REACTION PATTERNS TO PSYCHOTROPIC DRUGS
& THE DISCOVERY OF PANIC DISORDER
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My first encounter with your work was when I was in Cambridge, in 1986. I became aware of it through Martin Roth's involvement in the Upjohn trial of alprazolam in panic disorder. Even then in the UK, most clinicians weren't prepared to accept that panic disorder was a real entity. Your name was there as the person who created the concept. Now I am hopeful that this book will get beyond the psychiatric profession and out on the streets and panic disorder is interesting here in that its come from nowhere to being one of the concepts that everybody, even the person on the street, knows about now.

The next time your name came into the frame was talking to a colleague from New Zealand, Peter Joyce, about an idea I had which is that tricyclic antidepressants are potentially as antimanic as they are antidepressant. He said "ah ha, one person who has really tested this way back in the 60s was Donald Klein who when people came into hospital randomly allocated them to antidepressants, antipsychotics or whatever, regardless of the diagnosis and it looked like people with mania didn't do well with antidepressants". Do you want to pick up on either of those two points.

I think maybe I ought to start out with going to Hillside. Back in 1959, I was working in a research department at the Creedmoor State Hospital. I had gotten interested in psychopharmacology from the time I had spent in Lexington during the early 50s but my I was initially interested in being an analyst. In those days, it was really the only game in town if you were interested in doing something intellectual in psychiatry. I had actually started in the New York Psychoanalytic in 57 and in 1959 a job opened up at Hillside and I went to work for Max Fink.

Max Fink was a neurologist and psychiatrist and he ran the Department of Experimental Psychiatry there. He was a diagnostic nihilist and at that time that was not a stupid thing to be because there were extensive studies carried on during the 50's by psychologists showing that psychiatrists had no inter-rater reliability whatsoever. They could barely tell psychosis from non-psychosis and that was about it. So Max's attitude was that it was foolish to think in terms of diagnosis. I was perfectly willing to go along with that at the time. Now the way Hillside ran, it was essentially a long term psychoanalytic hospital. The average length of stay was 10 months to a year. Two hundred beds and they all got intensive psychotherapy. The deal that Max and I were able to work out with Lew Robbins, the Head of the Hospital, was that I would be the only person in the hospital who could write orders for medication.

Now I'd write anybody's orders. The way this worked was, if they wanted to medicate a patient, which meant that psychotherapy had failed and the patient was in the hospital for 8 months already and they were getting concerned about getting them out, they would have to call me before the patients were put on medication, which would give me the opportunity to ask why they wanted to put the patient on medication. Then I would see the patient and speak to the ward staff. I would write whatever order they wanted and then I would see them weekly and talk to the ward staff and talk to the therapist. And every time they wanted to change the dose, they had to tell me and I would write it.

It was the best learning experience I ever had. Because what it did was it gave me a tremendous opportunity to see how other people handle patients. They'd do all sort of things I

would never have done, sometimes right, sometimes wrong and also to get a real idea of the sociology of prescription in the psycho- dynamic framework. So for instance you'd have the following sort of story, they'd call me and say "look I want Mrs Jones on thorazine 200 mg" and I'd say "why" and they'd say "well she's schizophrenic" and I'd say "yeh but she's been here how long, 10 months, and she's been schizophrenic all along why do you want to give it now?" They'd say "well she hasn't responded to the therapy and we think that it's probably a good idea". When you'd talk to the patient about it, the patient would say its okay by me but it means the doctor has given up on me. When you'd talk to the ward staff about it and they'd say, "she kicked a maid last week and we're not going to put up with that".

Anyway it was tremendous. At the time everyone was called schizophrenic, nobody was thinking diagnostically. To think in terms of systematic descriptive diagnosis was a sure mark of a superficial mind because everybody knew that that was just the symptomatic manifestations of the internal conflicts which is where the real action was. So people got treated quite randomly and so my first couple of papers were on a hundred patients treated with thorazine and a hundred patients treated with imipramine. What I did was to isolate different reaction patterns. They were published in the American Journal and Archives back around 1962.

Now in that very first paper on imipramine I noted there were a group of patients who had periodic, I guess at the time they were called anxiety attacks, who got better on imipramine and that was very startling. It was a good clinical observation, if I say so myself. Now Frank Ayd did a paper in which he talked about the effects of imipramine on neurotic patients. Another guy named Doug Goldman, who is dead now, had also written a paper on imipramine and neurotic patients. But neither of them actually singled out panic attack as being the key variable that was changing with imipramine.

Now how I first noticed it was that some doc called me up and said that he had a patient who was schizophrenic and they tried thorazine on him and he'd gotten worse and would I see him. Which I did. And this fellow was hideously anxious, extremely dependent, extremely demanding but he wasn't delusional and he wasn't hallucinated and he didn't have thought disorder and he didn't have any restriction of affect. He was so impaired in his functioning they had concluded that he was schizophrenic. Thorazine made it substantially worse which it does regularly when a patient has panic disorder.

Going over the thing, it turned out that he had these periodic panic attacks or anxiety attacks - later I called them panic attacks. So I talked to the residents about that and said "I don't know what to do with this guy but I've been working with this new drug, imipramine, and it seems to have some funny anxiolytic effects when you give it to agitated depression and who knows maybe it will work here. So essentially we had a patient we didn't know what to do with and also we had a drug and we were unsure what it did so we mixed them together. It was pure empiricism. And so after each week we'd see the patient and he'd say "this drug is terrible and it's not helping me, I am getting worse, when are you guys going to help me?". And we'd up the dose and say "see you in a week". After about the third or forth week, the patient was still complaining bitterly, very anxious, "its terrible, I can't go around the grounds by myself". The psychotherapist said that this drug was a waste of time and the psychotherapy supervisor said it was a waste of time but one of the nurses said to me "he's better".

I said "well how do you know he's better?" I asked several nurses and they all agreed but they didn't know why he was better and finally one good clinical observer said that "well you know

he's been in 10 months and 4 times a day for the past 10 months he has been running to the nursing station saying he was dying. And we'd hold his hand and say no, there's nothing wrong with you it's just this terrible anxiety, the doctors have checked your heart out, you're not going to die and 20 minutes later he'd wander away and 2 or 3 hours later he'd be back and he hasn't done that for the past week". So I went to the patient and said "I understand you're feeling better" and he said "who told you that? What a ridiculous idea." And I said "well one of the nurses told me that". He said "well what do they know". And I said "well isn't it true that you've been running to the nursing station daily for 10 months now" and he said "absolutely". I said "and you haven't done that for the past week". And it stunned him. He had no idea he had changed his behaviour and he said "well that's right". So I said "how come"? And he said "um I guess I've learned they can't do anything for me" and I said "you've been here 10 months and this week you learned that they can't do anything for you". He said "well you've got to learn sometime". The guy's a premature behaviour therapist.

Now of course what happened, which became plain with a series of patients, is that it was the panic attack, that was the proximal stimulus that led him to run to the nursing station. When you panic you reach out for help. And that's what he did. And then when the panic stopped, he wasn't running to the nursing station but he was still terribly anxious. He still wouldn't go around the grounds by himself, somebody had to walk with him. What struck me was that we have to distinguish the panic attack from the state of chronic anticipatory anxiety - they are just not the same thing. And that for us to continue calling it an anxiety attack in the context of chronic anxiety is exactly wrong so that's why I came up with the neologism.

Where did you get the actual term from?

I don't know. It came out of the blue somewhere. If you look in Joan Riviere's old translation of Freud, which I had read because I was in analytic training; in the Standard Edition they use the term anxiety attack, in Joan Riviere's edition they are called panic attacks. And that was the edition I knew, so I may have picked it up from there.

There are always people who like to trace things back and they say well you can see the concept in the old German literature.

Oh yes you can. Freud in 1895 described it beautifully. In his 1895 paper on detaching the syndrome of anxiety neurosis from neurasthenia, he points out quite clearly that people who have agoraphobia remember the onset of the agoraphobia with the occurrence of an anxiety attack. That is the second thing I noticed - going back to the patients. Once I started focusing on the attack, it occurred first, and the phobia came second. Then I thought of it as a three-layer cake - the panic attacks began an anticipatory anxiety and then you avoid the situations in which if you got a panic attack there, help couldn't get to you and that's what called agoraphobia.

So I saw that as a nice sequence. And Freud says that. And Freud also describes in a number of case histories something which has just recently struck me as being the key issue in panic attacks, which is the extreme feeling of suffocation, the very marked respiratory distress that occurs in the panic attack and that's actually why for a short period of time Freud accepted Rank's birth trauma theory. He accepted this because what was the birth trauma - the birth trauma involved the cutting off of respiration and that's what Freud said very clearly. That's the trauma - the feeling of suffocation. Any way he gave it up very quickly. It was a rather transient idea of his. And long before Freud, Westphal described anxiety attacks and if you

talk to Pierre Pichot he tells me that some Frenchman described angoisse paroxysme back in 1830.

So, it's not like it's a new observation. What's new is that I put it together a different way. I think what's new also is that it's not anxiety and nowadays I'm saying it's not even fear and that is because you have no hypothalmic-pituitary-adrenal activation in a panic attack, neither during a clinical panic attack or during a provoked panic attack.

So, what is it?

I think it's a suffocation false alarm. I think that people think they are suffocating and I've got a lot of circumstantial evidence for it.

Are there two entities that may at times look the same, one which involves the respiratory symptoms and hyperventilation and one which doesn't

It's hard to say. The English psychiatrists, Brandon and Briggs published a reanalysis of the Upjohn study in the British Journal of Psychiatry, in which they had imipramine vs alprazolam vs placebo. What they did, which had nothing to do with my work at all, was they cluster-analysed the symptomatology of the patients and how they described their panic attacks. It turned out that 70% of the patients had respiratory symptomatology and about 30% didn't. When you lay it out, if you look at the whole group, imipramine and alprazolam are the same but in the patients with respiratory symptomatology imipramine is better than alprazolam and for the patients without respiratory symptomatology alprazolam is better than imipramine.

Well that's interesting, that sounds like we have 2 different processes. One panic disorder with respiratory symptomatology, another panic disorder without respiratory symptomatology. But one of the problems there is that it could be a misdiagnosis. Jerry Rosenbaum also re-did the Upjohn study. So I called him up and I said "look you guys have a chance to replicate what Briggs did", because one analysis you know you don't quite believe. They couldn't replicate it and the reason they couldn't replicate it was that well over 90% of their patients had respiratory symptomatology. So, what had happend to the 30% in the Upjohn study. Now I know social anxiety is frequently misdiagnosed as panic disorder so the possibility may be that they had a lot of social phobics in that study, who imipramine does nothing for, but alzprazolam is a good drug.

Can I pick up on one more thing. One of the things that happened with the coining of panic disorder was that the old idea of hyperventilation syndrome, which was common 10 years, at least in the UK - everybody was talking about hyperventilation syndrome and of course the treatment is to breathe into a plastic bag or whatever. Is there some interface between this and panic attacks then?.

Yes I understand but a panic attack takes 4 mintues, by the time you've got that paper bag up there you've got occupational therapy. You're giving the person something to do until the panic attack has gone away. There's a guy named Van den Hout, a Dutch psychologist, who's done a controlled study of re-breathing and there's nothing. The hyperventilation types claim that its acute respiratory alkalosis that provokes a panic attack but Jack Gorman and I have found that's just wrong.

We noticed that during our lactate induced panic attacks the patients did hyperventilate and we said well we really ought to address the issue of hyperventillation. So we thought for a while how can we get people to hyperventilate and not get a respiratory alkalosis. I forget who had this idea but somebody came up with the idea that if you hyperventilate in 5% carbon dioxide, you're in dynamic equilibrium because there's 5% carbon dioxide in the lungs. So you're blowing out as much as you're breathing in and you can't get an acute respiratory alkalosis under those circumstances. So we said great and the study we did was we had a new computerised plethysmograph, for measuring every breath, and we either put them in room air to hyperventilation or hyperventilation in 5% carbon dioxide. The theory going in was they would panic with ordinary hyperventilation and they wouldn't panic with carbon dioxide.

It was exactly the opposite. And we got no panics with hyperventilation and that's been now replicated by 5 other people. What happens when people with panic attacks hyperventilate is that they don't like it, they feel dizzy, they feel depersonalised but they don't panic. In carbon dioxide they panic like crazy. This is what got us to thinking along the lines about the suffocation alarm.

Basically if you look at the challenge studies, Pitts came out during the 60's with the finding of that intravenous lactate produced panic attacks in patients with panic disorder and nothing else. And he was instantly attacked on the same ground as David Clarke is talking about, that it's simply psychological. The person, they get symptoms, it reminds them of a panic, it frightens them, they get emotional, and they spiral into a panic attack. Pitt's answer to that was that he gave the patients EDTA, a powerful calcium chelating agent, it threw them smack into tetany but they didn't panic. So the idea that they are just reponding to a non-specific stress and they produce this syndrome is silly but that hasn't stopped it. Since then it has been shown that insulin doesn't cause panic and physostigmine doesn't cause panic and 5HT-P doesn't cause panic and all sorts of weird things that you give to people

Don't cause panic..But the cognitive therapists would say well okay but cognitive therapy works.

No better than simple non-directive support as Shear showed. There's nothing specific about it ... there are 4 different studies showing that when you compare cognitive therapy against an acceptable credible therapy the other therapy always works as well. So, I think that they both work is possible. Even then there has only been a single one, comparing cognitive therapy against medication against placebo in a sample where the medication is shown to be better than placebo. Black, in the Archives, showed fluvoxamine was much better than placebo but CT was barely better. David Barlow tried that but medication was no better than placebo in that trial. That's the story. Jack Gorman is doing the study now - the one that I've just described - and when that comes out we'll know something, but up to this point it's all fluff. Both the specificity is fluff and the actual demonstration of efficacy is fluff.

Can I ask you, this whole area has created - well wars is the word that comes to mind - the series of articles in the British Journal of Psychiatry where Isaac Marks and others attacked the Upjohn work, there isn't anything else quite like it in the psychiatric literature. Passions seem to get aroused on this one. How do you account for it?

I think it's Isaac. I've known Isaac since the early 60's. Isaac is an extremely smart man and his first book on Fears and Phobias was a wonderful book. It was just terrific but he missed the boat. I told Isaac back in 1963, "you know isn't it strange imipramine blocks panic attacks" and

he just scoffed at it. I told the same thing to Martin Roth. He tried imipramine on some of these people and said "its just poison". I can believe that because there are people who are hypersensitive and apparently he had some bad luck. But Roth converted later and took part in the Upjohn study, whereas Isaac has been relentless in his attempt to down grade the importance of panic attacks. He had the opportunity to run with this idea but he didn't. He did a study on imipramine in panic disorder and found nothing. When Al Raskin re-analysed his data, he found a big finding Isaac had missed.

I didn't know that one. No. It seems to be broader than just panic disorder. He seems to be anti-drug treatment because he had the same gripe with the use of 5HT reuptake inhibitors and OCD. With clomimipramine in particular..

Well sure, I think Isaac has converted into a learning theorist. I don't know if you've seen these articles by me and my daughter, Hilary Klein, that appeared in a book that Peter Tyrer edited for the British Association for Psychopharmacology. There's two chapters in which we say yes there's an argument and lets handle this argument and list 27 arguments about panic attacks according to Marks and refute everyone of them.

How important do you think the coincidence of interests with Upjohn was in helping get panic disorder on the map.

It was already on the map. I'll tell you how panic disorder got on the map. I was writing articles on panic disorder and I had got about four good studies, well controlled, showing that imipramine worked. And also Pitts had done his work on lactate and they got a lot of play. I think one of the major reasons the impact wasn't bigger was that I was working at Hillside Hospital, which is a small non-academic hospital. I had no university appointment. But then somewhere around 78/79, Ballenger and Sheehan published a paper out of Harvard, where they were both residents at the time, saying well we've decided to check Klein out and he's right - we did a double blind placebo controlled trial and by God it's true. That's what happened. I don't blame people for not paying more heed before because it's nice to have an independent replication. It was the first time there was a replication and in Harvard of all places.

If it comes from Harvard it has to be true!

Has to be true. That's what did it. So when the DSM III came along I was on the Task Force and Bob Spitzer, who was the chairman of the committee, was fierce about getting panic disorder into the thing.

Why was he so keen?

He had had some personal clinical experience and thought it made sense. And that the data was good. The data was actually better than it was for many other things and at the time ...

Could it have been, he was keen to sort out the whole neurosis concept and in a sense to do away with it. Was this the Trojan horse. Did he see one of the ways to ...

No, obviously I've been doing some thinking on this. Bob said to get into DSM III you have to have inclusion criteria and exclusion criteria and the concept of neurosis is basically a concept based on exclusion criteria only. What a neurosis means is a person who is not psychotic, but

there's no body of inclusion criteria. There is nothing in common between all the various things that are called neuroses in terms of inclusion criteria. That's the reason that they got rid of neurosis. It just didn't make any sense in terms of an organising principle.

The only sense it made was if you adhered to a particular etiological theory and we weren't having any of that. That caused a tremendous amount of political fights. I don't think that panic disorder was particularly brought in with regard to neurosis. I think it was just that Bob and the Task Force thought it was a good idea. One of the things that is funny is that we had an argument then about agoraphobia without panic disorder and I said that panic disorder was the necessary but not sufficient pre-cursor of agoraphobia. So is stand alone agoraphobia a real thing? I said probably not. Bob said shall we take it out but I said leave it in and we'll see how often it gets used. Clinically it's never used. But epidemiologically it turns out that ECA studies and the study done by Wittchen and Angst in Europe found that there is three times as much agoraphobia without panic disorder as there is of agoraphobia with panic disorder. That was used by Wittchen and by Marks as evidence that basically the relationship between panic disorder and agoraphobia is fallacious.

I never quite understood it. I looked at the criteria for agoraphobia and the criteria for agoraphobia are one out of six fears, one of them being afraid of being in a crowd. So finally Myrna Weissman did a clinical review and she got about 23 patients who in the ECA study had come out with agoraphobia without panic disorder and found that 22 of them didn't have agoraphobia. They all had simple phobias. They weren't massively restricted with regard to travel. Anyway, what happened was that the epidemiological criteria were such that a lot of people who were diagnosed as having agoraphobia just didn't have it.

One of the other things she did with all data of course was to flag up a link between panic and suicide.

That's a very controversial point. I think in the context of depression that panic is an exacerbator and that may well drive a person to suicide but that pure panic disorder is a increased risk for suicide, I rather doubt. But she said it did.

Lepine in France didn't find it and we went back in our records and we didn't find it. Let me tell you what we did find. In the ECA they register whether the person has suicide attempts and whether they have panic disorder but there is no timing, you didn't know which came first. In our family study, we have exact records. We found out that in pure panic disorder the increase in suicide attempts was there, except that we had a 7% rate of suicide attempts anteceding pure panic disorder. It occurred during adolescence and separation - anxious people are very prone to suicide attempts, with their displays of "you've got to help me".

The fact that panic disoders and mood disorders both respond to the same drugs, does that point to a link between the 2 or not?

No, not all of them work. First of all our best antidepressant is ECT and ECT did not work on panic disorder, it makes it worse. Maprotiline does not work for panic disorder, bupropion does not work for panic disorder, so it is not all antidepressants. Nonetheless it does seem funny and the incidence of depression in people with dyed in the wool panic disorder is sky high. Now, Myrna has just published a paper in the Archives in which she did a nice family study in which she says that they sort independently, so that they are not really related to each other. The fact that they happen to be together is just an accident. We did our own family study and

we've got some indications that that's not true - there are people with panic and depressions that run together in families. It's actually significant on one test so it's there but it's not tremendous. So I think that's an unresolved question. It comes to just what the relationship is then.

But certainly in terms of the common role of antidepressants that's not correct. And of course the high potency benzodiazepines work on panic but don't do much for depression.

Let me hop for a second. As regards depression you outlined the concept of endogenomorphic depression and argued that anhedonia is a key issue for people with mood disorders. Do you want to run through that? Listening to Prozac has popularized some of these ideas.

Well yes that was essentially derived from my inpatient experience in Hillside and you would see people who were just basket cases. We saw hundreds of guys with melancholia which you just don't see anymore. These people were profoundly changed, nothing made them feel good, nothing. Food tastes like cardboard, sex was nothing, and when their family came to see them they couldn't didn't care less. And then we'd give them imipramine and 3 or 4 weeks later the veil dropped and all of a sudden we had this whole new human being. On the other hand there were patients who had many depressive complaints and you'd give them imipramine and nothing much happened. But we had them in the hospital and I'd see these patients after they came in and I'd interview them and they'd tell me life was terrible, nothing moves them, they can't get any pleasure out of life and I'd see them 20 minutes later laughing it up in the corridor. Now those were the people who imipramine didn't help.

So it came to me that the difference seemed to be the ability to respond to pleasure and that's what led me to the endogenomorphic idea. I think on the whole for severe depressions, moderately severe depressions there's a useful distinction. I also now make the distinction that I don't think I'd made in that article between consummatory pleasure and appetitive pleasure. Essentially this comes down to is that I think there are two sorts of pleasure. Freud said that pleasure was a reduction in tension. And he obviously had orgasm in mind or being satiated with food. But as he himself says somewhere, it seems hard to deal with fore-pleasure on that basis; a very pleasurable period with rising excitement. What he says well links in with the descrescendo, the orgasm but that's not very satisfactory. There are people who do rock climbing, and they go jogging, all these things give you pleasure.

The ethologists a long time ago made the distinction between appetitive activities and consummatory actitives. Consummatory activities were largely highly stereotyped, species specific, devices for either self-preservation or procreation and appetitive activities were everything that got you in a position for doing consummatory activities and it struck me that there are two different sorts of pleasure there. In a sense you might say it's the pleasure of the hunt and the pleasure of the feast. They are not the same thing.

Looking at the severe patients it struck me that their pleasure of the feast and hunt were both shot. But that the patients who respond to MAO inhibitors as compared with patients who respond to tricyclics, their consummatory pleasures are intact but their appetitive pleasures were distinctly not there. Normally when you anticipate having a good time, you are already having a good time. You've already got a glow of pleasure in anticipation. They didn't have that. And you know you might say to someone "let's go to a party" and they say "parties are a bore" and you would say "that's funny I saw you at a party a couple of weeks ago and you

seemed to have a good time" and they'd say "no, no, I didn't really have a good time" but you drag them to the party and they do have a good time. In anticipation it's a bore, it's unrewarding but in the actual consummatory activity, not bad.

Now, although I think that's held up pretty well, there is one fly in the ointment. Recently Fred Quitkin, who's worked with me for thirty years now, a very good guy, did a study where he took 500 patients and did this comparative study on imipramine vs phenelzine vs placebo. They had to have emotional reactivity, and they had two out of four, what we call atypical signs, which are basically over-eating, over-sleeping, rejection sensitivity and a sense of tremendous fatigue. When we took people into that trial, people showed up with only one of the four. So we figured well why waste it, we will put them in and handle them separately. Then people started showing up and they had 0 out of the 4, but they did have depressive complaints with a reactive mood and they did not have endogenous signs. So, we took them too. We only had a small sample, about 60 I think. Amazingly, they responded both to imipramine and phenelzine. Whereas if they had any one of those 4 signs, imipramine was barely better than placebo and phenelzine was much better than placebo.

So I don't know, it's conceivable I'm wrong. Consummatory anhedonia may be an aspect of severity. It may well be that what I am calling the atypical signs are actually signs of a particular kind of disturbed physiology, which is like in amphetamine withdrawal. If you take somebody, anybody, and you give them 30 mg of dextroamphetamine a day for a month and halt it you can produce someone who is over-eating, over-sleeping, sensitive to rejection and completely fatigued too but I don't think that's a complete answer.

Mention of Fred Quitkin brings to mind the idea that it should be possible to work out what a drug does from the pattern of responses to it.

Fred and I worked on that for quite a while and Fred grabbed the ball and carried it. The logical analysis of drug effects has taken second place. We just did a Markov analysis with Don Ross, who's our statistician. Now a Markov analysis is like this ..in the simplest situation, you've got two states. You're either okay or you're not okay. Now you measure everybody every week and ask them whether they're okay or not- okay. Now you end up with 4 transition probabilities. You can either go okay-okay, or okay-not-okay or not-okay-okay or not-okay-not-okay. So you have a matrix of transition probablities between each week. There are statistical tests for analysing whether that matrix is constant over time or changing over time. And if it is changing over time, when does it change over time.

Well it turns out in our analyses that for placebo its a constant matrix, there is nothing that's happening obviously, it's all noise from week to week. Whereas with both imipramine and phenelzine there are marked discontinuities. That is a crucial issue for drug development. In phase II drugs, they don't have placebo. Now most drug houses look at people when they come in and people when they go out and they say "oh look 50% of them get better, it seems like the drug is working". But when you apply Quitkin's pattern analysis or this Markov analysis you can ask are they really getting better in the way that looks like an antidepressant response for instance.

Well why has the industry not picked this up because it seems to me that we need to get out of the rigid placebo controlled double blind randomised control trial.

Well I think the industry are very conservative. Secondly they've got the FDA on their back and the FDA and Paul Leber doesn't think badly of our work but nonetheless he could have a lot of second thoughts about accepting a study on those grounds. My belief actually is that it would be good for the industry in Phase II but in Phase III you're probably stuck with pretty much the usual thing.

Can I bring up a further issue, which sort of plays into this one, which is that you've been talking about clinical entities, the clinical needs of trials and trial design etc. I'm aware that within ACNP there's been a feeling for some time among the clinical people within it that ACNP is going the wrong way. It's going too much down the road of becoming a Neurosciences Society.

I said that back in 1980 when I was President of the ACNP. The ACNP was founded by clinicians - Frank Ayd, Heinz Lehmann, Nate Kline and others. It was bankrolled by the drug industry on that basis. First of all, they immediately set themselves up as a limited society - they were only going to have a certain number of members and they said they were only taking the best. The fact of the matter is that it's far easier to demonstrate your scientific skills in non-clinical areas. You can do very highly technical work on rats and you can study the physiology, the brain chemistry and you can do wonderful things so that when you start comparing the CVs, the bibliographies, of people who are doing clinical work with people who are doing pre-clinical work by any usual test the pre-clinical people were outstanding and the clinical people were finding out if this drug worked and if that drug worked.

Which looks much more..

Which looks much more pedestrian and uninteresting. Also the whole ideology is that the basic science provides the ground work for the proper understanding of clinical science. That's the way people think. It doesn't mean that they are right. They really hadn't got together close enough yet so they still have two pretty independent tracks.

What happened essentially was that I did an analysis of the membership of the ACNP back in 1980 which showed that the number of clinical people working with whole human beings in clinical settings was steadily dropping and that the number of non-clinical scientists was steadily rising and that we were on our way to being a neurosciences organisation. The charm of the ACNP was the attempt to integrate the two - you wanted the non-clinical scientists and clinical scientists in the hope that maybe you would strike a spark somewhere. What was happening was the ACNP panels were becoming more and more 5HT-14 receptor oriented and what that means to the rat - with no attempt even to get at clinical relevance.

There was one session at ACNP, where there was about one clinical panel only in the whole meeting and no attempt by any panel to take this into account. So I said enough is enough. The ACNP programme committee is trying to respond to that and more credit to them. I think that that's good. In the meantime, they don't have a serious commitment to the whole idea of educating practitioners and I think this is necessary because a number of studies now have shown that most practitioners are doing poorly. The RAND study, for instance, by Ken Wells in which he essentially tracked depressives through the primary care system. The vast majority of them never got diagnosed. And once diagnosed never got treated.

You did more though than just say to ACNP enough is enough. You went and formed your own society. Tell me about that.

Actions speak louder than words, that's all. It's interesting what happened actually. Paul Wender and I had been friends for many years. Paul's a terrific, guy who has done remarkable work in at least two areas, one being childhood minimal brain dysfunction and attentional deficit disorder. He is the leading figure showing that attentional deficit disorder persists into adolescence and beyond. And the second was his work with Seymour Kety on the adoption studies in Denmark. Now Paul and I had gotten friendly and we wrote a book back in 1981 on Mind, Mood & Medicine and somewhere along the line we decided depression had been treated badly and we formed an organisation called the National Foundation for Depressive Illness, which was a non-profit corporation - which did not do very well. We had difficulty raising money. Senator Hatch had a man on his staff, who was really depressed, and Paul's treatment of him opened Hatch's eyes. He said "my God this stuff's real". And he asked "is there anything I can do for you" and we said " you can raise some money for us". So he joined with Senators Kennedy, Metzenbaum and Kassenbaum and helped us throw a fund-raising benefit.

Now our funds were going steadily downhill. We had that one big bolus of money but amazingly we had been unable to really capitalise on that. At the time that we were getting fed up with the narrow focus of ACNP, we decided one reasonable use of NAFDI money would be to bankroll this other organisation and help depressives out by increasing the education of practitioners. So essentially the ASCP was sort of godchild of NAFDI. It has a separate board, completely independant and we've got a set of bylaws and so on, except that Peter Ross, who's our administrator for NAFDI is also the administrator for ASCP. And I guess it will stay that way for a while. So that's the reason we were able to get this organisation off the ground because we had some backup.

Will the industry move over do you think?

They haven't. That was one of the major concerns of the ACNP that we would end up cutting off their pipeline.

What would happen do you suppose if the industry did begin to move over.

Beats me. I presume what would happen is the ACNP would develop more clinical interests..

Or else they'd put a contract out on you!

There was a fair amount of hard feeling over that, but they recognise that we are not simply out to get the ACNP. We've got 2 Presidents of the ACNP on our board, myself and George Simpson. And they can recognise that they have got to change.

I think we're faced with just the same problem with the BAP at the moment. BAP like ACNP was begun by clinical people who brought basic scientists in and in recent years has begun to move down the road of becoming a neurosciences group ..

I don't think you have ever been a closed limited membership organisation. That makes a big difference because if you only take 10 people a year and you've got 75 applications, you go for the fat CVs.

One of the other problems is that the basic sciences are very much a case of doing crosswords as it were. Sort of problem solving. You pick the problems that you can solve at any particular time. Clinically though it isn't the same. People who work in the clinical field really don't have a choice about what problems they can tackle or not. They are faced with things that may or may not be solved by them and hence you get...

Do you know the joke about the drunk and the lamp-post? There's this drunk wandering around the street and the cop comes along and says "what are you doing" he said "my keys, I dropped my keys", and the cop says "oh you've dropped them by the lamp-post here". "No" he said "I dropped them down there somewhere". So the cop said "well why are you looking down here" and he said "well here's where I can see things".

So you're saying that basic science people are working around the lamp-post.

I respect basic scientists and was a basic scientist myself briefly. I was a chemist. But there is still an enormous gap between basic science and clinical relevance.

On that point, let me take you back and ask you why you went into medicine at all. What your career path was into medicine?

It's easy actually. I was 15 when I went to College .. stumbled on Freud. And he was talking about all the things that interested me. Sex and girls. I was always a sceptic. I never bought it. I said it's very interesting. So I got the idea of becoming a research psychoanalyst. That there would be some way of testing these ideas out and then it turned out to be a psychoanalyst you had to be an MD so I went to medical school.

Did you at any point think about changing on your way through medical school.

Well from my psychiatry courses I nearly did. They nearly made a haematologist out of me. The psychiatry courses were terrible. Terrible. We had one guy who would read to us from a book. And finally we delegated some people to go and talk to him, and said "we all know how to read". And he said "this was our resistance against understanding the real truth". So that was terrible. I had a good friend, a fellow named Norman Kretchmer, who was in my class, who already had a PhD in biochemistry. He had his own lab and I worked through College as his lab tech. So I got involved with basic science. It was a lot of fun. We built our own chromatography apparatus. But I maintained my interest in psychoanalysis.

I really did like Medical School and I liked medicine, I liked the whole thing about physiology. Then when I got out of Medical School, I went into the public health service. The US Public Health Service Marine Hospital. That was largely because the Korean War was on and I didn't want to go to Korea and if you were in the Public Health Service, the draft was not enforced. Essentially I was with the coastguard medical officers. I anticipated finishing my internship and then I would spend 2 years on an Indian reservation and that was okay. Better than Korea. In fact I got fired. At the end of my internship about 30 days before it ended, Eisenhower abruptly reduced the force in the public health service and they dropped out the bottom half of the entire class and I was out of job and vulnerable for the draft.

So I went scurrying around and I landed as a first year resident at Creedmoor State Hospital. At the time we had no medication, this was '53, we had 6000 patients and I walked in and said to the head of the male admitting services "Dr Klein reporting for duty sir". He said "yes Klein,

here's this little book which is going to teach you how to do a mental status. You'll be admitting 20 patients a week and there are 300 patients to take care of."

That was the extent of my psychiatric education. That was all I got and it was okay because I enjoyed being on my own then. I was being thrown into a snake pit. It was just terrific. I saw so many strange things. People were really untreated and they were completely out of it. At that time I began to get a little doubtful about psychoanalysis. It was very difficult to see how it applied to these people. I was getting noises from the Draft Board, so I called the public health service again and said "look I've got a whole year of psychiatric education now, is there a place for me?". And they said "yes as a matter of fact we have a place for you down at Lexington, Kentucky in the Narcotics Hospital".

So I went down there. When I got there they said "who are you" and I said " Dr Klein" and they said "never heard of you". It turned out my papers had fallen behind the files somewhere and I was really supposed to be in Anchorage, Alaska. Lexington was wonderful. It was a 1000 bed prison. It had 700 prisoners and 300 volunteers at any one time - women and men. I had zero experience with drug addiction so they put me in charge of the women's unit and in charge of withdrawal. I had to learn fast. It was the most interesting experience.

At the time, they had the best human research set up in the world. Abe Wikler and Harris Isbell ran the Addiction Research Center. Abe came out with probably the very first text on psychopharmacology. Its called The Relationship of Pharmacology to Psychiatry. It came out in 1955.

Pretty early.

Too early because he missed the antidepressants and he just had one reference of chlorpromazine so the book died. It's one of the great books. Wikler was one of the smartest men I have ever met. He was really something. And so in Lexington I got exposed to the first trials on LSD, reserpine and on chlorpromazine.

Tell me about all this.

I was running the withdrawal ward and Abe came over to me and says we've got this new drug, its called chlorpromazine and we think it may be like morphine - it's safe enough. I said "why do you say its like morphine" and he said "well when people take it, they get sort of quiet, they go on the nod, but they are not asleep and they are not ataxic and their pupils get small (which was not true). So they had this ward with prisoners and volunteers and they gave this guy a shot of chlorpromazine and asked him an hour later "how is it" and he said "doc, I don't know what that shit is, but it will never sell".

And he was right!

He was right. Its never sold on the street. But it was a wonderful ward. One day a foundation grant showed up for work on LSD, you know it was Korean War times and there was tremendous interest in brain-washing. They had these pilots who had been shot down in Korea, who were appearing on TV saying "I'm a tool of Western Fascists and they made me do this and every right thinking person will curse America". Everyone was saying how could one of our pilots do this. Its very easy, put a gun to someone's head and they'll say anything. But people got more concerned about brain washing and about strange drugs being used. LSD

had just been described by Hoffman and Stoll in about 1953 and do you remember how that happened?

Yes. Its curious though, Hoffman took the stuff around 1948 but as you say it was round 53/54 before I've seen anything in print.

Right. Well Stoll was the psychiatrist who wrote up Hoffman's experiences. He wrote this wonderful paper on LSD. And Stoll came to Lexington to tell us about it and they opened this foundation and gave us money. We found out about 10 years later that it was CIA money. The CIA had set up research studies on LSD all around the country and their interests were basically technical with whether you could use the stuff in war or for espionage and brain washing.

It was my job to select subjects for the LSD experiments. Our criteria were quite clear; they had to be hopeless cases, anti-social psychopaths who had at least two five-year sentences or drug addicts for twenty years and the chance that they would be rehabilitated was zero. And they were happy to volunteer - everyone volunteered. And so we had the opportunity of watching LSD being used. What was funny was that it was done very antiseptically. People were put in litte cubicles on a bed, filling out a questionnaire and there were none of these revelatory experiences ...

No that seems to be the group phenomenon of it, doesn't it.

Yeh you have to do a lot of introductory work to get a transcendent experience, which is an entirely strange thing. You'd walk in and say "how are you doing", and they'd say "fine", "anything unusual happen?" "no, you just turned green and the walls turned yellow". So strange things happened but there was no big revelation. LSD seems to be an amplifer. Then chlorpromazine came in and they did a double blind placebo controlled chlorpromazine trial and a double blind placebo controlled reserpine trial on my ward.

These were not my studies, I was in my the last 6 months of the two years I was in Lexington. They moved me over in charge of a World War I Veteran's ward. These people had been psychotic for thirty years. They were out of it completely. We gave some of them chlorpromazine and I remember a guy who hadn't said anything for thirty years comes over to me after a few weeks and said "Doc, when am I getting out of here?". It was Rip van Winkle. He had remembered nothing. The last thing he remembered was in 1916 going over the trenches. That was an honest to God miracle. The whole idea of chlorpromazine just making people quiet, you know, it's so silly. So, I was involved in facilitating these two studies. Essentially reserpine wasn't very good but chlorpromazine was great.

Tell me about reserpine. Had Kline done his trial prior to this or was this a trial that he was also involved with.

I think this was contemporary with Nate Kline's trials. There was some guy in India, who had done some reasonably good work with reserpine and there was a lot of interest as to whether reserpine and chlorpromazine acted differently in treatment or whether they were affecting people differently. In my opinion reserpine was just an inferior drug to chlorpromazine. It didn't work very well. It slogged people. On chlorpromazine many people who were withdrawn and almost mute actually woke them up. That never happened with reserpine. But I think reserpine has actually been insufficiently studied.

So after Lexington ?

After Lexington I went back to Creedmoor and I got involved in research at the Creedmoor Institute of Psychobiologic Studies. It was an outfit run by Arthur Sackler. Arthur was an amazing man. If you go down the mall in Washington you see the Sackler Museum. That's him. And he's got a wing on the Metropolian and he's got a Sackler Museum in Peking. I don't know where he got all his money from but he apparently got into medical advertising, when medical advertising was just starting post-World War II and he just cleaned up. He was a biological psychiatrist at a time there weren't any biological psychiatrists. He had two brothers. And he ran the Creedmoor Institute of Psychobiologic Studies and I was sort of kibitzer over there during my first year residency.

They had a theory histamine was the problem in schizophrenia and he would give patients histamine. At the time we were using sub-coma insulin on our acute admission ward. You give people small doses of insulin and they sweat and they lie in bed and they gain some weight. I doubt it did much for them but its a pretty good sedative. I convinced them to use this histamine biochemotherapy so we took one ward and we gave people insulin and another ward had histamine biochemotherapy. We never got to randomisation or blinding but the people who had histamine biochemotherapy did badly. And that was the end of that study.

When I finished my residency, I went to the Creedmoor to work full time. Somewhere along the line they had a study on autism where there were several analysts, who were convinced that autism was caused by the family. They had six families in treatment, the mother was in treatment, the father was in treatment, the child in treatment and the dog was in treatment. They got nowhere for a year. That was interesting. I was taking care of two autistic identical twins, who walked around on their toes, slapping their chest with their hands. I said to the chief analyst "their mother did that?" That programme was cancelled and we were shifted to geriatrics.

So we did a study on dicumarol in cerebral arteriosclerosis - a proper placebo controlled study. And essentially we found that they lived longer but it didn't help them mentally. That got published. It was my very first paper. Then we did a study on mepazine, which is a phenothiazine that is distinguished for being the only phenothiazine that just doesn't work. It came with glowing reviews. To our surprise it didn't help and it was eventually taken off the market. It made a very good active placebo.

Then the opportunity came to go to Hillside. I was in analysis, since 1957. My job in Creedmoor was frankly a sinecure and I was busy being analysed. I kept telling my analyst that I was interested in doing something more systematic and interesting in the way of human experimentation, which he told me was my sadism. We just had to work that through. I went to Hillside. Max Fink was there and he was really a dynamo. Extremely sceptical. He kicked me into high gear. From leading a fairly leisurely life at Creedmoor, I started working very hard and that was fine. I lasted in analysis for a couple more years. I told my first analyst that we are not getting anywhere and he agreed very happily so they gave me another analyst who was a complete idiot. I lasted about 5 months with him.

After our initial couple years experience of imipramine and phenothiazines, Max and I did this random trial. Everybody, no matter what they had, got randomised either to placebo, imipramine and chlorpromazine. We used big doses. We used 300 mg of imipramine, 1200 mg of

chlorpromazine and we did it on 150 patients. Max left to become the Director of the Missouri Institute of Psychiatry and I continued there and I did the whole study again. So we did actually 300 patients. I think it was the largest, randomised placebo-controlled study that had ever been done in one place. We published a series of articles on that trial, in which we showed a lot of things that have been forgotten, like chlorpromazine is an excellent antidepressant, which doesn't fit with any of the current theories.

Are the current theories marketing driven?

Yeh. And even the simple theory that Schildkraut came up with about noradrenaline deficit in depression and excess in mania didn't fit chlorpromazine.

So how come our theories went the way they did in the face of this kind of trial. People just don't reference your trial.

Contradictory facts never sink a theory. It's a better theory that sinks a theory. These theories were obviously no good but there weren't any better theories around. They account for 40% of the facts. They didn't account for 60% of the facts but we had no other theory that would even account for 40% of the facts. So that's the reason the theory survived.

Do we have one yet. It seems to me we're in a vacuum. People don't believe the amine theory yet the industry still builds drugs as though amines are what it's all about.

I think that when you look back over what we've learned in the past thirty odd years about drugs and psychiatric illness, there are two things that seem to me to be completely outstanding. One is that the major psychotropic drugs don't affect normal humam beings

Well chlorpromazine affects normal human beings - it gives you parkinson's, it demotivates you and okay right it won't show up on cognitive function tests but that's because we don't have good cognitive function tests.

That's not necessarily relevant to its antipsychotic activity. My understanding of antipsychotics is that they wake people up.

Well certainly they can bring you out of things that you are absorbed in. They bring you back. Sure.

So that's a little hard to reconcile with what you're saying. There are other phenothiazine like drugs that are not antipsychotic that all do exactly that - phenergan for one - people are quiet on that, they are unmotivated, but that's not antipsychotic at all. So, I think its probably a parallel but not the central effect. Imipramine doesn't do anything to normals.

My major point is that I think there are two different sorts of drugs. There are drugs that are rheostat drugs, that is what they do essentially is they alter your level, like an antacid, that is if you have hyperacidity we can make you have normal acid if you've normal acid we can make you subnormal. And then there are other drugs that are essentially like aspirin and the psychotropics are more like aspirin. If you've got a fever aspirin will bring it down to normal but if you've got a normal temperature it won't make it go lower. So its fixing a derangement and that's what I think these drugs are doing, fixing a derangement.

What's striking about chlorpromazine, for instance, in manic depression is that it will make the mania better but it will also make depression better. That sounds to me like if you had a thermostat that was insensitive. If we were to plug the sensor in backwards, you would turn negative feedback into positive feedback. So what you've got to do is fix the detector; I think that's a useful analogy.

One thing we've learned is that there seems to be normalising drugs, which speaks for a cybernetic circuit pathology. The other thing is that psychopathology is largely genetic. At present we lack an understanding of the functional circuitry of the brain. Things like receptors are just the very peripheral edge of the thing - all these wonderful things they talk about happening at receptors, happen ten seconds after you give the drug.

Yes, I agree totally,

So why does it take 6 weeks to get better? I'd say and have been saying for years is that the right way to go is behavioural genetics. We should breed animals for pathology. And they have actually done that to some extent, they have some anxious strains of rats. But I think you can breed for separation anxiety. I think we can breed for anhedonia. And that would be far more interesting. I have never been able to sell that to anyone, I can't sell it to the pharmaceutical houses or to NIMH.

Look at Eric Kandel, basically what's so bright about Eric is that he has a functional analysis strategy. He takes the simple organism and takes a simple function like siphon retraction and then he works out the circuitry, so he has a greater understanding of what happens when you do this and do that. But most of the stuff that's going on in receptorology is not related to a functional context. So no matter what you find it remains a mystery.

That's what actually got me so interested and excited in my recent stuff on respiration because with that I've got a functional context, which is the idea of a suffocation false alarm.

Can you flesh that out

Well I've got a general framework which is that many diseases are malfunctions of evolved functions. Now since carbon dioxide and lactate increments can cause panic in panic patients, you have to ask what causes this naturally and both are caused by hypoxia. Carbon dioxide goes up when you're not having enough oxygen and lactate goes up from pyruvate, again when you're not getting enough oxygen, so they are actually two physiological signals that you may be in potentially suffocating circumstances. Taking a functional viewpoint, I got the idea that panic disorder people have a hyper-sensitive suffocation alarm.

So I started to read the literature. The flip side of this is that some people ought to have hyposensitive suffocation alarm systems and I found them; these kids with Ondine's Curse. These kids are born, apparently healthy; they put them to sleep in the crib, they go to sleep and they die. This isn't sudden infant death though because if you catch them when they are just turning blue and you wake them up they start to breath again. They then go back to sleep and they stop breathing again. And you wake them up and they start breathing. They only discovered this twenty years ago.

Ought it to be more common, given that panic disorder is so common ?

Well look at the flip side... panic disorder doesn't kill you and so if it gets evolutionarily weeded out that's difficult. Anyway, they are now able to keep these kids alive with phrenic driving. They go to sleep at night and they have a radio-frequency broadcaster that zaps them every 5 seconds, so their diaphragm contracts and they're all right. They now have a group of these kids, who are in their teens. There's a woman named Debra Weese-Mayer, who's a paediatric pulmonologist out in Chicago, who I was lucky enough to hook up with. She has the biggest collection of these kids and what's really interesting about them is that they don't have any suffocation reflex at all. They don't know what it is to suffocate. You put them in pure carbon dioxide and it doesn't stimulate them, they turn blue quite happily.

Now the idea of a suffocation alarm signal, sounds like an unwarranted reification, doesn't it? You've got 3,000 different things going on in your body that depend upon a flow of oxygen. The oxygen gets cut off, everything goes to hell. With the suffocation alarm centre cut off everything should be signalling that things are going wrong but it doesn't work that way in these kids. Furthermore imipramine, I argue, downregulates the suffocation alarm signals and that's why it works. So what should these kids get from it - they've got barely enough suffocation alarm signals to begin with? - They stop breathing.

Do they?

In some ways they have panic disorder inside out. There's some quite interesting stuff there. Megacolon is one per 5,000 births but a third of these kids gets megacolon. Now megacolon is a segmental absence of nerves of the myenteric plexus in the gut which happens to have a high concentration of serotonergic neurones. So they've got an absence of serotonergic neurones peripherally, what about centrally?

Another thing about panic disorder is that half the people who have it have a history of separation anxiety. And how do you fit that together with suffocation? It struck me that it might have something to do with endorphines because endorphines down regulate carbon dioxide sensitivity and also down regulate separation anxiety. So, perhaps we have some sort of endorphinergic deficit. Which made me wonder just how anxious are all these kids with Ondine's Curse. You know the highest epidemiological risk factor for anxiety is chronic illness and these kids go to bed every night liable to die that night. If the machine malfunctions, they would die. Many of them have had tracheotomies, they get lugged into the hospital. Their parents are frequently so anxious about them, they stay up with them all night every night. They get dragged into hospital for a week in a year and they get probed. They know they've got this thing that isn't going to go away. Should that be an anxious kid?

Should be.

By any of the usual standards. I said if they are really panic disorder inside out, maybe they're not anxious. So we did a study with Daniel Pine. They are not anxious, which is remarkable. But the thing that recently has me the happiest because if this works out I will be very surprised and pleased is, one of the aspects of the suffocation alarm theory is that any suffocating circumstances should be panicogenic. And in fact this is largely true. People trapped in a mine, go nuts. However, the one thing that bothered me was carbon monoxide because carbon monoxide asphyxiates you but you don't panic. You just go off nicely and that was extremely irritating. And ..

Has Sol Snyder solved that for you?

He has. I commented on where the suffocation alarm system is in the brain. I said I'm not sure its in the brain, maybe its in the carotid body. The carotid bodies are actually measuring the oxygen and carbon dioxide and relaying it onto the brain so the sensor could be there. Now Sol has shown not only is carbon monoxide a neurotransmitter, it is the neurotransmitter in the carotid body. What does it do in the carotid body, it turns the carotid body off. So maybe the reason you don't panic is that you get the carbon monoxide and it knocks out your alarm system. If that's right carbon monoxide should be an anti-panic agent and should block the carbon dioxide effect. That's a study we're doing.

Who've hit you as the key people of the last 30 years.

Wikler, Fink, Sol Snyder of course. I naturally think of people I know, who actually trained with me like John Kane, Fred Quitkin, Arthur Rifkin, Jack Gorman and Mike Liebowitz. Leo Hollister did excellent work, Gerry Klerman, Jon Cole was a real leader. He is an extraordinarily erudite, funny man.

What about this book <u>Listening to Prozac</u>. It seems to me that this, for the first time 30 years later, is where the impact of the psychotropic drugs has begun to reach down to street level in the US. Now you're cited widely in the book as being a ...

Peter Kramer and I have been corresponding over the years. I always like the way he writes but I think the reason Peter's book is so popular is because it makes an appeal to wishful thinking. Why was psychoanalysis so popular? It appealed to the belief that you would be a whole new human being and that you would be not just taking care of a few lousy symptoms. It was going to change you radically. And that was tremendously appealing to people. Everybody wants to be saved or cured.

Now when people talk about medication, they ask does it cure. And I say it's not going to cure you, if you stop the medication you may very well have a relapse. It's not a radical cure, it's a symptomatic management and it does pretty good but that's all it is. That doesn't stand up in competition with the psychoanalytic goal. Well Peter comes along and says Prozac is going to make a new person out of you and all of a sudden it's all over the papers. He's appealing to the same level of wishful thinking and that's why it's so popular. The medications have not become popular because they work. They have suddenly become popular on the basis of the same sort of curative promise.

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