

## **ANGLES ON PANIC DAVID SHEEHAN**

**You got involved in the panic disorder, benzodiazepines and alprazolam story early in your career.**

To really get the full picture depends on understanding the context within which it occurred and how the Upjohn company heard the opportunity and saw it as an opportunity. In fact I had given the same information to other drug companies on the antipanic effects of benzodiazepines prior to giving this information to Upjohn - there was nothing unique in this regards about Xanax. The benzodiazepines were all good for panic disorder and there was a clear strategy about how a company might go about taking advantage of the confusion that existed in the classification system for anxiety disorders in DSM-III to create a perception that a drug had special and unique properties, that would help it capture market share and displace diazepam from the top position.

**So how did Upjohn get in on that kind of strategy.**

Most drug companies didn't understand in the 70s that panic disorder was anything more than some esoteric rare illness, when in fact it was quite common. They didn't understand the market implications of this at first and it was only when the whole scenario was spelled out to them that they appreciated what was involved. In fairness to Upjohn, they were the first ones that really listened carefully and gave it a lot of thought and grasped the implications of the situation, where others hadn't. I had spelt out exactly the same thing to the people at Roche a few years earlier but since they already had the largest market share they had no incentive to break new ground.

**Did Upjohn pick up on the opportunity before or after panic disorder went into DSM III.**

Before. Yes, basically the start of the whole thing was about 1979. I was giving a presentation in Washington at the American Psychopathological Association, where I was presenting data from one of the earlier studies on phenelzine, imipramine and placebo. I was trying to spell out the implications of the study and one of the implications was this. At that time, some felt that Don Klein, who had described this anxiety syndrome that was characterised by panic attacks, was really seeing depression rather than a distinct anxiety disorder. The implication of the studies I was describing, however, was that he was right.

**But he had also described endogenomorphic depression and done a range of other things**

Yes he had. It's interesting how retrospectively re-reading these things casts it all in a different light but basically at the time his contention was considered somewhat anomalous and it was not taken up by most academics.

**Because he was not from Yale or Harvard?**

Perhaps that's part of it. At that time he was at Long Island Jewish Hillside Hospital and it wasn't taken really seriously by some. But this is where the story gets complicated because you have to go back a couple of steps.

I presented this study and basically said that our observations in doing this study coincided exactly with Don's views. I couldn't help but say, even though I was only a young researcher, that I was very impressed at the extent to which Don's original observations about the syndrome, about its being different from depression and about antidepressants having an effect on an anxiety disorder that was separate from depression, really were strikingly similar to what I had observed. I saw no reason at all in anything I had seen while doing the study or afterwards to disagree with him, even though I didn't know him personally well at that time.

Then I said that there were a number of implications to this study that we had done. One of the implications was that in the future there would need to be anti-panic drugs. I thought that this was a much larger market than many perceived and that it was a huge problem. Patients seemed to me to be everywhere; we had no difficulty recruiting patients for our study. So I thought that the implications for the drug industry were that they would need to develop new antipanic drugs and that essentially what they needed were good animal models to identify antipanic drugs de novo. Given that there weren't any good predictors of antipanic drugs, one suggestion I had was that as all of the existing antidepressant drugs had an antipanic action in common, if any drug companies were out there looking for antipanic drugs that they should find a drug that had an antidepressant effect in an animal model and study it in panic disorder. The disadvantage of all the existing compounds was that they took 4 - 6 weeks to work and we'd have to find one that worked immediately.

As it turned out, and I didn't know this at the time, there were some people in the audience from some drug companies. Two of the people there were Jim Coleman and Bob Purpura from Upjohn. Right after my presentation, they approached me in the lobby and they said "tell us more about this panic disorder and tell us more about this notion of predicting which drugs might be antipanic drugs". After I told them, they said "by the way we have a drug which has an antidepressant effect in animal models and do you think it would be a good antipanic drug". So I said "yes, otherwise I wouldn't have said what I did". "Well the problem is it's a benzodiazepine - do you think a benzodiazepine will be a useful antipanic drug". I said "well the current wisdom is that benzodiazepines aren't antipanic drugs but nobody has done such a study, and may be you have a unique benzodiazepine. If it does what you say, maybe it would be an antipanic drug. At least here's an opportunity, why don't we test it out, why don't we do a study and either definitively show for once and for all, whether benzodiazepines have any antipanic effect".

I was ambivalent really at that point about which way it would go and I think that most people's suspicions were that it wouldn't work. At that point DSM III hadn't yet come out but I knew of the preliminary discussions and the drafts had already made their way through the system. I knew that basically the discussion favoured breaking up anxiety neurosis into at least 2 disorders panic and GAD, and that Don had found that there was a group of anxiety disorders that responded to tricyclics, characterised by unexpected

spontaneous panic attacks and there was another group in which they probably didn't work.

In a nutshell, over a dinner, a group of the Committee for the DSM III decided that, while they could identify panic disorder, they should invent another disorder that would be a benzodiazepine responsive disorder. So the pharmacological dissection was that panic disorder is the tricyclic responsive syndrome and generalised anxiety disorder was going to be the benzodiazepine responsive syndrome. They came up with the name over dinner one evening. It sounded like it had a good ring to it - GAD - somebody said "gee that's sounds wonderful, these people are generally anxious and they don't have panic attacks". But nobody really went out to test to see where one ended and the other began.

So at that point, I thought this doesn't make sense to me because I don't think there are two distinct syndromes that can be pharmacologically separated in this way and that really the anxiety neurosis concept is probably closer to the truth and maybe even hysteria is closer to the truth than what is being proposed. In my opinion, they were introducing new diagnostic chaos. But I was only a Young Turk so why should they listen to me. This was at a time, when in fact there weren't specialised clinics like you have now. I was probably one of the few people at that time in the States, who had a clinic that was seeing all day long patients with panic disorder. It was a large number of patients and so I felt very sure of what I was talking about.

Anyway, I said to the two guys from Upjohn, "why don't we do this study and test it out". Now this is where, of course you get different versions of the story but there are actually witnesses to some of these meetings and I have very clear recollections and I've written some of it down. What happened is that we started to design a placebo controlled study. Concurrently, Jim Coleman was doing some studies on prostaglandin research, which Upjohn had made a large investment in but which didn't seem to be going anywhere wonderfully exciting. There was evidence, from the haematologist at the University of Massachusetts, that non-steroidal anti-inflammatory agents had some anti-prostaglandin effect reflected in a lowering of platelet factor 4 and beta thromboglobulin and that this might have some implications for heart disease. Men with panic disorder had an excess mortality from heart disease. So this gave rise to the idea that maybe this is what exposed them to the excess mortality from heart disease. There was also some evidence from an author in Yale that non-steroidal anti-inflammatory drugs had an anxiolytic effect in severe anxiety.

Since they had some non-steroidal anti-inflammatory agents of which Motrin was one, they said to me "since it's just a preliminary study, why don't we use Motrin as a control drug rather than a placebo and we can kill two birds with the one stone - if it doesn't work out for panic, we have also investigated some heart disease implications of these drugs and we will see to what extent alprazolam drops the platelet factor-4 and has other anti-prostaglandin effects". So we dropped the placebo and introduced Motrin. It took quite a while to design and get the study up and going. We studied 32 patients. I

had been saving them up, in anticipation of this study, so we got all these groups to start together.

I think I got 16 patients to start all in the same week and then another block of 16 shortly, thereafter. I started a group of 8 of them in one group altogether one evening. It was dark; it was the Fall in Boston. There were 3 particular people that stand out in my mind. Two were sisters who were so phobic of the medication, especially that they might die from the medication at home, that they asked if they could take the medicine at the unit, so that if anything bad happened I could rescue them and bring them to the emergency room. I said, "fine that's no problem".

I had persuaded Upjohn that the biggest problem in most of these studies was under-dosing and they ought to give these people a really good dose and not fiddle around with paediatric doses. Get the ceiling up to rather high levels in case some people would need some higher doses than normal. So they got approval from the FDA to initially go up to 6 mg. We were to start with 1mg tablets. So the 2 sisters took 2 tablets in the waiting room and waited around for 30 minutes and then felt okay and decided to take the subway home. I was still in my office late that night organising the paperwork, when I got a phone call. It was the two sisters who'd returned home and, if my memory serves me correctly, one of them had already clearly gotten a phenomenal effect. In fact, she was sedated and a little ataxic from the drug and had to be helped by her sister to get off the train and get home. They called me up and they said this is incredible, she's cured. The other sister had no effect at all.

The next morning there was a guy in the same group who must have been about 6'6" tall and he called me up and he said "Doc, I'm lying here on the couch in my office". My first reaction was "oh my god that's terrible" and he said "Doc this is not terrible at all, as a matter of fact I haven't felt this good in 10 years, you have no idea what a relief this is. I feel so calm, I just don't feel any anxiety, it's really wonderful". He was an executive and he said to me "do you understand what the implications are? This stuff really works, you don't need to prove it to me, you don't even need to do a study, this stuff really works I can tell you that right now. If this works for all the other people in the group like it does for me", he said, "this is going to revolutionise treatment of this condition ". There were other vignettes and it was clear to me that something quite dramatic and unusual was happening.

Then a group of patients, a couple of weeks into the study, said to me "doc this is amazing - there are so many panic patients out there in the world, we don't think the drug companies realise how many there are. When you start to give this stuff to patients with panic disorder and you can give them such rapid and complete relief, this is going to take the world by storm. The company that makes this are going to make a fortune. You know you should buy stock in that company". I laughed and said "well first of all I don't own any stock - I don't completely understand how the stock market works. In any event, it would for me cause an awkward conflict of interest because I would be seen to be gaining from inside information". They all, I remember at the time,

shook their heads and they said "Doc, you won't have another opportunity like this".

So, it was already clear half way through the study that this was quite dramatic. I knew before the data was examined, this was definitely going to change the face of things. A couple of months later, the drug was approved for GAD and as fortune would have it about the same week the FDA approved another Upjohn drug and so there was a blip up in their stock. A week later patients of the group came into me and said "well Doc, did you buy Upjohn?" I reiterated what I had said before and they said to me "you're so dumb. We've got to tell you that after one of our group meetings we all went down to the lobby and we were talking about this and decided that this was so phenomenal that we were going to pool some of our resources and the group was going to buy stock in Upjohn. We sold out at a high price and we all made a profit". I couldn't believe what I was hearing. I thought as an outcome measure in a study that was phenomenal - that patients were willing to invest. These were not rich people but they were willing to invest their limited resources, they had such confidence in what the drug was doing. This was really quite dramatic.

A number of other things came up in the study. The first was that the drug did not work for 12 hours as people had believed. In fact, I got into a big debate with Upjohn telling them that it only works for 4 - 6 hours. They were adamant about the fact that it worked for a great deal longer - at least 8 - 12 hours. I explained that this was a terrible mistake and they wouldn't be able to show an antipanic effect in a study if they persisted in believing that. They had to move the doses close together in order to get good smooth blockade over the hours. The other point was that the average final effective dose was considerably higher than the approved GAD dose, which at that point was up to 4 mg a day. They would have to get an indication to go higher - up towards 10mg; the average effective dose seemed to be 6 mg. The third thing was that it was not an effective antidepressant.

So then they decided to fund a double-blind study of phenelzine, imipramine, Xanax and placebo for panic disorder. Now before they funded that study, they got involved in a whole load of discussions about what this might mean and how they might usefully pursue this. And I said "well here you've got a great opportunity because there's great confusion in the classification system of anxiety disorders in my opinion. The perception is that panic disorder is some rare exotic syndrome, that it's a very severe anxiety disorder. If you think of it in a pyramidal fashion, at the peak of the pyramid is panic and below it is this mass of GAD, which everyone perceives as very common". I said my belief is that it's exactly the other way around - that the GAD would prove to be much rarer and that panic disorder would in the end be perceived to be much more common. I saw patients the whole time who were called GAD and they clearly had panic disorder or depression or bipolar disorder if you took a careful history. I met with their marketing division - people like Dick Studer - in Kalamazoo. One agenda I had was to show that the existing classification was in error. Panic was not a distinct syndrome that's only tricyclic responsive. It was clearly responding to a benzodiazepine, which it

shouldn't be. In the meantime, I had gone and put several GAD patients on tricyclics and it was very clear that tricyclics work for GAD so the premise for making the distinction was lost. What I wanted to do was to get data that would show that the classification had it all carved up the wrong way.

I told them that if you go after the tip of the iceberg - panic disorder, all of your competitors, because I have talked to a lot of them about this, are going to look at this and say what are these turkeys doing - they are going after a rare, exotic thing, who cares, let them have it. They'll sit back and watch you doing this right under their noses. They won't raise a finger to compete because they'll think you're making a mistake and by the time they wake up to reality you will have done your studies, got approval and then turned around and persuaded the world that in fact panic is really much more common and GAD is much rarer. You will have captured an enormous market and you will have a big time advantage over your competitors. The other perception will be that you have a drug that will be the only drug approved for the tip of this pyramid. If this was only a drug for GAD, you come in at the bottom of the pyramid and you nibble away and say well we're just as good as Valium and people will say sure and use it for 5% of all GAD patients - so it becomes another me-too benzodiazepine.

But if you come in at the top of the pyramid and go after panic disorder with a vengeance, then it quickly gets the reputation of a super-powerful new and improved second generation benzodiazepine that has some kind of awesome power that the others lack. You don't tell them this. You're simply going after something that everybody perceives as the top of the pyramid because they have placed it there in their minds. So when this comes in at the top of the pyramid, GPs will say "this stuff isn't any more dangerous or hazardous than Valium, so if it's working so nicely for panic, why not put all our anxious patients on it". So you will get a downward displacement in the market place and you'll push out all the other benzodiazepines. You will then be the reference drug and the rest will be 5 - 7 years behind you and in the meantime your educational campaigns can help capture the market share".

Anyway they liked the sound of that strategy and they said "well we'll have to check this out to find out if it's as common as you say it is". They did that and they came back and said "we've talked to a lot of people and interviewed patients and you're right, it's a lot more common than we thought - it's a market that seems to be worth investing in". Then they visited my unit and interviewed a lot of patients that had been through the studies that they had funded and I think came to realise that yes patients did do better on the higher dose. That yes indeed the dose only worked for 4 - 6 hours and indeed that the one weakness was that it hadn't an antidepressant effect.

Now, ordinarily, what they would do, at that point, is their clinical research divisions would go after a standard set of research protocols and at a later stage after it was approved, the marketing division would put their funds into marketing this that and the other. I think they decided they would merge these two steps in one and they would use the money that would otherwise be used in the post-marketing research for research in order to speed everything

up. So we got going on a big double blind placebo controlled study and the lessons we learnt from that study were used as the basis for picking the outcome measures and fine tuning the design for later studies because in those days there weren't good designs for panic studies. At that point, they got a great number of other people involved who were largely people who had played a big role in depression research the previous decade - Klerman and Klein.

**But then the whole thing took on a further life which is the controversy with Isaac Marks on one side and Don Klein, Gerald Klerman and Danny Friedman on the other.**

Well I think what happened at that point was that Isaac and Don were always squabbling at these meetings. I was a young guy in the middle trying to say well "you know maybe there's some middle ground in all of this and maybe something can be worked out." I was naive and didn't know all of their backgrounds as well as I do now and didn't realise how entrenched the various viewpoints were. It took me a little time to figure out that this was not going to be resolved by discussion or even by scientific data.

Isaac was claiming, at the time, that one of the reasons these drugs were working was because they had an antidepressant effect and if you controlled for that you eliminated the effects of the drugs. Well in two of the early studies we looked at that issue very closely from several different angles. I honestly wasn't sure which way it would come out but it was very clear that he was not right. The drug was clearly working through mechanisms other than the antidepressant action. Most of the data was beginning to come out the way Don was predicting. Gerry Klerman was also much more in Don Klein's camp and so was Danny Friedman.

That spun off later in a different direction. I always hoped that if I could get Isaac involved in some of these studies that he would come around and be persuaded by the efficacy data. In fact, I was the one who arranged the negotiations that went on for two years that led up to the study that he and Richard Swinson ended up doing. I had hoped that at that point when Isaac saw the data that he would acknowledge that this was pretty good stuff and I had actually no reason to believe that he wouldn't think that. Obviously, I realise now that he doesn't hold that view and never did. Anyway, that controversy went off in a different direction but I was out of it at that point because at some point along the way I was becoming too much the focus of everybody's ire.

Sociologically, it's apparent to me now that it's very dangerous for a young investigator to stumble upon something that turns out to be important. Although one would expect that if you make a better mouse-trap, the world will beat a path to your door, the reality is that exactly the opposite happens and that you end up with lots of knives in your back. The amount of abuse that I suffered nobody will ever be able to grasp. The difficulty is when you're young and you don't have any power, you are a convenient lightning rod and you really have no means to defend yourself. Everybody needs a powerful friend in high places, who is willing to put themselves out to protect them. But

there were too many people with other agendas to be willing to serve that mentor role effectively. So, although many people will look at this and say well wasn't that wonderful and aren't you happy that you did all of that, I really look back on all of those years with a great deal of regret and dismay and sadness.

**The panic disorder story is full of people blaming other people for serious breaches of ethics and for leading to premature deaths etc.**

Yes. The only gratification that I get from it is that I've had a chance to travel all over the world and see people in various panic disorder studies in obscure, remote parts of the world being treated with alprazolam for panic disorder, that wouldn't ever have received the treatment for the condition. So at some human level, I've felt that if I hadn't done what I had done and put up with what I did, these people wouldn't now be getting the advantage that they are getting. From a career point of view, though I would never go through such abuse again.

**At some level, all this feels like it should link up with questions of why the benzodiazepines been such a big issue in the UK. They are these horror drugs and we have never had alprazolam.**

No, I think that some of that was probably originally economically driven. There were people looking at the bottom line and saying we're spending too much on drugs. Now which drugs are we spending too much on? Well there was huge consumption of benzodiazepines and there's the British approach to many psychological problems, the so called proverbial stiff upper lip approach, get your act together, pull your socks up and you'll live happily ever after. How dare anyone decide that they need to be on a psychotropic drug for a neurotic disorder? They ought to get off the stuff, save the government some money and get their lives back in order and everything will be fine. I think that sentiment amongst some government officials, who wanted to save money on this expensive class of drugs, was the original spark that got it off going.

In tandem with that you had the early development of the 5HT-1A agonists and several people in the UK saw this as an opportunity. Here was a class of drugs that they believed had the potential to displace benzodiazepines and a group of them, if you like, placed their bets on this option. This was a useful way of continuing to do anxiety disorder research, while at the same time continuing to malign the drugs that they were trying to get everyone off and save money but still be seen to be doing something constructive. In fairness, it was a gamble and I think they just backed the wrong horse. But unfortunately it became a rather aggressive strategy to pave the way for the original 5HT-1A agonists by generating a deliberate hysteria in the medical profession about the dangers of benzodiazepines

**You think all that was involved.**

I know it was. I know from people who designed the marketing strategy for the 5HT-1a agonists that it was a deliberate tactic. At major UK and international meetings, they would sponsor symposia on the dangers of benzodiazepines and all of those who everyone knew had feelings about this



issue were invited to speak. Hundreds and, in some cases, thousands of physicians would attend these well orchestrated meetings, would listen to this stuff and get into a panic that maybe they were doing some kind of social harm and that their colleagues disapproved of this practice. The public and the media certainly began to disapprove. The idea was that this feverish pitch would be built up so that physicians would see the first 5HT-1a agonist when it arrived as a good alternative and would switch their patients over to this other class of drugs. Then everyone would live happily ever after and the benzodiazepines would go the way of barbiturates or the bromides.

The problem was the horse, as you know, made it out of the gate and then stumbled and fell. The benzodiazepines, for all their disadvantages kept trotting along and when that happens - how do you save face? Everybody knew what had really happened and it was a very difficult situation to back out of. I think many of the people, who had placed their bets on the wrong horse, ought to have got up at a certain point and said look "we really didn't think that this was going to happen but we placed our bets on the wrong horse and it's now clear to us that these drugs simply aren't going to deliver. We are sorry for all the upset and hysteria."

**People wouldn't have said that though would they.**

I think some people would have. I honestly think that if Don Klein had done that he would have had the courage to get up and say "hey I made a mistake, don't pay any more attention to what I said about this." I have seen Don do this on a number of issues and I admire him greatly for the courage he has shown in being able to say - this is a data driven business and the data didn't bear it out. If you're going to make a lot of good guesses, you've got to make a couple of unsuccessful ones, so chalk this one up to experience and go on to the next one.

In fact that didn't happen and as it turned out in the UK you had a huge split among clinicians. You had a group of academics and people in the Royal College of Psychiatrists or maybe it was the CSM, who got very aggressive in trying to impose standards on practitioners, restricting the use of benzodiazepines. The practitioners were quietly furious about what was being done to them because they had to face the patients, who were doing badly off the drugs or on tricyclic antidepressants for instance. They were left holding the baby and feeling badly when they had to put some of these patients back on benzodiazepines again. So they were being made to feel like bad guys while some of these other characters, who often didn't see large number of patients were perpetuating other recommendations

There was a tension that you could feel at international meetings if you were at a dinner with both groups. There they'd tell you what they really felt; the surface veneer would drop. The media picked up on this and then you got the active encouragement of class action suits against the makers of the benzodiazepines. A lot of people began to see the profits that this presented and the whole thing began to get out of control, at which point it wasn't easy for anyone to get up and say " wait a minute guys we're galloping down a dead end street here. This isn't going to go anywhere and maybe we're

actually causing a great deal of social harm in the process". There were all these rationalisations - everybody's falling over and fracturing their hip on benzos or all of the road traffic accidents in the UK are caused by benzodiazepines. This is not to say that at some minor level that there were occasional cases, where benzos contributed but, in the end, in the absence of much data, I'd have to say these were rationalisations.

What some people in the UK didn't understand was that outside of this island in the North Atlantic, the rest of the world were watching this and laughing at them and saying "they've lost their marbles. It's not that the rest of us haven't got some insight into the disadvantages of all classes of psychotropics but this has gotten so far out of control that it's comical or actually embarrassing".

A lot of drug companies looking at CNS drugs during that decade were saying "the UK is hysterical about psychotropic drugs - this not a good market to be studying CNS compounds. Why don't we just give them a vacation for a few years and invest CNS research money in other countries". Then you had the rather sad scenario of a lot of younger talent leaving the UK and seeking jobs overseas and really the demise of a golden era of British psychiatry. So, I think that the whole thing in many ways was very sad. I think when history is written in a couple of decades from now, analysts will revisit the story and see it in a very different light to how it has been portrayed in the UK.

More recently, the US has been getting hysterical and being nasty about drug companies and their research. The company response will be there are plenty of other markets out there, we don't have to deal with you guys. When you want some new treatments for some illnesses that you're worried about, come talk to us we'll still be here but in the meantime we'll profit elsewhere. They don't come out and say that aggressively. It's just business has to go on. They have to trim their budgets and make things work efficiently and maximise the value to their shareholders. Anyone who doesn't think that they are going to respond that way is naive. Even if their own executives deny that this is consciously what they are doing, they are definitely doing it unconsciously. Within the few months following Clinton's health care reform proposal and Congress painting drug companies as bad guys to be regulated with price controls you saw that happening in the United States.

The hope is that people will get a little bit more foresight and see that this is not a good guy/bad guy scenario anymore. That in order for the entire system to function effectively, you have to have adequate balances built into the system and that as long as everyone lives within the constraints of this balance, the whole thing could work out remarkably well for society, for the drug companies, for academics, for everybody. But the fuss in the US spelled a turning point in the United States as the pre-eminent power in medical research in the world – at least temporarily. Although that has been rectified somewhat in the last two or three years and things are going well because the US economy is going very well, it's still clear to me that we have lost a step and Europe has gained a step. What you see now is when you go to meetings is that the quality of the research in Europe, the quality of the presentations of teams and the organisation is superior to what it was 15

years ago. In tandem with that the quality of the research in the United States has become a little more fragmented and disorganised. It remains to be seen how this will all play out in the long run.

I think the other trend we are seeing in is a globalisation of research. Fifteen or 20 years ago, it was very national or even local, so that even within the United States little pockets like a University would become a powerful even a world class research centre. That's no longer true. You now have networks of centres and the networks, which were originally within a nation, are now crossing the boundaries of nations. You see all of these links between several people in different countries who have just their network in common. They may in fact talk to each other more than to people, who work down the hall from them. I think that trend is going to accelerate and become more important. The capacity of universities and nations to influence research will become far less important and people will spend more time in invisible colleges spread around the world, planning projects in which they have a mutual interest in a way that would not be possible in their local or even national environments. At international meetings, this is more obvious. Teams of people get together and there may be 6 countries represented on one project. I think that's a good thing.

### **Where did the Panic Disorder story go after the Benzodiazepines - the SSRIs came on stream then.**

Well I think the first thing that happened was as quickly as SSRIs came on the market for depression, people figured well tricyclics and MAOIs work for anxiety disorders so why shouldn't SSRIs. So very quickly most clinicians both in Europe and in the United States figured that they were good anti-panic drugs, good in GAD, in social phobia and even in PTSD. There was a lag before the research and even the early papers of case studies began to catch up on what every clinician already knew. This was a scenario of the research following the everyday experience of the trenches. And at least in the case of panic disorder, while many companies did panic studies, the research findings were disappointing.

### **What went wrong?**

Well my perception all along has been that it was a horrible mistake, even by Upjohn, to have chosen panic attack frequency as the main outcome measure in panic disorder studies. I think that is an epiphenomenon in panic disorder – it's not at the heart of what's going on. Using the frequency of a behaviour as a main outcome measure is unprecedented in psychiatry - there's no other precedent for it for any other disorder. If you look at any other disorder major depression, OCD, social phobia just to take three prime examples, or schizophrenia, what do they use as their primary outcome measures in a study? They use a scale that basically lists the symptoms of the condition on a mild, moderate, severe, continual basis. That's one outcome measure and the second outcome measure is a global improvement measure. They did this with depression, OCD, social phobia and so on. Then you come to panic disorder and suddenly they take leave of their senses and they say no we're not going to do that, we're going to count the number of panic attacks.

They did this, even though we've known for 15 years that panic attack frequency data is not normally distributed and therefore you couldn't use parametric statistics to analyse such data. When you have to use non-parametric statistics you're punishing the sensitivity of the data analysis and so you're making the outcome measure analysis less sensitive and because of this the chances of getting more failed studies are very high. You've got some people who will be close to zero or one panic attack per week and occasionally you will have patients in there who have 300 panic attacks per week. With all these outliers, it's chaos. So many SSRI companies spent a lot of money doing panic studies, which they thought ought to be the first anxiety indication they should pursue. Many of these studies failed and the world has never seen these studies. Some of the companies got luckier than others and just about managed to get the data presented in a way that convinced the regulatory agencies that it worked. But of course by this point everybody who was on the regulatory agencies or on the Advisory Board who looked at the data already themselves personally had patients on it so they knew quite well that the drug worked. It was one of these strange situations where many years after the entire world had been using these drugs for panic disorder the regulatory agencies were in the dilemma where disapproving an application wouldn't make any sense. But they have to play the game the best they can by the rules. More than half of the drug companies lost out in that game, even though everybody said why don't you do more panic studies.

The net consequence is they've all been burned. Even the ones that were successful came close enough to getting scorched that it made them gun shy. Now they've all started to look at things like Social Phobia, GAD and PTSD and even with the next generation of drugs coming along, the companies are being advised not to go after panic disorder. Go after social phobia first, GAD second, PTSD third and then panic disorder. They get an apparent return on their investment of research dollars in getting an indication and subsequently they're going to get a return from the world market that way.

So what's happened in the last few years is that there have been very few major panic studies done in relation to disorders that are much less common in clinical practice. And we have seen a withering of the importance of panic disorder on the vine. There has been no significant developments at all in our knowledge about its pathophysiology, its genetic basis or in anything to do with it in the last several years and I think it's all tied in with this. Contrast that, for example, with what happened in the case of alprazolam back in the early 80s, where there was a wild fire and an explosion of research on this condition largely spurred on by Upjohn's work because they found something that worked quickly and fast.

I hope that we can get the world back to using a symptom scale. I had both a symptom scale and a panic attack frequency scale when I was first approached by Upjohn. They asked me which scales they should use. I laid out the options, and advised that panic attack frequency be only one of the peripheral scales. I said I've got this panic attack scale but you don't want to make that important. But for political reasons it got elevated to centre stage. I kept saying to them they should stick to symptom scales, like the Patient

Rated Anxiety Scale or the Clinician Rated Anxiety Scale. These are very sensitive and you get nice normally distributed data and you can use parametric statistics and they usually separate drug out of placebo. When a couple of companies get over their phobia and abandon panic attack frequency as an outcome measure, with a modest level of investment they'll get more positive and fewer negative studies.

In clinical practice the rates of presentation of panic disorder are higher than the rates of other illnesses like social phobia. You can't let community study rates entirely guide you. If you look at the rates in the community of things like social phobia they appear to be very high, whereas if you look at panic it appears to be lower. But if you look at the patients coming into the family physicians office or the psychiatrists office, the number of panic disorder patients is much higher than all of the others because the disease itself drives the patient into treatment. At the point of contact, where a prescription can be written, the point at which drug companies would in fact be getting their revenues returned, it's the most common disorder. The epidemiology of the point of contact and the point of prescription arguably should be the driving force in drug developments as opposed to community rates.

**Does this not link to prescription only arrangements? If we were to change that then obviously things could look quite different. If you were to get your SSRI over the counter then the companies would be able to market it completely differently.**

Yes, I think what would happen is you would have panic disorder patients going in their droves because every time they got a limited panic attack they'd feel so compelled to seek relief that they'd be in the pharmacy getting a supply of medication. Whereas the patient who is socially phobic would wonder who am I going to see in the store, will I run into a neighbour, I don't want to see them, what happens if the person I'm buying it from over the counter sees me trembling in front of them. So they'll stay away more. The same is probably true to some extent with depression. Depression patients generally aren't treatment seeking in the same urgent way that panic disorder patients are, until they start getting anxious and then they are more driven to seek treatment.

I think that's an interesting policy question you raised about whether for example, we should have SSRIs available over the counter. If you can have H2 antagonists available over the counter, how is that any different from several of the SSRIs and what great social harm could come from making them available. You know I haven't thought that issue through carefully enough but it seems to me that you could certainly have a very interesting discussion and come close to justifying making many of those SSRIs available over the counter. Many psychotropic drugs are available in some Asian countries over the counter and its not clear to me, that this causes any great amount of social damage, although I don't have access to any data on this. It might do a lot of social good actually to make these drugs available over the counter. If you had a public education programme about how these are to be used correctly, you might even save a lot of misery in the world.

**When you raise the issue about how hard it is to show the SSRIs work in panic disorder, you triggered off in my mind a debate that I think happens much more in the US than in Europe, which is the use of SSRIs or antidepressants for teenagers. There's been this big fuss about the evidence not actually supporting it.**

Yes, there has been a lot of discussion about this and I'll tell you my read on it as a clinician. In early onset depression you have a disproportionately large number of adolescents who go on to develop bipolar disorder. Not necessarily classic bipolar disorder but rapid cycling bipolars, mixed state bipolars and bipolar II disorders, the softer spectrum bipolar disorders. And as you know a large numbers of bipolar patients go for many years with what looks like a standard recurrent unipolar depression that doesn't respond very well to traditional antidepressant treatment. Most of these people who are later bipolar, when we get histories from them, they say oh yes I began to feel like this when I was 8, 9, 12 years old and then they had recurring episodes and it was only in they 20s or 30s they had a manic or hypomanic episode. So given that all the antidepressants can induce produce at least low amplitude rapid cycling, if you are treating adolescent depressions, because of their genetic loading, you're going to get an over sampling of bipolar patients in whom the result is going to be less than wonderful. You'd have to have either an enormous sample size to wash that out or what I've suggested to a number of drug companies is to exclude every adolescent in the study who has any family history of a first or second degree relative with bipolar disorder. That won't totally eliminate the problem but it may get you a purer sample of unipolar depressions and then my expectation is you would see the drug and placebo separate out from each other.

Clinically of course that's what happens. A lot of the time I see these adolescents who have recurring depressions that haven't responded very well and even though they've never had a manic episode, I may end up taking them off their antidepressants and putting them on a mood stabiliser and they get better. I think a lot of clinicians in fact are adopting that strategy but it hasn't looped back into the research protocols yet.

**That seems like the kind of thing that's not going to be supported by the clinical trial evidence for a long time to come if ever. The trials are almost too hard to do.**

Well for Glaxo's lamotrigine, the data so far looks very good and certainly a lot of us use it clinically. It appears clinically to be an effective anti-manic drug and certainly a good mood stabiliser. Depakote is another one. Both of these drugs I would put at the top of the list of potent mood stabilisers. They are not entirely safe for children and so one wouldn't want to recommend those as first choices. Nonetheless looking at drug development, I have to believe that we will have safer versions of lamotrigine and divalproex sodium in the next 5 to 10 years, that can be used for children and this will allow this treatment effect to be seen.

Gabapentin is another option but probably it might be a little bit less effective as a mood stabiliser than the others but its possibly safer. I think by the way this is another area that drug companies have not yet properly understood. I

think bipolar disorder is maybe the single most under recognised and mistreated disorder by family physicians and psychiatrists. Once people catch on to that they'll start both diagnostically teasing the groups out and developing new drugs that would help these people. But I think that psychiatry has not done a good job in doing that up till now.

### **We don't recognise bipolar conditions over here in Europe the way you guys do in the US. Why is that?**

Well there are probably many reasons behind it. I think that you may be calling the same phenomenon a different name. Many physicians may be looking at what they think is a unipolar depression. Some of us have a rule of thumb, that if you see a patient with depression failing on an adequate trial of more than 3 antidepressants that's a bipolar disorder unless proven otherwise. What we would do at that point is make the judgement that that patient would probably do better off an antidepressant because all antidepressants will induce rapid cycling much more than the world has acknowledged. I don't mean that it flips them into mania because such manic episodes are relatively rare. But if you get a patient to keep a daily mood chart, you'll see all kinds low amplitude cycling that you would probably call cyclothymia. Take that antidepressant away and that low amplitude cycling will lessen or stop, especially if you've got them on an adequate mood stabiliser. For slow cyclers we would use Lithium but if they are mixed state, rapid cycling, or bipolar II patients, we put almost all of those patients on anticonvulsants first. The problem clinically is that there are very few papers in the literature that in a cook book fashion describe how these drugs should be used, so that the average clinician is poorly informed about how to get the patient well - what doses to use etc.

If you line up the 20 or 30 of these patients, who might be in anyone's regular practice and take them off their antidepressant and just use the mood stabiliser alone, I think that most clinicians in practice are going to be surprised at the effect. They are going to realise I've managed to reach these patients that 10 years ago we thought were hopeless untreatable people. I think more and more clinicians are switching to mood stabilisers even before using augmenting agents, for just this reason.

I am always troubled when I see psychiatric residents assign the label borderline personality disorder as a primary diagnosis. This still happens a lot, when we should be using a multi-axial diagnostic system. Behind the label is often the belief that this patient is a hopeless case, that they are impulsive, intermittently suicidal, unpredictable, irritable, difficult and have failed all the common treatments in the past. The assumption is that this will continue, the prognosis is hopeless and therefore the expectation for a good outcome should be low - a "don't blame me if I can't fix this chronic mess" attitude. Many psychosocial treatments in the past and even the use of antidepressants in some cases perpetuated this view. However, I think many such patients have a bipolar disorder. They have a rapid cycling, mixed state or bipolar II irritable rather than the happy/grandiose type of bipolar disorder - what some might call soft-spectrum bipolar disorder. We need to find more effective biological treatments for these patients.

When their “personality disorder” changes with anticonvulsants we will have to revise our concept of personality disorder. I am concerned that thinking in “constitution, personality and psychosocial” terms, we restrict our vision of treatment expectations and options. We need to give such patients the benefit of other options. When a significant number of them respond long term to anticonvulsants, pharmacotherapy climbs the ladder of therapeutic options and calls for a revision of some of our past cherished views on their disorder. I believe this will be an area where we will see major revisions and improvements over the next 30 years.

**Now you clearly think this is a breakthrough but its a breakthrough essentially driven by clinical practice without the evidence of the conventional trials behind it which seems hard to reconcile in the climate of Evidence Based Medicine we are now in.**

Yes. Most great observations come from clinicians working with the patient and observing closely a clinical phenomenon. After the observation comes the empirical testing of the observation and its consequences. The great insight must always encounter the granite rock of experimental interrogation. Only after that do we have some evidence. The evidence is the survivor of this encounter.

**But its interesting isn't it in the sense of yes this has been observed for the past 5 to 10 years but its extraordinarily hard to put together the clinical trials that would have the power to really show the effect.**

Yes, some of that depends on another issue in the case of bipolar disorder. People still haven't adequately figured out the right outcome measures. Some of the early trials with divalproex sodium and lamotrigine produced data that did not look especially wonderful. But when you look carefully at the choice of outcome measures you realise that it was actually a miracle they worked half as well as they did given the lack of sensitivity of these outcome measures. Bipolar is one disorder where its trickier to pick an outcome measure - are you going to measure the mania, hypomania, depression or both. You are really looking to shrink both the mania and the depression or reduce the amplitude of the cycling. If you've got a slow cyler in the study you may have to go through several cycles before you can see that occurring. That might mean 6 to 12 months of treatment, so you can't really easily do an acute treatment short-term trial and expect to see efficacy in bipolar disorder. Every clinician who uses the anticonvulsant drugs or lithium will tell you that its a year or two up the road before the patient is saying listen my life has changed. I was out of the woods maybe in two months but its really so much better now than it was a year or two years ago. So I think that what we probably need to do, while we are waiting for all those trials to emerge, is to go out teaching clinicians showing video tapes of real cases, showing how we measured this and what they can do in a cook book fashion and get them all going on this.

**I can see what you're saying but in some odd kind of way we seem to be back 50 years ago where what you've got is the expert saying this works because I say it works.**



Well as a first step yes. But the clinician can say “I don’t believe you but I’m willing to give you the benefit of the doubt for these 10 patients that are not improving”. What have I to lose and if it works out the way you say by golly I’ll keep doing it and if it doesn’t I’ll abandon it. And I think if you look back over the last 20 years, this in fact happened in panic disorder. Don Klein and I would run around saying you know tricyclics or MAOIs worked for panic disorders. People did not accept this view and said these patients should be in psychoanalytic psychotherapy but they were willing to give the benefit of the doubt because they all had a number of refractory cases. So they tried it and it didn’t take anybody long to figure out that it was true. The same was true originally with alprazolam. Everyone said it couldn’t possibly work and must be less effective than tricyclic antidepressants. But people were willing to give it a shot in a few cases and again it caught on like a brush fire. I have great faith in the intelligence of the average clinician. They are very discriminating and they give everything a run and if its successful they will keep doing it and if its not they’ll abandon ship very quickly.

We have an obligation to our patients. We can’t wait 10 years for all this wonderful clinical trial data while people are suffering. In the meantime we ought to be trying to do everything we can to help them. And if the world has collectively agreed that this is helping a large number of people that they couldn’t reach before it doesn’t bother me that there is no clinical trial data and people like me are promoting an idea without good evidence. But I should stress that it can’t end here. We must expect that such ideas will then be empirically tested to see if they hold up under rigorous scrutiny

**In US psychiatry at the moment there’s an almost anti-bug view about what psychiatric diseases are and what the drugs do to them. Whereas in Europe I suspect we are much less oriented that way - its much more constitutionally oriented still. How do you see all that?**

Well in the United States, maybe unlike other countries, there isn’t a uniform view of anything. You get a diversity of opinions amongst clinicians all the way from herbs and aromas at one end to core biological psychiatry at the other. But its fair to say that most of those involved in academic psychiatry, who are at the cutting edge of neuroscience, probably hold a fairly hard core biological medical model view. The orientation emerged from places like Washington University, St Louis and many of those mid Western Universities, along with Pittsburgh, Mass General, Harvard, Yale, Columbia, Stanford. These universities generally hold that position and certainly the way I was trained at Harvard. These are diseases of the body and brain just like multiple sclerosis, diabetes mellitus and thyroid disease and to the extent that you approach them in that way you’ve got a chance of moving the field along and being able to get a handle on making better predictions.

So the view is very medical model, very disease oriented like in pneumonia caused by bugs and we have to find the right antibiotics to kill each of the bugs. You can think of the pneumonia as equivalent to panic disorder or major depression and this is the model we use as a co-ordinating strategy for our research efforts. Those viewing this from the outside may say these guys actually think that panic disorder and major depression in DSMIV are real

diseases but we think major depression and panic disorder are probably closer to being like coughs and fevers. Either way, they have some predictive power in that just like people who get coughs if you follow them you can make certain predictions what will happen them compared to people who don't have coughs. Some of them will end up with tuberculosis and many of them will die and some of them subsequently get fevers and so on and many of them will respond to antibiotics etc.

When I look at ICD 10 and DSMIV, I see these diagnostic labels as predictive clusters. They predict symptoms the patient has not yet complained of, complications they are likely to develop, the natural history of their illness or symptom cluster, family history to some extent and what treatments they are likely to respond to, which may be the most important thing. Like the cough I expect that underpinning these predictive clusters will turn out to be at least a number of real pathological entities. I think that model has been useful in international research in driving new discoveries, in leading people to think about the illness in a way that they find things out faster because the central focus of their research is how can I predict things better. Improving predictive accuracy and finding better predictors is a driving force.

**But if you have this bug or cluster view, you get into saying there's a different bug in one area of the brain which underpins OCD and in another area underpins social phobia and in another area mood disorders. But the SSRIs treat all of them. How do they work on 4 different bugs in 4 different ways or do they all do one thing which is they reduce emotional reactivity in a way that cuts across all these syndromes. If that's the case you can't make any statement at all about the nature of the syndromes from the action of the drugs.**

I wouldn't say you can't make any determination at all but you're absolutely right that you are limited in what you can speculate. You can speculate that serotonin and norepinephrine are probably more important than dopamine and histamine in depression but we're not even sure on that.

**Well D2 antagonists and stimulants have just as big an effect size as the SSRIs for mood disorders.**

Fine but we can narrow down the domain to serotonin, norepinephrine or dopamine as opposed to histamine receptors and cholinergic receptors. That doesn't necessarily tell us anything other than that these may be simply remote arms into the centre of the action. Its a little piece of a giant jigsaw puzzle and its only really with the passage of time and more discoveries and a wider diversity of the drugs helping the condition that will put more pieces of the jigsaw puzzle in place.

This is one thing that I've become more patient about. At the beginning of my career, I wanted to find out all the answers today. The passage of time has taught me that there really is a limit to the speed with which you can figure all of it out and that historically small bits get figured out and build a bigger picture and you have to do it systematically and you have to be prepared to be patient and methodical. We may not figure this out to our satisfaction in

our lifetime but I do believe our grandchildren will have it all figured out the way that we wish we could do tomorrow.

**To come back to the point on the SSRIs I outlined above - the idea that they reduce emotional reactivity across a range of different syndromes. If this is the case, and I would say that the actual treatment effect size for OCD for instance is larger than the treatment effect size for mood disorders, then you could argue that the SSRIs in some respects would be better anxiolytics than antidepressants. How much do you think they end up as being seen as antidepressants because of the anxiolytic market got wiped out because of the benzodiazepine controversies?**

Well God didn't talk to Moses at the top of the mountain and say here are SSRIs and they are antidepressants. It could have actually happened historically that we would have discovered that they were anxiolytics years before we ever discovered they were antidepressants in which case we would be telling all our depressed patients that we've got a wonderful anti-anxiety drug for them. The patients would then wonder why we are giving them an anti anxiety medication for their depression. These are man given titles about products that are really neutral to the concepts we attach to them.

The drugs don't respond to labels such as "antidepressants". The way we slice up all of these disorders may have less to do with anxiety, depression or constitution or any concept we've used so far. There may be a better way to model these illnesses as they are in nature - a better predictive model. I think we just have to keep an open mind about it. But I think in the end, its going to come out closer to a disease model like the bugs in pneumonia or even more like insulin and diabetes mellitus. I am happy with that model, even if its a wrong one, because I think using this model we will find out things faster than if we subscribe to a constitutional model which has a way of going around in a circle. Its not as heuristic a model as the medical model. Some of the time what we're doing is adopting models not because we necessarily believe in a religious sense that its absolutely 100% true but rather because the model is useful in a practical way to help solve problems. I think that's a view that is widely subscribed to by American psychiatrists. Increasingly, American psychiatry is moving closer to the model of the endocrinologist running a diabetic clinic.

**It's an extraordinary flip how you guys have gone from Freudian dimensionalists to bug men.**

Well it's a matter of pedigrees. If you look back at the pedigrees of the people who are the biological psychiatrists they often trained with teachers who were themselves very biologically oriented and would trace their heritage back to people like Kraepelin.

**So you don't think its people who were once analysts becoming bug-men. People like Klerman were analysts becoming Kraepelinian. Is this a case of a key convert?**

A key convert yes. In those days many of the brightest people went into analysis because that's where the action was. But what happened was at some level, after they had done their psychoanalytic training they felt there

was a distance between what they were seeing in reality and what they had been taught and they were looking round for better explanations. I think that was true of Klerman who was an exceptionally bright man. He had a curious, enquiring mind and he found that many of the things that he was looking at weren't answering his questions. Then he sort of stumbles into this group of people who share his need to enquire in the same way and who have partially solved it. It wasn't an accident that he ended up at Mass General because in fact that's probably one of the key sites where the tradition began. The people that started this trend in psychiatry in St Louis, which was really the main school that germinated the central ideas in the DSM III with Columbia University, originally trained at Mass Gen.

### **Eli Robins**

Yes. He trained with Mandell Cohen at Mass General. Mandell Cohen didn't even have an appointment in the Department of Psychiatry in the 1970s, that's how much on the out he was with the analysts, who back in the 40s and 50s ran the Department of Psychiatry at Mass General. Basically he was too biological for them and they cut their relationship with him. He had an appointment in the neurology department, even though he was a psychiatrist. But he was a very concrete medical psychiatrist. He was very clear minded, very blunt and very direct. He would easily and quickly engage in debates with people and challenge them when their thinking got fuzzy.

A long time back in the 30s or 40s he said diseases of the mind have to be studied like any disease - you have to define your diagnostic criteria precisely and apply them consistently. He influenced some residents and they went out to Washington University in St Louis and collected a group of like minded faculty. A similar parallel tradition happened in Columbia University that influenced people like Bob Spitzer. It was an axis of graduates from St Louis, Columbia University and Mass General that led to DSM III. They claimed that their classification was atheoretical. I used to have interesting discussions with Klerman about this because I never felt a need to claim that that was so. I used to say that its clear that its driven by a medical model and you shouldn't have to apologise for it because any good scientist has to be prepared to stand up and state clearly what they say and expose their ideas clearly so that they can be shown to be wrong, if they are. You can't hide behind saying I have an atheoretic model to make yourself look pure. "Don't attack me, I'm neutral". I thought it was better to stick your stake in the ground and say this is where I stand and if I'm wrong, well science moves on by showing that things are wrong rather than trying to prove that things are right. In this sense I am heavily influenced by Karl Popper. So it was a medical model, driven largely by medically oriented psychiatrists and all of the original thinkers behind DSM III, although less so IIR and certainly not IV, were absolutely Kraepelinian to the core. When you talked to them privately that's what they would all to a man acknowledge.

### **How come Mandell Cohen is almost an unknown?**

The sad thing about it is he was so badly treated by the Department of Psychiatry at Mass General that, even when I was a resident there they still refused to have any dealings with him. Even in the 80s for heavens sake,

they still refused to give him an appointment in the Department of Psychiatry. Historically, he may turn out to have been one of the most important figures to have been associated with that department. They insulted him in this way, when he single-handedly was the spawning influence behind a huge trend in American psychiatry. I think history will not look kindly on them for having done that but at least the department of neurology appreciated what he was doing. The neurologists there looked at the psychiatry department as somewhat archaic and not medically oriented enough and their view of psychiatric illnesses was that these were medical diseases.

### **How did you find out about him?**

When panic research started to flourish just before the world-wide panic study, around 1982 or 1983, we tried to organise a conference to bring together all the world's top experts on anxiety disorders. It was organised by Mass General in Boston. We were sponsored by Upjohn and we got together all the top names at the time. People like Braestrup from Denmark, Don Klein, Isaac Marks, in my opinion the best concentration of anxiety experts in one room ever assembled where I was present. It was a fascinating conference. Anyway since I was involved in the planning, one of the things that I wanted to do was invite Mandell Cohen because I knew about the history. You cannot imagine the level of resistance that I ran into at the Mass General in getting them to allow me to invite him even to speak at the meeting. They were absolutely opposed to doing that.

### **Why - was there something about his personality?**

Probably. I don't know. Some people claimed that he was too direct with them. He didn't suffer fools gladly and he was not afraid to tell people directly what he thought of the nonsense. They were worried that he might speak out and that they might be embarrassed or something. I don't know what their concern was but I suppose it was something along those lines. I had chatted to him quite a number of times and I always found him exceptionally intelligent, bright, direct. A no nonsense guy. Way ahead of his time.

### **Do you think he was too far ahead of his time?**

He was an entire generation ahead of his time. He was in a different galaxy. At this point Mandell himself was conscious of how he was perceived in psychiatry. "Well I don't think I can do that, I wouldn't be welcome", he said. I said I'm the one organising the conference I really want you to come. It's important historically. These people have forgotten the things that you did 10 years ago and 30 years ago and I'd like you to come along. He said you know I haven't kept up with the research and so on. And I said yes but some of the research you did 30 years ago would still look sophisticated. So he said I haven't looked at some of those papers and slides for years. I said never mind, see what you've got and review the research that you did on anxiety neurosis back then. A little later, he said he had found some old glass slides - they used to put them on these big glass plates, epidiascopes - so we arranged for a special projector that would show these glass slides.

I put him first on the agenda because of the interesting historical background but also as a way of letting the assembled demi-Gods know that although they

all thought they were at the cutting edge of what was happening that here was this guy who an entire generation earlier had anticipated almost everything they had done and even taken it one step beyond what their most of them were thinking. I remember a lot of people were saying who is this man, who is Mandell Cohen. And this little old man gets up and proceeds to give his talk. He apologises that he hasn't been in research in anxiety over 20 years, he's probably way out of the loop but here's what he thought. He talked about how in those days they couldn't measure much in the blood but they knew the patients had exercise intolerance and they measured their lactic acid level. They figured they had an aerobic metabolic defect and so then they looked at CO<sub>2</sub> and then gave the patients all these provocative challenges. He put up slides that were never published and other interesting physiological data. He plots out the whole thing.

Don Klein and the others are sitting in the audience thinking Holy Mackerel this was done nearly 30 years ago. This sounds intelligent and is actually ahead of even where we are today. The group was bowled over. He stole the show on everyone including alprazolam as a new discovery for panic disorder - that was even trivial by comparison. This guy had anticipated almost everything we had done and understood very clearly where the field was going to be. That resurrected him in all of the gurus eyes. I ran into him in the hall a couple of times after that and I noted Don Klein's group invited him to come to Columbia to give some talks and I think he was invited to Yale to give talks. He kept apologising that he was out of the loop and they kept saying just tell us what you did then that's interesting. I think he was very gratified by it and far from causing any difficulty I think what it did was he made everybody feel that Mass General had actually done something useful in this whole area and that he was an advantage rather than an inconvenience.

**Where would he have got his ideas from - who would he have got the operational criteria line of thinking from back in the 40s?**

I don't know and I'm sorry to say that. I never actually sat down and interviewed him along those lines. I was into the details of what he was doing. I never asked him that question and I don't know if anyone else did either. Its a pity. He spent a lot of his time with other departments in the hospital and did a lot of research collaboratively interacting with other departments. So some of his drive may have come from being exposed to psychoanalytic theory and thinking this was not a helpful research model and that it didn't translate into anything useful therapeutically and then becoming oppositional about that and as he became oppositional and they marginalised him, he then found comfort in talking to the other departments and specialities. There he probably found people thinking about psychiatric diseases as though they are real diseases and he starts to think well let me adopt that as a model.

I may be completely wrong about this but I didn't even get the sense that he had been specifically trained to think in this way as much as that it was driven really out of opposition to what he perceived was the nonsense approach. For example one of the people he worked very closely with was Paul Dudley White, who was one of the Granddaddies of American Cardiology. He was

Eisenhower's cardiologist. He got one of these early EKG machines and was one of the first people to document the particular abnormalities in certain cardiac illnesses on the EKG and then on the exercise EKG. Mandell was involved in doing treadmill exercise and stress EKG studies with Paul Dudley White and seeing them investigating heart disease by looking at these waves on paper, I'm sure he must have thought if you can do this with the heart, you can do it with the brain. So he was also into EEG and brain waves. Essentially translating all of the technical approaches cardiologists had into another system - the central nervous system. My sense was that was probably a much greater influence than any guru who said this is how it is and planted the seed of operational criteria in his mind. I think he's a seminal figure in American psychiatry without people knowing about it and history will elevate him to a much higher level.

**Well what about the neo-Kraepelinian school to which you belong.**

There was a Professor of Psychiatry in the University of Florida, Roger Blashfield, who wrote a book on classification of psychiatric disorders that I read when I was in Boston. I stumbled across it. He was an expert in cluster analysis and he had done a cluster analysis on psychiatric citations in the literature. Using clustering, he found that there were certain people who cited each others work. And in one cluster he described this axis of Washington University in St Louis and several of the mid-Western universities along with Columbia and Mass General. Without knowing how they were linked he kept seeing this as an influence and described this cluster. Many years later when I moved to Florida, I invited him down to give Grand Rounds and had dinner with him. I said you know when I read your book a couple of years ago I couldn't believe when I read it that many people outside of that group knew of this invisible college and how they work. Did you realise this or how did you find out the information on all of this. I told him some historical anecdotes about this group. He told me he didn't know that at all. He said he put it all together directly through the cluster analysis. I could hardly believe that he could have arrived at it in that way. He told me some specific things within the cluster analysis that he had observed and I told him the real life anecdote equivalents of how Mandell Cohen begat Eli Robins, who begat Sam Guze and then how Washington University in St Louis decided they were going to attract people who would become Chairman candidates for all of the other departments in the mid West - they would basically seed the professors for many psychiatry departments in the mid West. And this in turn bred this view of psychiatry across all these training programs in psychiatry.

When I described this lineage to him he was fascinated. What's interesting is that it could be seen in the math of the cluster analysis. Its worthwhile taking a look at his book again because it's like a skeleton on which you can put all of this historical meat. Somebody probably someday needs to write a history on the neo-Kraepelinian school. That's how they referred to themselves, although I think if they fully understood what Kraepelin said they wouldn't actually subscribe to all of his views. To the extent that they understood he was a medically oriented psychiatrist they support him. Somebody should write about all of these people because a very small core group were the central influence behind the radical shift in thinking embodied in the DSM III.

That was a major and radical departure from everything that had gone before. In turn, using Spitzer and Klerman as frontmen they influenced ICD 10 and basically caused a major shift in the direction of the psychiatric ship worldwide. They brought it back into the arena of medicine and away from being a division of philosophy or social work.

It would make a fascinating history. Many of these key figures are now at retirement age. Somebody needs to document it before it's all lost. They have some great stories about how they did what they did and how it all came about. They were all our immediate teachers. What's interesting is of that group, many of their off-spring are now the ones that are key figures in academic research in the United States. If you look through the programme of major meetings, you'll see all these names, who look like they're scattered in different places, but I see people were all taught by the same few people. Nobody knows except the people on the inside that they were all brought up in the same cradle together. You'd be surprised at the extent to which that is true. It's not an accident. The equivalent of the Maudsley or the Salpetriere in Paris or Kraepelin's group in Munich.

It's an invisible network. Those involved know it. They never comment on it. It's understood. Like they are all wearing the same college tie. The conspiracy theorists could make a great play with this. What's interesting is they actually rarely get together in this conspiratorial way. In fact some of them hate each other and are jealous of each other, fight with each other undermine and backstab each other. But yet while they have this sibling rivalry and stab each other, they still belong to the same family. That should be your next book.

#### References:

Blashfield R (1984). *The Classification of Psychopathology*. Plenum Press, New York.