set up its first task force on TD.

**You chaired that. How did you get pulled into it why particularly you?**

Because I'd done a fair amount of theoretical work by that time and I'd written some clinical papers actually. The story on the theoretical work was that I was visited by a disciple of David Marsdens from London who had actually just come from spending some time with David, a fellow named Daniel Tarsy, who is now chief of a neurology division at one of the Harvard teaching hospitals. He was then and still is very interested in extra-pyramidal disorders and taught me a lot. I knew very little about it. I was reading about l-dopa work going on in Parkinson's and I had some vague understanding of that. But the idea that there might be a knowable pathophysiology and differentiation to be made among these things that we were still calling EPS at that time was just beginning to sink through in my head. With him I learned to sharpen up differential diagnoses between acute dyskinesias, late dyskinesias, akathisia, Parkinsonism and all these things that have a differential diagnosis, a differential management and probably a very dissimilar pathophysiology, much of which we don't fully understand yet. Particularly akathisia which for me is public enemy number one. It really causes an enormous amount of clinical disruption and fortunately the attorneys around haven't caught on to that yet. They are still after tardive dyskinesia because it's easier to sell to juries.

So when in this collaborative work with Dan Tarsy he wanted to do a lab project, we began talking about whether it could possibly be that long term exposure to an antagonist at a receptor might lead to a regulatory change in the up direction leading to supersensitivity. This was not a totally new idea and it turned out that there was a young resident in the department at the time who had trained in classical neuropharmacology at NYU and had worked with some of the people there who had done some of the earliest work on denervation supersensitivity in the adrenergic and cholinergic systems. I think through talking with him and with Tarsy and the influence indirectly from Marsden we put this idea together that maybe we could actually demonstrate this. We'd been reading about some European studies giving dopamine agonists to provoke behavioural responses. We thought we could treat some

animals with antidopamine compounds and provoke a behavioural response. The very first thing that we did was ended up being one of the few things I ever got into Nature. This was a series of tests of long-term treatment with reserpine, alpha-methyl-dopa, chlorpromazine, haloperidol and so on. And every one of these conditions led to increased behavioural sensitivity to apomorphine.

Now at the time I didn't know it but the same kind of thinking was going on in Chicago. Harold Klawans and Randy Rubowitz, working with him, had been doing very similar work around the same time. We later went back and forth as to who did what when and all that. I think that we were probably working simultaneously and independently. And it doesn't matter any way because we were both scooped by an obscure Russian paper that appeared in the late 60s. It was a man named Schelkunov, who I know nothing about. I only know this one paper that I found out about maybe 10 years after this work was done. In the late 60s, he had done a very similar experiment with I think chronic chlorpromazine provoking behavioural responses to dopamine agonists. But it was an idea that clicked and made sense and I think became popularised as the dopamine supersensitivity theory of tardive dyskinesia. I don't believe it myself. I mean it may be a factor, a contributing component. The fact that at worst only 20, 30, 40% of people under the worst clinical conditions develop TD means there must be other host factors involved that we really don't understand.

Anyway that kind of thinking actually led to some clinical collaborative studies on Tardive Dyskinesia. I worked with an epidemiologist in the state hospital system in New York, Jim Smith. We did some of the early work showing quantitatively that certain factors increase individual risk for tardive dyskinesia. I think the most compelling one from our work in the late 70s was age. The older people got, the higher the risk rate, the greater the severity, and the less likely a remission when you stopped the treatment. So that got me into the middle of this whole furore.

I kept up with both the descriptive, epidemiological and laboratory bases for TD. And I actually tried to do something about it. I think that the one of the things that I was impressed with at the time was when we were looking for risk factors was a "lack" of dose risk relationship between neuroleptic treatment and risk of TD. As a pharmacologist I just couldn't accept that. I mean everything has a dose risk relationship if the drug has anything more than incidentally to do with the condition. I figured that at least in North American papers all the dose risk data that I saw ran from the range of like 300, 400, 500 mgs a day of chlorpromazine equivalents up to 3,000mg. And my guess was that maybe people are up around the top of the dose risk and we needed to look down the dose curve a little bit.

Around that time John Kane in New York was beginning to do some of these prospective dose response studies with dilutions of depot fluphenazine. And one of the not much talked about but critically important parts of that data is that buried in one of the early papers there's a relationship not only with the dose benefit following a classic Goodman and Gilman type dose response

curve but if you do a 10-fold reduction of dose from standard dose to ridiculously low dose, say going from 300 to 30 chlorpromazine equivalents you can reduce the TD incidence risk by 2-fold. I guess to a toxicologist that would make perfectly good sense, that there should be a log-risk relationship.

So the point of all that is that that got me very interested in the whole problem of appropriate dosing of antipsychotic drugs. I ended up spending a lot of time combing through the literature and doing this kind of thing that I'd done a time or two since then of being too lazy to do experiments and going to the literature instead to pull out nuggets of gold from other people's work. What we worked out was a semi-quantitative way of looking at dose response relationships. It ended up coming to the conclusion that European colleagues had it right all the time and that we had been playing at North American classic cowboy pharmacology - overdoing everything. If a little bit is good, a lot must be better.

**Perhaps fortuitously though your article on all this, saying that we've had the dose wrong came out in Archives at much the same time as we got the ability to radio-label D2 receptors so that we could show that the kind of doses that you'd begun to recommend really were the ones that occupied D2s to the optimal amount. This was fortuitous was it?**

Well it was a good thing for this point of view because I think it helped to solidify and objectify.

**There's a sense though what you are opening up here and this is a theme that I'd like to chase a bit further with you. Is once you open up the idea that there is the optimal dose range and there's no point going any higher if the patient hasn't got well with this dose you're accepting that we're not therapeutically omnipotent. That there's only so much we can do. Which is not from the point of view of the average psychiatrist in the street what we want to hear okay. You also had been saying in your earlier writings such as your chapter in Goodman and Gilman in 1980 on the neuroleptic drugs, when all the rest of the field were saying these drugs are anti-schizophrenic etc, you were there saying no they work across syndromes and they work to reduce agitation and tension. A much more limited goal you're actually saying we should aim at. This can't have been hugely popular with your colleagues or with the pharmaceutical industry**

Probably not. Let me take a step back and give you a philosophical preamble to this. One of the things that I'm exquisitely sensitive about particularly in North American psychiatry as a teacher of psychiatry and a trainer of young people is that American psychiatry, I think less so than European psychiatry, has been the most fad prone group of professionals that I've ever known. Whatever new trendy thing comes along, we've got to buy into it and not only buy into it, we've got to package it, market it, push it to extremes and just overdo it. That's fine if you left it at that but what we usually do is end up killing it.

I think we did it with psychoanalytic thinking which is a very powerful way of looking at certain problems in life. It was not a cure. It didn't answer all the

questions. But we over did it and it came to dominate the field to the point where people said this is ridiculous and we've got to move on. Then it fell into a background position, which it probably shouldn't have fallen into. It should be still in use. And then we did it with community psychiatry and de-institutionalisation. We really did it properly and we wrecked that and I think we proved that it was a crazy idea. If you had no place to send people then you can't just throw them out on the streets because they are going to get in trouble.

We've done it I think again in much of biological psychiatry and I sure don't want to see it happen in psychopharmacology. I don't think we've done it here quite yet, but it could happen. But in the kind of biological psychiatry that I've known over the last 40 years, we have these pharmacocentric theories where we know what the drug does therefore the opposite of what the drug does must equal the pathophysiology of the illness. We did it with depression, mania and schizophrenia. I don't know whether it's quite happened with anxiety disorders but there's a bit of it there as well. The problem with that is that it may be a brilliant tool to get an insight but it's a very risky venture.

When I try to explain this to residents and medical students I say if you knew that willow bark extract helped people who had fevers and coughed you might do great things but developing a whole theory about the pharmacology of salicylates might lead you not a step in the direction of discovering the pneumococcus. Or if you knew that mercurials were very good for people who retained fluid and swelled up and you studied the pharmacology of mercury and you knew what it did at the nephron, you might still miss the point that this is congestive heart failure. It's nothing to do with the kidneys.

**I guess on that line the other thing that we could have done if we'd had these drugs earlier we could have managed GPI with neuroleptics but it wouldn't have been the answer.**

That's right. That would have been tragic. So what I'm saying is I'm really very uneasy about throwing babies out with bath water or this American tendency to commercialise and overdo, oversell, and push to the point of the ridiculous and then you crash and then you go up on a new high with the next game in town. It just seems too costly to me. You're killing off too many good things along the way. And you tend to devalue that which has been set aside and not try to take from it some worthwhile things. I don't want to see that happen with psychopharmacology. I don't think it's happening yet but there's a risk from this tendency in the United States to come in with the six guns blazing. I remember vividly when I first started tracking down what clinicians were doing in the Boston area and found out that the average dose of neuroleptics was getting up into the thousands of milligrams a day of chlorpromazine equivalents because it was trendy. Megadose and rapid neuroleptisation and all these wild and crazy ideas. And worse yet they sort of worked. And then you're caught and they say see we've shown you that it works.

**So how did people actually respond to you article then.**

That article in the Archives came a bit latter. What was going on in the meantime was some smaller articles decrying overdosing and overdoing and a lot of spade work with clinicians and teaching activities and rouding and consulting, saying to people it's great that you're achieving these wonderful outcomes but please don't leap to the conclusion that because it took 75 mg haloperidol to get this person well that you should therefore design a 10 year maintenance programme based on 50 mg a day for the rest of that time. Please try to figure out what the minimum dose is. With that kind of pleading and encouragement people began to get the point. The other thing that was happening at the same time was that the fear of adverse effects was beginning to penetrate. There was a mentality in the early 70s at least in the Boston where you could make rounds and see patients twisted up like pretzels and just keep walking and say well that's the way they are and not realise that most of it was iatrogenic. When the lawsuits started hitting the fan and there were deaths, and there were people who were having respiratory crises from acute dystonic reactions, and people with NMS who were dying these things scared people. I haven't seen a classic fatality from a neuroleptic drug in some time - I've seen people with cardiac arrest with some of the modern drugs. But I haven't seen NMS fatalities and respiratory arrests and things like that in many years. I think it's because of the conservative doses. I think that the risks pushed people to listen.

What has happened now is very interesting. We've been monitoring drug dosing in our programme at McLean hospital, and what we've seen is that the doses have come down and have stayed down and our average neuroleptic equivalent now is somewhere around the 200 – 300mgs a day range as it had been in Europe. What has changed is that we've become cowboys of another kind. Where one six-gun was sufficient, now it's gattling guns going with six drugs are better than one. Polypharmacy is the new kind of cowboy pharmacology. It's scary because there are all sorts of unpredictable drugs beginning to happen.

**For a person who is so keen to make sure we don't throw the baby out with the bath water and for one who has been so persuaded that we need the drugs you've done an awful lot of work though to draw out the hazards. You've also pointed to the discontinuation syndromes.**

Because I value them so much that I don't want to see them killed by negative press. The argument is that if you use them wisely and well and safely you can get a lot of good work done and not kill to many people.

#### **What about the discontinuation syndrome story?**

That's a newer theme. It's a very intriguing tale, like a mystery. It started at a case conference in McLean Hospital – I'd moved out there in 77. I was increasingly involved in part of the clinical and academic management of some inpatient units with psychotic patients. In 1989/90, we had a very interesting young woman named Trisha Suppes, who was a resident at the time. She was a superbly trained neurophysiologist, she was trying to figure out whether she wanted to go back into the lab or become a clinical investigator. I spent a lot of time with her and helped her through going back into the lab, saying it's not really what she wanted to do and helping her to get

into more of a clinical track. Anyway she presented a case of a young man who had had an acute episode of mania. He was in College in Boston at the time, was acutely psychotically manic, came in, got treated with mostly lithium and maybe with a low dose of antipsychotic for a while. Did quite well. In following him up, he had a less than perfect course over time. One of the things that she was struck by was that he got to a point in his treatment after a couple of years where he was really bothered by side-effects - he put on a lot of weight, his acne was flaring up and things were not going well. He was fed up with it and he really wanted off and he convinced his private psychiatrist to get him off. He did fine for a couple of weeks and then all hell broke loose and he ended up back in hospital and Dr Suppes ended up taking care of him.

It was like trying to put Humpty Dumpty back together again, it was just a nightmare. Weeks and weeks of trying this, trying that and he eventually got sort of better, enough to leave the hospital. Anyway, she asked this innocent question is there more here than not treating a bad illness that came back? I said whatever do you mean. And she said you know damn well what I mean. Is there an iatrogenic component to this? If we'd pulled the rug out from under somebody who had adjusted to a new steady state neurophysiologically by being on a foreign substance for a long time. I said what a curious, provocative and crazy idea.

I said this reminds me of the first time I ever met David Marsden at a meeting in of all places Sardinia, many years before. I gave a talk on antipsychotic drug therapy and one of the slides I showed had a meta analysis of the world's literature of the kind that John Davis had done before I did another one showing risk over time on drug, versus risk over time going to placebo. There was an enormous difference. David looked at it and tongue in cheek said gee have you thought that this might be an addiction model. I said bite your tongue that's a nasty thing to say. He was kidding I think. But I think also he was tuning in on something we weren't thinking about and I think he was a little bit prescient in thinking this way. It may not be addiction as we know it with opiates and alcohol, but the idea that a drug could lead to an altered state of adjustment of the nervous system and that if you stop suddenly that there may be hell to pay was an interesting thought. At the time it was just not historically ready for at least my ears to get it. Everybody in the room laughed and thought it was a funny story and so on.

But here again this physiologist brought it up again and I said my God that's Marsden thinking again, maybe there's something to it. So I said lets go to the library and find out what's known about this. There was nothing known but while we were in the library we dredged up a lot of data on discontinuation protocols with lithium and we put it all together and did a massive quantitative survival analysis with it. What we found was that if you had been on lithium and were stable and you stopped the lithium you had a very high probability of getting sick pretty quickly. Trisha Suppes said well lets publish this, isn't this interesting. I said it's interesting but the first question reviewers are going to say is compared to what. All you've shown is that people got sick. You don't know that you've got an iatrogenic component.

We got very lucky. On a very small handful of patients, there were data in the publications where you could dope out the relapsing interval in those patients before they got on lithium and then we could do on lithium and off lithium. What we did was a bit crude and presumptuous but just to be squeaky clean we took the shortest cycling interval before lithium and compared that within subject to the time from stopping lithium to getting sick off lithium. And there was like a 7 or 8-fold shorter interval after stopping. That really opened the key to getting it published.

Then in 1992, the year after that paper came out I had another very peculiar experience. I got a very peculiar phone call about 1988 from Alan Fraser who was at Penn at the time. I knew him fairly well. He called me saying have I got a deal for you. I've got a very good friend of a friend from the University of Cagliari in Sardinia. He has been trained by very good people, he worked in their pharmacology department and he's just finished a psychiatric residency and he wants to come to this country for a year and work in somebody's lab in psychiatry. I said that's fine why don't you take him to Penn. He said that the Fellowship that he has was designed by a very peculiar person who had some reverential attitudes towards your university and not my university. And it is written in the contract that he has to go to Harvard. So I said okay if that's the case. So he came over and this was Jonny Fader who has worked with me on and off since that time. He spent a couple of years in the lab, we did a lot of work on characterising D1 receptor pharmacology, designing new radio ligands for D-1 and things like that. He liked it and did very well out of it but he really wanted to be a clinical investigator. In fact he liked American psychiatry so much that he wanted to leave home and complete a training programme in psychiatry in our programme.

Any way in Christmas in 1991/92 he went back to his family in Sardinia and he brought me a Christmas gift which was a set of data from a clinic where he had trained when he was a resident over there. This was led by a man called Leonardo Tondo, who I'd never heard of at the time. There in this set of data he had 65 bipolar patients who had been on lithium maintenance and done very well who had come off lithium and done not so well. The data were so precise that he could tell exactly to within plus or minus a day how long the tapering had been coming off lithium. I was still not getting it. Johnny said look if you really believe that there is an iatrogenic component to this then the rate of coming off may make a difference. I said wow what a great idea lets look.

So we took these 65 patients and ordered them by length of tapering time and did a median split which happened to be 2 weeks and that's why I've got hung up on this greater or less than two weeks. We worked out a survival function and it was dramatically different. The people who came off rapidly fell apart very quickly. The people who came off slowly came down very little and it look dramatically wonderful. Jonny said lets write it up and since the first paper by Trish Suppes got into the Archives, lets send it to the Archives. And I said not on your life. And the data sat on the back of my desk under a brick for weeks.

## Why not?

I said I might seem like an ingrate in response to your wonderful Christmas gift and it's a nifty idea but lets look at the data and I'll explain to you why I can't put my name to it. We had data on follow-up all the way out to as long as five years of follow-up and these two survival functions went down in parallel all the way out to five years. I said you mean to tell me that five years later that a little fiddling around for a few days at time zero is going to influence somebody's life for the next five years. People will laugh at you if you try to publish that. So it's sad.

And one night, this is a true story, I had a dream. It was a classic psychiatric dream. There were snakes in it. It was like the Kekule story. And I woke up in the middle of the night and I said eureka I understand what's going on here. I didn't know what the survival curves and the snakes had to do with each other but at least that was in my head at the time. So I got up and scribbled some notes, fell asleep and forgot about them. And a couple of days later I glanced at the notes and I finally figured out what I was thinking. The deal was that these two survival functions were different only in the first six months or so. What was going on thereafter were parallel functions. The displacement was maintained. It was good news. Slowing down the discontinuation not only delayed the inevitable, it actually prevented something from happening. The sparing of risk was maintained. This supported the idea that there probably is an iatrogenic component and it may be remediable by slowing down the discontinuation, giving the system a chance to readjust as you come off. We did some formal curve fitting and found that in the first six months there was a 10-fold difference in rate and thereafter the two functions were virtually identical.

Since that time, I've gotten more and more uncomfortably drawn into this area, the idea that perhaps this is not a unique phenomena with lithium. The next thing that we got into was looking at the neuroleptic literature. I started working with a wonderful young psychiatrist named Adel Viguera, who was on the program around the time that the work with Suppes and Fader was going on. We started doing a meta-analysis of the neuroleptic discontinuation studies. As luck would have it just as we were putting our data together, Dilip Jeste and his group had a massive meta-analysis appear in the Archives. I said well we got scooped, lets forget about it.

But what held us into it was that one of the things that I was struck by in the Jeste analysis was another phenomena was that if you follow people who had been treated with antipsychotic drugs for a long time, doing okay and then get switched to placebo and you do a survival function over time what you see again is that almost all the action occurs in the first six months. If you get beyond that then almost nothing happens thereafter. This probably has something to do with heterogeneity, either diagnostic and/or clinical heterogeneity or something or variance in vulnerability.

What we did was to further into the literature and tried to find studies that segregated by rate of discontinuation. What we ended up finding was a very instructive piece of negative data. If you tried to pool data across studies you

don't see a fast/slow difference at all, there's too much noise, you just end up with messy grey data. But we found three or four studies and we got some unpublished data from Alan Green in Mass Mental Health Centre finding that within the same study people had been segregated to different rates of discontinuation and we also were able to compare in the same study depot versus oral medication. When you put all that together it showed again that slow discontinuation markedly reduced the risk.

We did it again a third time with the antidepressants again with Adel Viguera but that didn't work out so well. The finding of a marked risk in the first six months and not very much thereafter, we were able to demonstrate very nicely. But we couldn't find a single study in the literature that compares slow and fast discontinuation with antidepressants. We were forced to compare across studies and when you do that you get noise and greyness and you can't see anything. We did long acting drug, and short acting and compared MAOIs versus short acting drugs - nothing. But I suspect that it may be buried in there and it's going to take a proper study that compares rates.

Now there have been recent reports comparing fluoxetine to short acting SSRIs with a different syndrome that is the sort of physiologic syndrome of aches and pains and headaches and twitchiness and things that come after stopping SSRIs fairly abruptly and there apparently the rate of drug clearance makes a difference. It may also happen with the clinical rebound of depression. It has been a lot of fun. The problem with all this is that it's a political quagmire and I feel very uneasy about it when I think deeply about the implications all this.

**Can I throw one more piece into the jigsaw? I think the good thing about all this work is it has been done by a person who is clearly an advocate of pharmacotherapy. But in addition to highlighting all these problems of pharmacotherapy, one of the other pieces of work you've done has been to track the frequency with which people make different diagnoses, where you show that lo and behold as a particular treatment becomes available the diagnosis that goes with that treatment seems to actually increase in frequency. Now that can be read two ways. There's the good thing about it which is yes if we actually have the treatment we should go out and try and help people who have the condition. The other way it can be read is the industry sells the illness in order to sell the treatment and they help to raise the apparent frequency.**

There may be an industrial deliberate overselling marketing dimension, I hadn't really actually thought about it like that.

**I'm not saying it's done consciously. I mean the industry don't do these things that way but they are awfully good at being able to get the information out. You say to them look this drug works for OCD and they go into the computer and find all the literature on OCD and they hand it out and somehow it's just..**

I think that what happens is that the way in which the eyes of the clinician perceives the problem gets shifted in very subtle ways. I think most of it is quite unconscious and not deliberate and not skulduggery and not being sold

a bag of goods. It just happens and I think it's driven by good will. I think it's because clinicians want to help people and if there's a way of seeing something in a different way that gives you an opportunity to help them, that's what they're going to do. At least I like to believe that's what they are going to do.

**Sure but you're into this point where if we look at the changing frequency of a diagnosis, if we look at withdrawal syndromes, if we look at TD, you are into a political quagmire.**

Yes well there's the political issue and there is the other nosological quibble I suppose that it leaves on the table. It doesn't prove but it suggests that differential diagnoses are still, despite DSMIV and all the other goodies that we have, an art form and still one can kind of see things either this way or that way, with perfectly good will with no fraud intended. I'm reminded of another story many years ago when I first moved to McLean. I was advising an outpatient clinic that was setting up some new drug trials. The fellow running the program at the time had had two site visits back to back within two weeks. One of them was an antidepressant study and one an anxiety study. And it turned out that one joker in the visiting team was the same person so he heard the presentation of each thing. He was sitting there at the second visit, this colleague tells me, with his calculator adding up numbers. He said may I ask you an embarrassing question. You told us the throughput through your clinic and you told us the number that you could get per unit time last week and now you're giving a number for this week. Last week it was an antidepressant story, this week it's an anxiety one, can you explain that? The colleague blushed a bit and he said yes many of them are the same people. Depending on what the needs are, you can see them this way or that way.

**But if you were to go out there and say just that to the people at an ACNP meeting, there would be those of us who would say yes sure, but there would be others who'd be fairly horrified. I mean the neo-Kraepelinian school really believe there's a different bug causing this disorder and a different bug causing that disorder that there are different treatments to get all of them rather than just general nervousness.**

Let me give you one more anecdote of a personal experience that brought this home to me. Back in the late 80s, there was a young investigator in our program who was studying a physiologic dimension of the behaviour of psychotic patients. He had collected about 100 patients and he needed a verification of diagnoses. He asked me if I'd join a panel of three independent people and put together a group diagnosis. The story was that we worked independently and then got together as a panel and we had agreement in 99% of the cases. But there was a trick. The trick was we could diagnose schizophrenia, schizoaffective, some affective syndrome with psychotic features, and then we could say I'm really not sure. If we allowed all those choices we had perfect agreement independently. Now do you want to know what percentage of people were either schizoaffective or not sure.

**Tell me.**

About 60%. 10 or 15% were clearly schizophrenic and another group were clearly some kind of major affective illness. And then there were these people

who were very complicated psychotic, suffering, unhappy persons that had illnesses that I didn't understand and nobody else on the panel understood. And if we were allowed to be honest, that's where we came out. I worry a lot about false precision.

**Did you publish that?**

No it was too embarrassing. You've captured it here so maybe that'll serve the purpose.

**Saying what you've just put to me now would, I'd have thought, have worked fairly well at meetings before 1980, before DSM III, but once DSMIII becomes the orthodox point of view I can imagine you had to pick your words with care.**

Yes it's hard for people to hear things like this.

**What I'm left with is a feeling of who would pay to hear this point of view. I don't want to in anyway suggest that payments from industry would cause people to think along a particular way, but industry I think can fairly legitimately pay people who have particular points of view to give talks, lectures, workshops and things like that. They'll pay for the points of view that fit in with their interests.**

Let me give you another anecdote that may address this question about the industry. I've talked about this point of view with people in industry a lot more than maybe I wish I had in retrospect. I have made the point since I got onto this idea that you picked up in Goodman and Gilman that the neuroleptic drugs are not anti-schizophrenic, they may be that too but they do a lot of other things. They're broad spectrum. My suspicion is that many drugs that the industry brings out for particular indications probably could be very broadly useful in lots of other things. We've certainly learned that recently with the SSRIs and this whole range of panic disorder, OCD etc that they work for. There's a lot of things that they're very useful for and that's been great from a marketing point of view.

Particularly with antipsychotic drugs I've encouraged people in the industry to think more broadly than just going after schizophrenia. And I keep making the marketing argument to them, because this is going to put bread on their table if they listen to it. That if you think about psychotic illness broadly my hunch is that the majority of persons with psychotic problems are in fact not schizophrenic but are probably affective or organic or the combination. Schizophrenia is a big piece of the problem but it's not the biggest. In fact just recently working on a study of long-term outcome in some first break psychotic people and we found again in going back over that experience that the great majority of these people are affective.

It sounds good from a marketing point of view but the problem is that you then run into a culture clash. Just as American psychiatrists have had a theoretical history and baggage that have led to certain ways of thinking and certain folk ways of practising, diagnosing and so on, industry has it too. I'm still discovering the sociology of industry. It's hard to tune in as an outsider but there is a certain way in which business is done and you don't muddy up your

drug development programme by shotgunning at six different indications at the same time. If you do, it's going to lead to an impossibly expensive series of trials to do. And if you go the other way and you just bring out your new drug as a blockbuster for all psychotic illness or all affective illness or something, nobody is going to pay any attention because FDA has a culture too. They're used to receiving data pitched in a certain format and if you step too far outside the guidelines and people are just not going to listen to you and it's bad for business.

So I understand the nature of the conservatism and where it comes from. Anyway finally after whistling in the wilderness about this for now at least 20 years I was at an advisory board meeting for a company selling a product and I was talking to one of the executives in the company and mentioned the spiel again and he said oh yes we know that. In fact we're developing our drug to go after indication X, Y and Z. Wonderful times have changed.

It was very refreshing to see some hints of an experimental therapeutics beyond the usual six week experimental efficacy trial, a trial that involves anything having to do with maintenance treatment or long term preventive interactions and things like that. Almost every protocol that I've reviewed in the literature and not just in psychiatry but in medicine, almost always the protocol is treat the acute index episode, get people as well as you can, get them into a maintenance situation and then at some point you've got to randomise them into group A or group B. Group A and group B if you're lucky as a patient may be to treatment alternatives, or if you're not so lucky it may be to discontinuation to placebo. This goes on in cardiology, infectious disease, arthritis research, diabetes, probably in all experimental medicine.

I don't like to think those thoughts because it makes me very uncomfortable about the question of when you look at protocols that compare drug and placebo long term, and they show these big differences, I have to keep asking Marsden's question and it keeps haunting me - how much of the difference is a iatrogenically based. How much has to do with coming off the treatment that you've gotten your brain or your body adjusted to and how much is some sort of a rebound. It's an evil thought because it implies several things. It implies that a big chunk of variance between drug and placebo could be artefactual or iatrogenic. I'm not saying all of it but some of it.

The minimum worry from an academic point of view is what percentage of the variance stems from this source rather than the difference between treatment and no treatment. The theme is that stopping treatment is not the same as not treating. You're doing an active intervention.

The not so nice part of all this lies with the financial and practical implications - how do you design studies. Does it mean that every study that involves discontinuation you've got to do a one month, two month, three month taper. That's going to increase the cost of the thing by one hundred million dollars. Who's going to do it how can you do it?

**Just on that score you've raised an issue which is beginning to haunt me a bit recently. When I come over to the US one of the things I see is that over here you guys are using a range of different anticonvulsants for mood stabilisation purposes. Not only that you've actually began to pull in people who formerly would have been thought as being personality disorders you're saying look there's probably a rapid mood change here which we can treat. We can treat what has been called a personality disorder - lets call it bipolar disorder 2 instead. And you're treating an awful lot of people with results that clinically people on the ground feel are actually quite good. But they've done this because they've heard the experts say this is the thing to do and they believed the experts and they've tried a few patients and yes it has worked out. But almost in principle we cannot design an RCT that's going to work. You've got these huge companies with vast resources and they can't get the indication. It can't be done. Have we been deceived by the apparently clear results we get from acute term RCTs done in simple conditions like depression?**

I think that what you're raising is the general philosophical and practical point. I think ACNP and other learned organisations need I hope take some of these questions a bit more seriously and not just dismiss them as annoying. The other thing that's happening right now that's very timely is the all the bad press that we've been getting about doing anything with psychotic people. Anything having to do with drug discontinuation has suddenly taken on a very menacing political tone. Then there's the whole dimension of informed consent - what do you tell patients? Do we have to tell people that if I take you off your medicine and I do it too quickly you may in fact have a 20% higher risk than you would if I took you off in a more clinically reasonable fashion over some weeks or I kept you on it all together what do you tell people. And I don't have answers but I think that those are questions that people really need to be arguing about and trying to get data about.

**Absolutely. Oddly enough we seem to be back where that anticonvulsants are concerned at least almost in the Freudian days where clinically people are doing what the expert has said and they've seen it work themselves in a few cases but they haven't got kind of the RCT evidence. I mean I don't think we're actually doing the same thing as people were doing with the psychotherapies during the 1950s and 60s but curiously we're in the same position.**

There may be the seeds of our potential destruction in that tendency. I think the more psychopharmacology relies on authority rather than objective data the riskier it's going to be that somebody is going to say hey wait a minute you really don't know what you're saying. Somebody is going to say the Emperor doesn't have any clothes.

I'm not sure exactly what the answers are but I think to figure out some more cleverer scientifically acceptable and humane and clinically appropriate ways of designing long term trials I think is a major challenge for the field right now. I've thought about it a bit I don't have any easy answers I think designing some kind of buffer zone of time where you move people from clinical

treatment status to protocol status, maybe giving some period of adjustment, tapering or readjustment.

One of other things these days is it's getting to be a very difficult problem to design even a short term trial in an unambiguous fashion because you almost cannot find virgins any more to sign on to your study. You almost always have to have people who are on standard something or other get them off and then take them into your protocol. In a number of recent trials for example with atypical antipsychotics, where you really don't expect to see much EPS and you probably don't if you're treating a newly treated person, but if you look at the data longitudinally what you typically see are high EPS ratings in the first weeks maybe a month or so then it washes out and then you get down to a very very low level and stays there. And my hunch is that a lot of that has to do with drug washout material. I would think that the companies in order to help market their product and give it the best chance of showing itself at its best would want to work at reducing this kind of ambiguity as well. It's an enormously complicated problem.

I thought about maybe shifting more in the style, doing more dose response protocols rather than you know something versus nothing. But then you get into the haggle about the ethics of too little or too much and do you know that and how do you know it and when do you know it and when you know it what do you do about it. There are also ways of designing trials where you can keep a benign observer neutral observer unblinded and run preliminary analyses, month by month and as soon as you get your 5% data you say that's it the trial is over. No more risk to these people. So I don't know there have to be new technologies and new design methods that might help to minimise this kind of problem.

**From the bits you're saying you appear to think the new antipsychotics are a fairly significant step forward versus old high dose regimes. What about versus the old agents used in a low dose?**

From an extrapyramidal point of view they're better but the larger picture is a very difficult question. Clinically I am sceptical that there's an enormous difference. I've even seen a couple of trials that compared low doses of standard drugs to modern drugs and EPS values are pretty similar. Again that's hard to interpret because some of that has to do with drug carry-over. I guess I'd encourage people not to jump on the new bandwagon and forget everything we've learned from the older drugs.

**It's a bandwagon, we have to jump on it, that's what it's there for.**

In this country we do, but at least in Europe you can be a little more sane about it. The old quote about be not the first to take up the untried nor yet the last to leave the old aside.

There are too many good things out there to just dump and move on. They're still there especially in a pinch, when things aren't going well with what you think is the latest fad. Even lithium which has had a very bad press in recent times.

**We've talked a lot about the hazards of treatment and yet here at the meeting we've got an awful lot of work on genes to predict who is going to have the adverse reactions so you can prevent them. We've got new neuroimaging techniques which may allow us to work out again what's the right drug for you etc etc. How do you feel about the future?**

I have mixed feelings about it because you know I feel like I've been waiting for Godot for 40 years, for the biological revolution to come. I go back to what I said about my visit to Joel Elkes rose garden where he layed out this vision that there was going to be this biological revolution, we were going to understand the causes and cures of this and that you know and it was right over the horizon and if you get in on this business now you'll be able to back out in 10 years and so on. But it's been a very bumpy road. There have been some very interesting ideas. A lot of hard work, a lot of good people doing very clever experiments testing this hypothesis and that but most of it has not really panned out clinically. It has led to a lot of terrific biology and a better understanding of physiology and pathophysiology but not many clinically useful ways of helping with diagnosis or treatment.

**Is there not a feeling that neuroscience will begin to pay off within the next 5 to 10 years?**

I have to believe that. It's my religion. I can't be untrue to it. But it does take an act of faith. Sometimes close to the irrational act of faith. Because if you look back at where we've been, it's been fairly disappointing from a therapeutic point of view - not from a scientific point.

The other work that I've been heavily involved in in recent years is trying to develop new probes and drugs for dopamine receptors and I've spent a lot of time working on D2 partial agonists and recently been working on a lot novel approach for D3 and D4 receptors. That's been a lot of fun. It keeps the lab side of what I do going.

**Why have you gone down that route? Is it in anyway an answer or trying to look at why clozapine does what it does?**

Not really, it's interesting that clozapine has a complicated and subtle pharmacology that will keep the basic pharmacologists busy for a long time. The fairly simplistic models of clozapine, that it's a D4 antagonist or whatever are a bit too simple. But those simple ideas are good ideas and they've paid off quite well in developing improved drugs that are based on the D2-S2 approach. And I think that the story of D4 is not finished yet, I'm told that the Merck experience with their drug may be because it's actually an agonist and not an antagonist. And there are some real antagonists there in various pipelines. Even though the drug development part of these ideas may not have paid off very well, I think that we've learned a number of interesting things about how receptors work and about plasticity mechanisms and things like that.

Another interesting resident, who currently is a very highly placed officer in a well known North American pharmaceutical company, called me one day when he was a senior resident in an outpatient clinic. He said I've got this weird story that one of the patients just told me. I don't know what to tell him

but I figured maybe you'll know. It was a woman who had a fairly minor anxiety condition and was mainly there for psychotherapy. I don't think she was even getting any medication but she had been working with this resident for about six months and at that point she said I think I know you well enough to be able to trust you - I'm going to tell you something that I've never told anyone before. I'm a cocaine addict and I'm very good on it. I'm very functional and I make a good deal of money and I can afford to sustain my habit. And she said, last year my breast started to swell and become engorged and started lactating. So I went to the family doctor and he said you need to see an endocrinologist and she got worked up and it turned out she had a microadenoma and she was hyperprolactinemic and got put on bromocriptine.

She said I don't know a lot about pharmacology but I have to tell you that I've treated myself as my own guinea pig and I've done on-off on-off trials let me tell you the results. She said when I'm taking my bromocriptine, my breasts are fine but I get nothing out of the cocaine. Can you explain that doctor? She said I stop it for a while and I go back to the cocaine and it works great again. And she said I really need the bromocriptine medically but she said the habit is getting very expensive and I can't keep it up. The doses of cocaine are going sky high and I'm afraid I'm going to kill myself. What's going on here? I said well it doesn't make any sense pharmacologically - you're mixing direct agonist with an indirect agonist, they should potentiate each other not block each other. I said I don't know what it means but tomorrow in the lab we'll do one of our Friday afternoon bio-quickie experiments. We'll give some rats some cocaine and we'll give half of them some bromocriptine. Well bromocriptine blocked cocaine.

This got us into trying to understand something about partial agonists. I didn't know anything about bromocriptine but the more I read about its pharmacology the more complicated it turns out and at best it can be described as a partial D2 agonist and it may even be a D1 antagonist by some measures. The story is that if you work in a denervated system or apparently in an unregulated system like the anterior pituitary or the denervated state of parkinson's disease, the receptors will respond very nicely to a partial agonist because they are in their maximally expressed and sensitive format. If you work with an intact system, the partial agonist will look like an antagonist in competition with the endogenous agonist, so if you pit bromocriptine against dopamine bromocriptine will block dopamine. There have by the way been some studies trying to use bromocriptine to treat cocaine addiction that have never gotten anywhere but the phenomenon is interesting.

Anyway it got us into the whole idea that it is possible to work with drugs that rather than being sledgehammers of the dopamine receptor might be able to tickle it into submission by being partial agonists, mixed agonists-antagonists. We have spent a number of years trying to work with developing drugs like that. Some of them had very interesting properties and we found for example with some of our work with plus apomorphine??? compounds that they are not only antagonistic against dopamine direct agonists like apomorphine but they are actually quite limbic selective. If you micro-inject dopamine into the limbic

system for example some of these compounds selectively block dopamine but if you put them into the striatum, they have no effect. Whether drugs like this will ever make it into clinical trials, I don't really know. Sandoz did a lot with partial agonists and Boehringer did a little bit. The problem that you run into is that you can try to predict as best you can in the laboratory or in animals what will happen but when you get to the clinic all bets are off. Most of these drugs have turned out to be either very agonistic or very antagonistic when you get to the clinic.

**In a partial agonist as a group from the opiate partial agonists right through to present day they haven't quite made it have they?**

The problem is it's very hard to target exactly the right balance of agonism and antagonism based on laboratory models. We need to know more about receptor theory. We'll get there at the theoretical level. Whether we'll invent the perfect risk free drug, I don't know.

**Receptor theory is very much the magic bullet view - we just need to work out what receptor is down to the 5HT 17c level and once we have things that pure we'll get the drug that will hit it. But Merton Sandler was here earlier this afternoon talking about trace amines and Sol Snyder was here yesterday afternoon talking about a range of agents which aren't classic neurotransmitters at all. Maybe the whole thing is going to be a much more mysterious than the classical receptor story.**

It no doubt will be. In fact the trend that I see in the field that makes me extremely uneasy right now, its probably my age showing and not being as nimble as 20 years ago in keeping up with all the latest theories and part of it has to do with the broader perspective gained by coming into the field originally as a physiologist, but I'm really very uneasy about the molecular preoccupation.

We have to go this way - it's a phase of life that we've got to get through. And it's important, it's a big story, the technology is just too powerful not to do it. But I wish that some younger folks coming into the field will try to keep a point of view that at some point after we've gotten the 19<sup>th</sup> receptor sub-type that somebody's got to put it back into a working nervous system and develop a predictable pharmacology and actually figure out what it is doing to human beings. I think people right now are frankly overly infatuated with this idea that the molecular approach, pure and simple, is going to go directly to the right endpoint. It will raise more questions than answer but it's a phase we have to go through.

**How long will it take before we can begin to build things up again?**

Well it's already happening. The things that have been with us for more than 5 or 10 years are beginning to move into a more physiological and outcome predicting phase. Every new thing will take a few years of people being enamoured with it before we get beyond that and say you know where does this fit into the working brain and how does it work.

**One of the things I've heard from clinical people here within ACNP is that ACNP has become almost a neuroscience society. When do you suspect it's going to be able to return to clinical neuroscience?**

Well I've been in a real state of dissonance for the last few days as I've been flipping through the abstracts trying to read as many as I can when I have a few moments free. There's a very sharp biphasic distribution. There are the most esoteric basic molecular papers and then there are very traditional applied clinical drug trial outcome papers so apparently the society continues to be broad enough for all sorts of bedfellows and that's good.

Back in the late 80s, a young investigator in our program, studying a physiologic dimension of the behaviour of psychotic patients, had collected about 100 patients and he needed a verification of diagnoses. He asked me to join a panel and put together a group diagnosis. The story was that we worked independently and then got together as a panel. We had agreement in 99% of the cases. But there was a trick. The trick was we could diagnose schizophrenia, schizoaffective disorder, some affective syndrome with psychotic features, and then we could say I'm really not sure. If we allowed all those choices we had perfect agreement independently. Now do you want to know what percentage of people were either schizoaffective or not sure.

About 60%. 10 or 15% were clearly schizophrenic and another group were clearly some kind of major affective illness. And then there were these people who were very complicated psychotic, suffering, unhappy persons that had illnesses that I didn't understand and nobody else on the panel understood. And if we were allowed to be honest, that's where we came out. I worry a lot about false precision.

Did you publish that?

No it was too embarrassing. You've captured it here so maybe that'll serve the purpose.

When I first moved to McLean, I was advising an out-patient clinic that was setting up some new drug trials. The fellow running the program had two site visits back to back within two weeks. One of them was an antidepressant study and one an anxiety study. It turned out that one joker in the visiting teams was the same person so he heard the presentation of both. He was sitting there at the second visit, this colleague tells me, with his calculator adding up numbers. He said, may I ask you an embarrassing question? You told us the throughput through your clinic and you told us the number that you could get per unit time last week and now you're giving a number for this week. Last week it was an antidepressant story, this week it's an anxiety one, can you explain that? The colleague blushed and said yes many of them are the same people.

Depending on what the needs are, you can see them this way or that way.