

A CEO LOOKS AT PSYCHOPHARMACOLOGY

David Horrobin

I usually ask medical people why they went into medicine, but in your case it's more appropriate to ask why you left it?

Mainly because I was interested in too many things. I didn't want to get railroaded down a particular speciality. I felt that from a position in clinical physiology, I could do lots and lots of clinical projects. So I stayed in basic science but have primarily spent my life doing clinically oriented work.

Physiology in Oxford involved what?

I did a year working with Geoffrey Harris. He was the person who first demonstrated the pituitary is controlled by the hypothalamus. And that really I suppose in many ways shaped what I was interested in from then on – how does the brain control the hormonal system? I did clinical medicine but I'd worked as a flying doctor when I was a medical student in Kenya, and was so fascinated by Kenya that I wanted to go back. So when a new medical school there was looking for a clinical physiologist to start their physiology programme, I went out and worked for four years in the medical school.

The odd event that really shaped the future, and that directed me down a psychiatric as opposed to other routes happened there. A physiologist called Howard Burn from Berkeley, California, a real superstar in the field of prolactin research, came out, funded by the US embassy, to give a lecture. The way these things used to work – the US Embassy had no idea who he was supposed to be lecturing to or anything, it was a sort of cultural thing, so I got a call from the US Ambassador saying "I've got this hotshot from the University of California can you find an audience for him?"

It was the middle of the vacation so the only people around were a zoology professor called Mohamed ?? and myself. What we did was collect all the cleaners, gardeners, technicians, and secretaries and put them in the lecture theatre and Howard gave his lecture.

Did he know who was he was lecturing to?

No, not at the time. I got to know him moderately well later and ten years later I told him, and he was highly entertained. What he was talking about was prolactin. Essentially he was a zoologist and what he had pioneered was an understanding of how prolactin regulated fluid and electrolyte balance in fish, reptiles, and other organisms, the way salmon moves in and out from fresh to salt water and that sort of thing. I asked him whether anything was known about prolactin in humans and he said "nothing at all, we presume it's to do with mammary development but actually nobody knows."

So I thought the only way to find out is to do an experiment ourselves. So I got all the staff in my department, got some bovine prolactin from ? in Sweden, and

on a placebo-controlled basis we injected it into ourselves and saw what happened. And in fact it has profound effects on fluids and electrolytes. The paper was published in the Lancet in 70 or so. Then Gwyneth Hemmings saw this. She was very concerned about neuroleptic induced prolactin secretion and indeed she still is and so she said “some of these findings might be relevant to what’s happening to our patients, can you advise us on this?” I got to know her quite well, and became totally captivated by schizophrenia.

At this point she was just starting the Schizophrenia Association of Great Britain. Her husband was probably schizophrenic, maybe bipolar, a reader in zoology in Bangor. She had three schizophrenic children and was totally unhappy about how schizophrenia was being handled because still at that time most people were saying to schizophrenia families it’s your fault. She was trying to get interest in a broader view of schizophrenia - what other aspects of the body are affected and what are the drugs doing and so on.

I became totally captivated by that. Then I became aware of this old data on arthritis and schizophrenia – from the New England Journal in 1936 – suggesting that if you are stressed you can react either by becoming arthritic or schizophrenic but not both. I was interested in that because we had just shown that prolactin stimulated prostaglandin production. And so I became interested in the possibility that prolactin may be contributing to the therapeutic effect of traditional neuroleptics. No one has ever really properly investigated that because prolactin production is an inevitable consequence of D2 blockade.

The negative association between arthritis and schizophrenia suggested schizophrenics might not produce prostaglandins normally. As prolactin stimulates prostaglandin production there seemed to be a role for it here. I became interested then in the apparent absence of pain in during acute psychotic episodes and similar details. Then I began to read Wagner-Juaregg’s stuff and while of course malaria therapy was quite effective for cerebral syphilis, interestingly if you go back and read that literature, he and others also later said that other types of psychosis benefit but you only see a beneficial effect when you get elevation of temperature. As soon as the temperature comes back down again the effect disappears.

Now Gwynedd used to organise these patient meetings, where there were large numbers of patients and their families, and I started asking patients and their families “have you noticed any effect of fever?” In fact if you do this you’ll find that surprisingly frequently its been noted by the families of schizophrenic patients that they become more connected, they become less psychotic if they have influenza or any feverish illness. I had some quite dramatic anecdotes. So that was how I really got involved in this whole idea of inflammatory mediators, prostaglandins, in schizophrenia.

From Kenya then you moved back to the UK and then on to Montreal?

Yes via Newcastle. The medical school in Nairobi was an aid project, which was supported by a number of independent people and then both the University of Glasgow and McGill. So I got to know a lot of Canadians in Kenya, and developed contacts with Montreal and got invited to become a Professor of Neuroendocrinology, at the University of Montreal, with a part time teaching position in McGill. I was running a neuroendocrine lab in the Institut Recherches Clinique.

I was beginning at this time to be really interested in mechanisms of psychotropic drug action. We were looking at things like clomipramine and coming up with potential effects of prostaglandin antagonism. We have about ten papers in the specialist prostaglandin literature showing that tricyclics appear to be prostaglandin receptor antagonists. Now this of course fits with the interesting fact that MAOIs are really quite potent cyclo-oxygenase inhibitors. This cyclo-oxygenase effect was discovered after the MAOI effect, and it's a nice speculation to wonder what would have happened to history of psychopharmacology had the prostaglandin effect been discovered first.

I linked up with Julian Lieb at Yale, who was running the Affective Disorders Clinic there. He was also very interested in non-psychiatric aspects of psychiatric disease. One of the things he'd come up with was that depressed patients bruise easily. One possible explanation of this is that it has to do with platelet function and we published a paper in 1983 showing that depressed patients have strikingly elevated thromboxane levels, which is a measure of platelet activation.

Then I got interested in mechanisms of action of diazepam, and we developed some evidence that diazepam was a thromboxane antagonist. I had a group at my lab who were oncology people and therefore we had some transplanted rat tumours. Very stupidly perhaps, one day I put diazepam into this model and the tumours grew like crazy. We published this in Cancer Letters without any trouble at all. Nobody noticed it.

Then people from Kings published something in The Lancet about the idea that people who were passive and depressed and had breast cancer did badly. I wrote a letter to The Lancet saying - maybe it's the depression, the anxiety, and the passive mood, which is the problem, but on the other hand this work does not distinguish the possibility that it's maybe the drugs that they are taking which produces the end result. And all hell broke loose.

The letter was published in the Lancet and then the press called. I gave them what I thought were perfectly sensible and reasonable views on this saying, "look we haven't proven anything in humans but this has to be a possible explanation". Now Roche had their Canadian headquarters in Montreal and they were giving money to the University. Its very difficult to nail down but the boss of the Institut,

Jacques Genet, a hypertension guy who was very well known in Canada, came in and said “you’re out”.

And did you not have a contract of some sort that would have meant that he couldn’t do this?

There was a contract and I probably could have done something but I made a conscious decision. I said, I can fight this, but if I fight it I’m probably going to spend the rest of my life tied up with this, or I can just put it behind me and do something different. So I made a conscious decision to do that rather than fight.

But it was really quite bizarre because Roche organised a worldwide media thing to discredit me. They hired a guy called Francis Roe who was a pathologist at the Cancer Research Campaign, who made all sorts of remarks saying I was a useless scientist and had no reputation. He went on the radio and said all this sort of stuff. Only much later did I find out the real reason for all this fuss was that there had actually been no carcinogenicity studies on diazepam. It had been approved at a time when these were not required. And so Roche was legally fine but morally where you have diazepam being given to every fourth woman in the Western world it’s at least arguable that even though they might not have been legally required they should still have undertaken them.

And has any further work been done on this since?

A lot of further work has been done and in general it’s been supportive, including a study from NIH on cancer in animal models. There is multiple supportive work in animal models, but in humans at present, the last epidemiological study was done about 10 years ago and that was negative. But there is evidence of course about teratogenicity and diazepam.

That’s been kept very quite

Well interestingly one of the few people who really supported me was Alice Stuart. She is still alive at 95. She was the person who first demonstrated back in the 40s that X-rays in pregnant women led to leukaemia in children. All hell broke loose with her back then. Anyway she said, “no this is real possibility that has to be looked at”. I don’t think there is a strong effect from diazepam and I don’t think we actually know yet what the risks are but it took 40 years for the evidence on smoking to come out. So that was my encounter with the pharmaceutical industry.

Was this your first encounter with the pharmaceutical industry?

Well I got to know George Beaumont quite well. George used to give us clomipramine and funding because he was actually quite interested in this idea that antidepressants might be working by regulating calcium movements. He was very open-minded and he was interested because of the evidence that clomipramine might be different, so I had quite a lot of contact with him, but that was about it.

So from Montreal you went where?

At this point I decided that basically academia was corrupt.

Was there any other reason to think that other than what had happened to you?

Well I had been writing about peer review since the 70s because it seemed to me that the peer review process was fundamentally corrupt. I have a long article on this in the BMJ. The event that led to it came about like this.

Normally the peer review process is supposedly anonymous and confidential. If you submit a grant to any body, what you get back is a very doctored version – if any – of what the peer reviewers have said. Now we were doing a lot of work at that time on prolactin, following on from the Nairobi work, and applied for some funding to extend this work. Interestingly, the granting Body sent back the full-review. It was so nonsensical, and so ridiculous, that it made me question the whole peer review process.

Why is it anonymous? Why do grant-giving bodies feel the need not to give the applicants the full reasons for rejection? Why do they feel the need to be anonymous, if the statements are objective or valid?

I began talking to lots of other people and began to build a dossier, which indicated that the peer-review process was essentially being manipulated by the great and the good in academic science.

Were there any other incidents that brought that home to you?

Well that was the main one for me, but other people told me the same thing. Another example involved Tim Crowe. I think he misuses his dominant position in schizophrenia in the UK. He's not in the remotest sense open-minded about any views other than his own. Anybody who produces concepts, which are in anyway different from Tim's will feel his wrath.

I happen to know this because when one of my grant applications back in the 70s to the Canadian MRC was sent to him for review, he didn't realise that, partly as a result of my sort of agitation, the Canadians actually did send reviews back to the originators. And it was not a rational review at all. Totally dogmatic, appealing to authority, I know what I am talking about and this is rubbish. When anybody says something else is rubbish, they rarely have an argument.

I really can't see why somebody who has a rational argument would not be willing to put it down and sign it. But I am not optimistic about the system changing because it gives too many advantages to the limited group of establishment people.

I was amazed however that the BMJ published a long article on this called Research Referees and Research Administrators - Barriers to Scientific Progress. So there was a lot of support for this particular view.

Anyway, I felt that if you were really trying to be innovative and do something new the prospects of actually getting anywhere in academia were remote. And I think that has got worse and worse. We really have an absolutely lunatic situation. In every other aspect of life the Soviet system has been discredited and is believed to be nonsense – it is recognised that if you try to control things centrally you inevitably make huge mistakes. The person at the centre almost always gets it wrong.

And very few scientists in fact have any sense of history. If you look at the history of science, two things stand out. One is that the expert consensus at any period of time is always wrong. The consensus at any point of the last 500 years has always been wrong. And second, the expert consensus always opposes change, which moves it towards a better description of the world. So the expert consensus is both always wrong and always opposed to innovation.

We used to have a situation where it was the responsibility of the Universities to support researchers so that until about the mid 60s if you were a lecturer in the University here in the UK you got a few thousand pounds to do whatever you wanted to do. And this was the golden age of UK science, when we were winning a Nobel Prize every year and so on. Now it's the job of the lecturer to support the University and you have the central Soviet telling everybody what they are allowed to do and maintaining "research quality". We have a system where twenty people in London or Washington or wherever essentially decide what is being done, and what you can absolutely guarantee is that if you have a structured system to maintain research quality you will get top of the third division.

When you say 20 people in Washington and London, you mean 20 people across medicine or 20 psychiatrists, and 20 cardiologists?

In this country you've got two sources of funding with bits and pieces outside – there is the MRC and the Wellcome. They have their evaluation committees who are all carefully chosen to be responsible members of the establishment, to show political maturity. So what you have is a group of experts who you know will be wrong but who have an absolute stranglehold on what is done.

You're describing a bunch of Cardinals aren't you?

Absolutely, and research has become more and more controlled. And the reason these people advocate peer review is not to ensure quality, it's to ensure control. So that's what I felt about academia. I felt there was no prospect of me ever being properly funded in academia, so the only way I can do what I want to do is to make my own money.

Did this gel at any one point – was there one night when the coin dropped and you felt this?

No but there was one seminal experience back in my medical student days, when I was doing pathology, worth mentioning. Florey, of penicillin fame, ran the course. And he brought in star lecturers every week or so to give a research seminar and we were all expected to go along. Around 1962, a young Australian came and gave this absolutely brilliant seminar on how immunology was going to transform medicine. This was just after the discovery of T and B lymphocytes. It was captivating. He showed how this was going to solve not only inflammatory diseases, and cardiovascular diseases but all sorts of things.

I remember sitting there and thinking this is the future, and we all clapped like crazy. Florey, who was a very dry guy, got up and said “don’t you think that the ratio of the unknown to the known will always be infinity?” Of course I think he is right, but it’s been the grand illusion of every generation of science since Aristotle that we have just got to give a little push and we are there. But that grand illusion has always be wrong, and this is what Florey was drawing attention to. The complexity and diversity is such that we only know a tiny fraction. But, the way in which the system is controlled ensures that we only look at a tiny fraction.

So in the early 70s I was interested in ideas and had begun to realise that it’s very difficult to publish ideas or criticisms of ideas in medicine. You try and publish a sustained critique within any area of medicine without having done experimental work or clinical work and you get nowhere. And yet if you look at chemistry or physics you have a different picture. You have groups of people who are recognised to be exceptional thinkers and theoreticians, and you have other groups of people who are good at experiment and in fact it very rare to have people doing both. So I began to think that medicine lacked a theoretical structure and I founded a journal Medical Hypotheses to fill this gap.

I contacted Linus Pauling, who was interested in ideas, Karl Popper, and Jack Eccles whom I had known at Oxford, MacFarlane Burnett, and they were all enthusiastic about this and became advisory board members for Medical Hypothesis which started in 1972. And it’s still going very strongly.

How does it support itself?

Elsevier publishes it now but I started it myself, and then I sold it to Churchill Livingstone after about three years. They were expanding so they bought the title but I continued to edit it. Then Churchill Livingstone were acquired by Harcourt and later Elsevier. What I was trying to do was provide a forum for highly innovative ideas but which were nevertheless expressed in a way, which connected with the biomedical community. It was not a forum for the absolute lunatics but it was a forum for people who had interesting things to say. And I think it has been very successful. My guess is that 90% of the articles in it come from mainstream Universities, so there is a perceived need for it.

These articles aren't peer reviewed?

Well yes they are peer reviewed but the review process is different. What we are looking for is not whether it's right or not but whether it's interesting, and that's quite different. Interesting and at least makes a real attempt to connect with the existing body of biomedical knowledge. There is no point in having people who don't want to connect in any way. That was beginning to go quite well, and initially I thought I could make enough money out of publishing to support research.

Then we really began in the 1970s to understand essential fatty acid metabolism. Now one of the interesting things about essential fatty acid metabolism is that the main fatty acid in the diet is linoleic acid and this has to be converted to gamma-linolenic acid and then on to long chain polyunsaturates to be incorporated in cell membranes and so on. I began to understand that actually all sorts of things could go wrong with that first conversion step. In particular diabetes and stress hormones, cortisol and adrenaline and so on. And then we found that atopic individuals also had an impaired first step. If you look at the other series of fatty acids, the omega-3 series, you have the same situation, where alpha-linolenic acid, which is found in green vegetables and things, in order to be useful in the body has got to be converted to eicosapentanoic acid, and ??, which are present in fish oils. This led to the notion that there are plenty of people around who appear to have adequate nutrition, but because they are diabetic or atopic or stressed in various ways, they were effectively deprived of long chain omega-3 and omega-6 fatty acids. So I set up a business to develop fish oils and a thing called Evening Primrose Oil, which happens to contain gamma-linolenic acid, which by-passes this stress-blocked, diabetes-blocked step. So we eventually built that into a substantial business and used that to fund the research I was interested in.

So when did you actually become a pharmaceutical company?

It was about 81, about a year after Montreal. We looked around for places to start it and the only place that would combine any sort of funding or loan guarantees was Nova Scotia, so that's where we set up Scotia Pharmaceuticals.

As a model it worked quite well because I never had to apply for a grant ever again. The only real constraint was obviously that you have to make things into a financial success, which is a different sort of constraint.

In terms of trying to make things a financial success, how did you go about that?

I had close contacts with a guy called Robert Mansell, who was then a Senior Lecturer in Surgery in Cardiff and he's now a Professor of Surgery. He became the world's leading authority on breast pain, which is largely premenstrual. I knew Robert and I said look "there's an interesting theory here that maybe gamma-linolenic acid might attenuate breast pain". He did some studies and said "this really works". It ended up in the Lancet. So people picked this up and

started buying the product. We then used the funds from the sales of the product as a nutritional supplement to fund clinical trials and the toxicology work, which was required to get an approval.

How did doing this look in the mid 80s?

What we had to do was clearly demonstrate in randomised placebo controlled studies that evening primrose oil was effective as a pharmaceutical agent. There was a hell of a lot of opposition in the academic world. People thought this was really flaky. There still is this huge opposition to nutrition as a treatment for anything.

Why do you suppose that is?

I think it's because of the ultra-reductionist approach that filters through to the way medicine is taught in medical schools. It is absolutely amazing how little medical students know about nutrition and how uninterested they are in it. Just as a side-line, Alex Coppen has always been interested in things like folate. Well he and I eventually did this study which was published in the Journal of Affective Disorders, giving them all fluoxetine and half of them folic acid and the others placebo with stunning results. Instead of a 60% response rate, there was a 90% response rate. But nobody is interested. No pharmaceutical industry is interested in adding folic acid to an SSRI even though the difference in efficacy is far greater than any difference in efficacy between one SSRI and any other. It is really quite remarkable and I find it totally bewildering that there is so little interest among either psychiatrists or the pharmaceutical industry in ways of enhancing the efficacy of their drugs, if that way involves something as simple as giving a B vitamin.

Paradoxically all that clever work that Julius Axelrod did for his Nobel Prize all relates to folic acid and methylation but psychiatrists have forgotten it all. They will say what a wonderful guy Julie Axelrod is but they have completely forgotten the biochemistry he did and how he demonstrated that folic acid and B12 were absolutely intimately involved in neurotransmission. It's a constant puzzle to me why nutrition is so downgraded.

If anybody were now to market a folic acid - sertraline or fluoxetine product it would be patent protected until 2016. Given the amount of effort the industry are putting into finding minor variances on current SSRIs, I find it absolutely incomprehensible that they wouldn't go for this.

Another recent example has been the work of Bernard Gesch who started life as a probation officer and became totally horrified at the food his clients were eating so he began to give them multi vitamins and got really good results in his probation service this way. He became obsessed by this and eventually persuaded the Home Office to allow a randomised study of a multivitamin tablet and an essential fatty acid capsule in Aylesbury young offenders institution. Half of the prisoners were given active and half placebo on a completely double blind

basis. The results were absolutely extraordinary. Over all violence was reduced by 30% in the active group compared to the placebo group. In people who had committed violent events previously, violence was down 60%.

It took him about 5 years to get this published because of all sorts of absurd antagonisms. Nobody wants this result. Sociologists don't want it because they don't want to think that all their sociological explanations might be as simple as nutrition. Psychopharmacologists certainly don't want it. Nobody wants to know that it just might be that nutrition plays a crucial role. It will be very interesting to see what happens when it is published. The Home Office although they allowed the trial, you'd think would be falling over themselves because the costs of a nutritional intervention are so trivial compared to any other form of intervention and this is the only form of intervention, which has ever actually been shown to work in terms of things like violence and so on, but nobody wants to know.

It's fascinating that among all social deprivation literature nobody has considered that some difficulties might be a nutritional problem. There are some discussions about nutrition but this is where middle-class dieticians come in and say oh what we've got to do is make these people eat more fruit and vegetables and so on. The idea that these socially deprived kids are seriously going to change their diet to eat more fruit and vegetables is just absurd.

And I think the same thing applies to the whole of psychiatry. We know that schizophrenic patients eat appallingly. We know that all these essential nutrients are important for brain metabolism. So at the very lowest level we can say that the brain is not going to function normally unless people have proper micro-nutrients and the first thing we should do with schizophrenic patients is give everybody a multivitamin and then give them their drugs. But trying to get that message across to psychiatrists is not an easy one.

Has anybody offered you any views as to why?

They all think its low science, and this is not really the image they want to project. They want something that they see as a "rational theory", which is why I am interested in the things you were saying in The Antidepressant Era about how the industry and the FDA structured the concept of how antidepressants work. I think you can very rationally fit the folic acid story into that but industry can't see it. I think in fact a lot of people in the industry are just not very bright, and there really is a herd mentality and they just don't want to do anything out of line. And in academia, nutrition is seen as not something of any real interest - it's something that middle-class ladies and dieticians do but it's not seen as anything that would have any real impact on mental health.

I think in the broader context it's a very interesting issue, because you have the same sort of thing with homocysteine and cardiovascular disease. I mean the evidence is huge that lowering homocysteine levels is likely to have at least as

big an effect as lowering cholesterol but you get billions being spent on statins and nothing being spent on folic acid and B12

Isn't the issue there that the industry were faced 20 or 30 years ago with just this evidence and calculated that we can patient drugs to lower lipid levels, whereas people can manage the homocysteine story purely by eating the right foods but no one makes any money out of that.

I think this is a core reason, but I don't think explains why academia doesn't get involved - unless you then begin to be very paranoid and say the reason academia is not involved is because they are not independent anymore. One doesn't have to be too conspiracy oriented to see that basically people go where the money is.

So you have two trends which completely inadvertently have worked together to achieve what I think is a totally disastrous situation. On the one hand you have got the positive trend if you like – money. If you look at the way industry funds research, basically there is a huge sum of money coming in from industry. Now completely inadvertently the regulators and the ethicists and the people who are anti-industry have paradoxically played distinctly into industry's hands. Because what's happened is that industry is so corrupt that we must watch them. But not only do we have to regulate what they are doing we have to regulate the research process, and it has effectively become impossible to do clinical research which is not industry funded.

Can you give me instances when this came home to you?

When I was in Nairobi I was interested in anything and everything and the obstetricians came to me and said - look we have a problem with delayed labour. Lots of women are not delivering until 41/42 weeks and they are delivering dead babies. Normally in a developed country you could bring those women in and induce them with oxytocin and so on. In a Kenyan environment, you can't do that. So, how do we solve the problem?

Well I knew a guy called Mort Liggins in New Zealand, who had done absolutely brilliant work showing that labour is initiated by the foetal pituitary and he demonstrated that what happens is there a surge of ACTH from the foetal pituitary which then causes a surge of cortisol from the foetal adrenal and its this surge of cortisol from the foetal adrenal that then triggers labour. I was thinking about this and wondering if we could exploit this somehow. What Mont was doing was these wonderfully elaborate experiments in which he was catheterising the sheep foetus and collecting blood samples from the foetus and so on. So I thought OK how can we simplify this process? Well, the first way to simplify the process is not to infuse ACTH but to see if a single shot of cortisol into the foetus initiates labour. And we showed that that could happen. So you didn't have to do all this elaborate stuff, you could palpate the foetus through the abdominal wall, and give a single intramuscular shot of cortisol. Then we thought OK well maybe if we give a big enough shot of cortisol to the mother, we can do

the same thing, and we found in sheep that if you gave a big enough shot of betamethasol intramuscularly to the mother you could actually initiate labour in the sheep whenever you liked.

So we then did a randomised study of this in women who were post-mature. Published in the BMJ, showing that if you inject betamethasone into women first of all its safe and second it initiates labour within 48 hours. This paper then enabled people to use betamethasone in pregnancy where they wanted to induce lung maturity. And of course this now standard practise.

But what brought home to me the problem regulation poses more and more is that people said to me how the hell did you get permission to inject steroids into pregnant women? We didn't. We sat down with the obstetricians and looked at the clinical problem and we said we think this an ethical thing to do and we did it, and as a result steroid injection into pregnancy is now a world-wide practice. But it probably wouldn't have happened if we hadn't done that in Nairobi. People would have raised all sorts of objections elsewhere.

So that was a seminal experience that brought home the progressive impact of ethics committees and regulation on what was possible in clinical research and of course its got progressively more difficult and expensive. Now if you want to do a clinical study you've got to show that the stuff you are using is stable for six months, with two manufactured batches, you've got to produce a toxicology dossier, and all sorts of basic science stuff which effectively means that without the resources of the pharmaceutical industry, with very limited exceptions no-one can do clinical trial work anymore. Basically these ethical concerns about the regulation of chemical research have handed therapeutics over to industry.

And there are all sorts of other implications. I was doing medicine at Mary's in Stan Pierce's (?) department in the 1960s. This was a very lively department, where there was a constant stream of South Africans, Canadians, New Zealanders and Australians who would sit around for weeks or even months and then decide what they wanted to do and then get on and do it. That process is now becoming impossible because if you're a research fellow coming in for a year, the process of getting ethical approval will take up your year. So all you can do now is latch on to an existing research programme, which in clinical medicine is almost certainly funded by industry. So industries tentacles have taken over medicine.

What's the way out? If people have produced the problem by trying to control industry, do they just drop all controls?

I'm not sure that there is a way out. I think the real problem is there has been a loss of the environment of trust. For instance, Maurice Papworth raised some of these questions in his book Human Guinea Pigs because he got mad at some things that were unethical that had been going on in research at the time (? Date). That was very influential at the time and got all sorts of people exercised

and set things in motion. That of course and the Tuskegee Experiments in the State and a number of other real horror stories.

Researchers had behaved really unethically and people said we have to control them, but of course predictably according the law of unintended consequences in essence clinical research has come to a dead stop. I don't think that was ever intended by anybody but it is actually an inevitable consequence of the suffocating layers of control that have been put in place. What we have ended up with is a situation in which the control system is in the hands of industry, and the system has been made so expensive that even industry cannot afford to invest in clinical research unless it's for a product that has got strong patent projection, which makes for an even more restrictive situation.

So the universe of what is now done is absolutely tiny compared to the universe of possibilities, which I think is terrifying. In a paper in JAMA on peer review in 1990 I suggested that essentially with two exceptions therapeutic research had essentially stopped in 1965. The exceptions were peptic ulcer control and transplantation but apart from that it is very difficult to find a medical intervention where the outcome is clearly better than the best that was available in 1965. Then in the second issue of Nature Medicine Dick Wurtman published an article saying exactly the same thing. What's fascinating is that neither of us was challenged. There was really no response.

And of course in psychiatry this is absolutely true. There really has been no therapeutic progress for 50 years. There have been bits dressed up as though they were major breakthroughs but in fact in terms of patient care very little has happened. And I think this is down to the lack of a large body of clinical researchers doing things off their own bat. You documented this in the Psychopharmacologists. People were testing things on a few patients; they were looking for big effects, and so if they didn't see something in 10 patients they essentially dropped it

In my view, one of the more pernicious things that has happened is the view that is perpetrated by a lot of statisticians that it is unethical to do trials which are not powered to look for small effects. What that means is that all trials have to be very large. It's only quite recently that I've become aware of this as I've had to think about organising clinical trials and find I am being told by ethics committees that your trial size is too small. Now I think it's actually unethical to power a trial to look for a small effect, because what this means inevitably is that a very large number of people are going to be exposed to placebo. And secondly it dramatically reduces the number of trials that are being carried out and the number of things that can be investigated,

In a situation where we are actually therapeutically not doing particularly well, I think its unethical to have system which requires you to do large scale trials. Now interestingly you'll get nobody to put this on the record, but I also know from

off the record conversations and pharmaceutical contacts that where there are relatively limited numbers of patients, companies will very deliberately do extremely large trials to keep their competitors from getting access to the patient population.

This feeds through into the quality of clinical trials you end up with. I think that the SSRIs work but if you look at the FDA databases 7 out of 10 roughly of all SSRI trials that have ever been done don't work. If you look at the ones that don't work I think you'll find that a very high proportion of them are done by CROs. And the way CROs work is all they are interested in is patient throughput.

I think companies are in fact totally stupid, because they pay for time and patient throughput but they don't pay for quality. A lot of CROs advertise for patients, and I think if you are advertising for patients in an environment where there are lots of indigent people, whether it's a US city or an Eastern European country, you can be sure that a lot of the people who volunteer probably will not have the illness you think your studying, but they will quite rapidly become quite good at simulating that illness - especially in psychiatry where you don't have a blood pressure measurement or anything like that to constrain them.

And secondly to put the best face on it they will not be representative of the whole population. They will be heavily biased toward the unemployed, street-drug takers etc.

Well all of this is fairly obvious as you say but one of the interesting things is why academia fails to recognise this anymore. These trials are done on samples of convenience, and once the drug is on the market this is where the science should start, but its all but been handed over to the companies Why faced with this evidence that the evidence that gets a drug onto a market is evidence of a treatment effect from a sample of convenience – at least in psychiatry – do academics roll over and say its evidence with a capital E and it should shape public policy?

Absolutely. I have an article on evidence based medicine coming out in July. Because I am the medical advisor to the Schizophrenia Association of Great Britain I get a lot of patient queries. One of these recently came from a medically qualified statistician who is a real enthusiast for evidence based medicine, whose son of 19 or so has a presumptive diagnosis of schizophrenia. He called me up and said "what do I do I about this?" I said "well there is actually a really good evidence base. You're an enthusiast for evidence based medicine. So I sent him the Kahn papers, and Ian Anderson's stuff and referred him to the Cochrane databases.

He came a back a couple of weeks later and said look this ain't no good. First of all there is hardly any therapeutic effect. You've got a 16% improvement with olanzapine and risperidone on the BPRS. This is not compared to placebo, this is actual improvement. And the placebo trials are really misleading, because you

taking people off drug. So none of these are helpful in assessing what I do with my son. Secondly when I look at the inclusion and exclusion criteria and the actual description of the patients, they bear no relationship to my son. I find this very interesting - almost always when physicians either become ill themselves or have a family member who is ill they realise that the evidence base is actually almost useless when you are dealing with real life individual patients.

It's not bad for pain relief, or infections, and maybe for acute asthma. But it's actually very difficult to find anything else. In cardiovascular area you have NNTs of 50 or 100 and so on, so you actually have no idea whether the intervention you are giving has any impact on that individual patient sitting in front of you

I had a lymphoma last year so I got to know a lot of other physicians and people who'd got cancer and they all said the same thing, that the evidence base is actually useless when it comes to making individual decisions about you personally, and it is almost equally useless when it comes to making individual decisions about the patient in front of you because the trial populations are so different and the treatments effects are so small that it's roulette.

But again coming back to my point, why don't professors of medicine, or psychiatry ever say this?

Well I think it comes down to the peer review system in a sense. They all want their funding, they don't want to upset other people too much, and so they conform. They don't want to cut themselves off. They don't want to do what you have done. Because what's happened to you is an indication of how the system works, how the ranks close, how things operate.

I don't think professors of psychiatry are very clever. They're not interested in the philosophy of medical research. They are totally uninterested in history. I think one of the other things is that the load on any academic now has become so overwhelming in terms of the administrative load. If you're a chairman in any senior position in any major university your whole day is taken with administrative matters in a way that it never was. And if you don't turn up to committee meetings one of your colleagues will screw you.

So I think structure, and a this must never happen again mentality has created an environment where innovation is very difficult and where reasoned criticism of the status quo is also very difficult.

Another control seems to be peoples' fear of being sued by industry for having views at odds with industry.

I don't know that many people are frightened of being sued. I think they are frightened about the sort of thing that happened to you and to me, happening to them. They are concerned about their grants disappearing. Also you don't have to be sued, you just have to have a complaint against you, and you end up in a 3

to 5 years process of trying to clear your name. I think that's what people are frightened of.

Also what drives me crazy in this country is the way people are controlled by merit awards, by CBEs and by Knighthoods. I have become so antagonistic to honours for medics because as I was going through my life, I could see people getting to around their mid 40s, and beginning to think I should be getting a CBE and changing their behaviour to fit.

Absolutely, and sitting on committees that they don't really want to be on but in order to be seen to do the things that you've got to do

So they get their CBE in their late 40s and if I behave myself I'll get a knighthood, and then if I behave myself I'll maybe get a peerage. It is so destructive, but I mean it such a wonderful controlling system. And I think its one of the things that accounts for the fact people don't speak out. In retrospect being fired because of the Valium affair was actually the most liberating thing. I clearly had a tendency to shoot my mouth off before that, but what that did was to give me real freedom to do things without any concern.

But you've been able to put views like this in editorials for the BMJ and the Lancet which suggests that you are either very well connected to the establishment or for some reason the establishment has decided to tolerate you. Do you have links to Richard Horton, Richard Smith and people like that?

I don't know them any better than others would, but I do know them personally, so maybe there is something there. An Oxford background counts for something and I had these contacts with Popper, MacFarlane Burnett, Eccles and all those sorts of people so I think nobody felt they could dismiss me as stupid. They might dismiss me as crazy, and maverick and so on, but not fundamentally stupid. And I think to be fair, Richard Horton and Richard Smith are both aware that there are real problems. But they are also under huge commercial pressures and they are by no means as free to do what they might want to do.

What are the pressures on journals that outsiders just don't see, what are the commercial pressures that Richards Horton and Smith are under?

Well the Lancet is owned by Elsevier. They would never put it in writing, but Richard would be aware that the Lancet has to be a commercial success. So that while it is possible to be critical you can't be too critical. There are legitimate things as well. If you are editing a JAMA, Lancet or New England Journal, you do have a responsibility to be balanced. And of course balance means that you have a responsibility to reflect not just the opinion of the minority but also the opinion all those professors of psychiatry who are taking huge amounts of money from pharmaceutical companies. So journals like that can't be campaigning in that sense - they would lose their advertisers and they would be seen not to be representative.

You think the industry has the power to walk away from the British Journal of Psychiatry, the British medical Journal and the Lancet?

Yes absolutely. For instance, I know the medical director of Lichtfair who make St Johns Wort, and it is quite clear that that paper which was published in JAMA which showed St John's Wort was no better than placebo really downplayed any role of Zoloft in the trial. Zoloft did equally badly and in the first drafts, Zoloft was in the title of the paper, but in the published version it disappeared.

Now can you to reconcile this with the fact that Drummond Rennie from JAMA is the editor who goes around the place most complaining about the influence of industry?

Well Drummond is the West Coast editor. He is not in Chicago so he ultimately doesn't have control. Drummonds a good guy, and he is quite influential but in the end, look what happened to Lundberg - if you step out of line too much you go. But its not only the journals - CME basically has been handed over to the industry.

Can you date all this?

No. I am just conscious of the fact that whenever you go and give a lunchtime lecture on anything now that there is always an industry stand there. And it's the stand of the people who have paid for the lunch. At a conference in Australia a couple of years ago I was giving a few lectures and there were some very nice lunches laid on. They were all paid for industry and there was always an industry stand, and people don't seem to be at all conscious of this any more. They seem to be very confident that they aren't influenced.

Why do you suppose that is? You presumably have to have a marketing arm to Scotia and now Laxdale?

We basically sold nutritional products ourselves but the pharmaceuticals we licensed to Searle. So Searle were really responsible for the marketing. But I had some liason with marketers and it was always very difficult to persuade marketers to sell on the basis of the science. And depressingly they were actually right. You actually can't sell drugs on the basis of science.

At the Berlin Psychiatric Congress a couple of years ago I was absolutely stunned by the fact that Astra Zeneca were giving away kites - maybe three dollars worth. And they had psychiatrists round the block at the Seroquel stand waiting for a kite! What is so fascinating is how little it take to seduce so many people. It's very odd, very strange.

Now while the rest of the world, me included, has been saying the future is genomics and pharmacogenetics, for some time now, back as far as possibly 1990 or thereabouts you've been saying – Don't you realise there is a problem here. Industries need to have a vast market to get a return on their drugs and all of these scientific developments are going to fragment the market. How did these heretical thoughts evolve?

I think it dates back to that Florey seminar and that sense of the real complexity of human biology and a feeling talking to scientists in companies and so on of how little they actually understood of that complexity. They understand it less and less in fact. This reflects more and more on the fact that biological science courses are more and more molecular biology

You find they know all about a particular cell rather than the whole animal

Not only a particular cell, but a protein or a gene. People are simply no longer educated to think about complexity. And the clinicians in the pharmaceutical industry are on the whole not clinicians. They are not really interested in clinical research or in science. They are interested in the organisation of large clinical trials and so on, and they are not very curious about the world. And the people who used to think about complexity are all dead or dying. You know, Glaxo fired 107 pharmacologists in one day back in 1994/1995 because they said look we are going to do all our drug discovery in future by high throughput screens and in vitro techniques and so on. We don't need these people who work on whole animal pharmacology anymore.

I think it's a peculiar scientific arrogance, which again I think is fuelled by this peer review system which keeps research within a rather narrow group of people who can be trusted and there is very little philosophical criticism of company research programmes and so on. Then when a few companies said look we are moving away from animal screening and we are moving to high throughput screening, and we will be able to move from screening 100 compounds a year to 50,000 a day, the senior executives bought it. And of course once one or two had bought it they all had to have it.

I think in retrospect, it will be seen as the biggest suicide move that a technology based industry has made, because the techniques are just not working. And they are not working because they are too simplistic.

Look at Glaxo. Glaxo is now a mix of at least three companies – Glaxo, Wellcome, SmithKline and Beecham. But the last major discoveries that were made by any of those companies actually came when David Jacks was running the R&D programme and it was the tryptans in the mid 80s. Since then Glaxo, SmithKline and Wellcome together by my estimations have spent something like \$30 billion without bringing a single novel compound to market. Thirty billion dollars is one hell of a lot of money to spend without discovering really important.

But almost all of the companies are in the same boat. I think Abbott has probably never come up with a new therapeutic concept. Their compound valproate was discovered in the South of France in the 1960s. I suspect if you added up how much Abbott have spent since 1960 or so when they started to spend money on pharmaceuticals, it's probably about \$40 billion without a single protect. There was this article in the Wall Street Journal a couple of weeks ago saying Bristol

Myers Squibb had spent \$14 billion and not come with anything, but I think that's actually a considerable underestimate.

So what you are getting is the situation where you can argue about the details but almost everybody recognises that there are several companies, which are spending in excess of \$10 billion dollars without coming up with anything. What this tells you is that something really quite horrible is happening. What's going on

I think that high throughput screening is really at the core of it. Because the way high throughput screening works is that you either have a target, which is dissolved in water or attached to some sort of fixed bed, or over-expressed in some cellular system. Now if you think about quaternary protein structure, not just the tertiary structure, but the precise configuration in a normal cell, its absolutely critical because by changing even one phosphorous on one amino acid you can change the quaternary structure sufficiently to switch it from an active to an inactive state. And really the whole of signal transduction depends on tiny changes in the protein, switching the quaternary structure from one state to another.

The companies have not thought about this issue. It sounds so bizarre as to be almost inconceivable but it is actually true. They have simply assumed that the proteins in their high throughput screening systems are in the natural in vitro state, but the great majority of them are almost certainly not for all sorts of reasons. For instance most proteins are not in aqueous solution and they are certainly not in fixed beds and they are certainly not over-expressed in cells. So you've got all these wonderful assays but actually the proteins are in the wrong configuration, and the things that do stick to these proteins won't stick to the relevant protein in vivo while the things that don't stick will be the interesting drugs that you are now missing.

In contrast with the old in vivo screening techniques you at least knew the proteins really were in the right configuration, so you could screen a far fewer number of proteins. Apart from that though, if you're injecting something into an animal you actually get a huge spectrum of information, which again industry hasn't thought about. You find out whether your drug is actually interacting with not just your target protein but with a whole lot of other proteins, which might generate toxicity or unexpected side effects, which your in vitro high throughput screening techniques with your single protein can't even begin to tell you. When you talk privately to all these big companies, they say high throughput screening is not delivering.

Can you see a way out of the problem?

The dilemma is they have fired all the people, who used to discover drugs in the old ways. And the new way of doing things has now been going on for 10 to 15 years or so and all their management structures in science are filled by people

who are absolutely committed to high throughput screening, combinatorial chemistry and so on.

Another thing which is so stupid that it is almost inconceivable is because high throughput screening works with these tiny tubes and tiny systems it can only work with highly water soluble molecules – if it's lipid soluble or if it sticks to your tube, your screening system clogs up. But if you look at the universe of drugs which work a lot of them are not very water-soluble and these drugs which we know work get excluded by these systems. Looking at it from both inside and outside perspectives I just can't imagine how these decisions were made. They are just so managerially awful

But they would have to look good from a business point of view haven't they I mean - where business is all about being reproducible, we know what we are doing because we have a protocol.

This is why I am tremendously alarmed that Richard Sykes is now rector of Imperial College. Because Richard Sykes has presided over the destruction of the UK pharmaceutical industry. He has turned out to be a very skilful business person. But his business skills have had to function because his scientific skills have completely failed. The only way he could save Glaxo was by taking over Wellcome. Glaxo had failed to produce anything but by taking over Wellcome he could obscure that failure. And then when Glaxo Wellcome failed to deliver, the only way that could be obscured was by merging with SmithKline Beecham.

But the merger scenario only works for a while. You can certainly generate a lot of savings from a merger but what you do is then make the overall problem even worse, because if you are that big only products that will sell a billion will save you.

Is the future then large marketing companies who get products from a much smaller research based companies?

I think that the first pharmaceutical company to say that we are absolutely useless at R&D so we are closing our R&D operation and becoming a sales and marketing company - if its presented properly to the investment community - will be hugely successful. They will immediately generate huge savings. Each of the top 10 companies is spending more than 2 billion a year with Pfizer and GSK spending 4-5 billion a year. So if somebody had the courage to say, look our R&D is not working we are going to abandon R&D and we are going to become the most efficient marketers there are.

But the problem surely is that the public gives the pharmaceutical industry the leeway they do because of the supposed blue skies research that they are doing, that's the supposed ethical core of the companies. If they become frank marketing companies, they are potentially at risk aren't they?

I think that you are absolutely right and I think that this is why that they don't want to abandon their R&D because they all know now their R&D models are a disaster. So it's a marketing ploy to keep on appearing ethical

How much does the current patent system contribute to the problem. Compound rather than use or process patents of the type we had during the 60s create an incentive for companies to go for blockbusters so they go for Prozac's and not even a drug for epilepsy, because on its own, unless you can sell off-label, epilepsy is too small an indication?

But you see the fascinating thing about the pharmaceutical industry is that it has never been able to predict what is going to be a blockbuster. There is a wonderful letter from Abbott to Astra in 1980 or thereabouts – its documented in a biography of Ivor Ostholm, who was the Astra R&D director at the time, about the US rights to Losec. The letter was returning these US rights to Astra on the grounds that market research had indicated that US sales of Losec would never exceed \$ 15 million. US sales of Losec 15 years later were \$ 2 billion dollars.

In just the same way, the ICI marketing department were against Jim Black developing beta-blockers because they thought the sales, now this is 1960, would never exceed £ 200,000 per year. SmithKline's marketing department were against the development of Tagamet because they said worldwide sales would never exceed £15 million a year. So in the case of three of the worlds biggest ever blockbusters, the companies, which were involved all completely failed to predict that these were potential blockbusters.

I think another of the things that's gone wrong in the industry is the dominance of marketing departments who are only interested in drugs, which will sell \$ 200 million to a billion dollars. The fact is that marketing people can't predict this although they think they can. And the reason they are useless at this is because all they can do as a marketing person is look at the existing market. So the ICI marketing department were looking at nitrites because propranolol was being developed as an anti-angina drug. Look they said we can't compete with nitrites, because they are dirt cheap, and all can do is to take a proportion of the nitrite market. The SmithKline people said antacids are dirt cheap you'll never be able to sell an H-2 antagonist. The most you can get is a chunk of the antacid market. The Abbott people said look H-2 antagonists are so successful that there is no room for a proton pump inhibitor.

But we are now in the situation where the marketing people are telling the research departments what to look for. There's a lack of sense of history. If you have a sense of history you know that you can't predict this and you certainly can't do it by giving them to marketing executives who have no sense of medicine or biology whatever.

So I think the industry is actually truly in crisis. It's been a long time coming, concealed by the mergers, but it was predictable in 1990.

When you began to write that kind of thing back then how much of a lone voice were you?

Totally. Nobody was interested in those things. But now I'm getting invited to give plenary lectures at major conferences. The German pharmaceutical industry invites me to give the plenary lecture at their think tank. Now lots of people are listening but in many ways it's too late, because they've fired all the people who could help them.

The thing that I think is crucial is clinical research. Pfizer's Viagra for example is not basic science driven. They were developing it as an hypertensive, or an anti angina agent but all their trials failed and it was only because of an alert clinician noting the erectile side-effect that they developed it. But it was not planned at all.

I heard a Merck guy a couple of months ago talking their new anti-Alzheimer, anti-inflammatory drug and he presented it as though this was an entirely basic science driven programme. But it was actually Pat McGear in Vancouver noticing that his 80 year old arthritic patients were not demented. When he asked why, he began to realise that the arthritic patients who weren't on NSAIDs were dementing but the arthritic patients who were on NSAIDs weren't dementing. Constantly you find that the new ideas coming from clinical research, but that is so downgraded now, so dismissed that the industry doesn't know how to take note of it anymore.

When are we going to have the crisis? When is the centralised system going to collapse?

I think it's collapsing now. If you were an investment manager running a pension fund for old ladies, a few years ago, you couldn't have picked better investments than Bristol Myers Squibb, Merck, or GSK. But GSK is down 30% from its peak, BMS is down 70% from its peak. Merck is down 20% from its peak. So huge companies that were the super stars of the industry are losing capital value rapidly. And what that means is that it restricts their ability to raise money and to take over other companies. And as the patent expiries come through, they are suddenly going to be faced with the need to massively restructure, because they are going have to retrench.

At the time of the Wellcome Glaxo merger, James Neidel, the Glaxo CEO, said that the merger was going to generate these wonderful new benefits because what Glaxo needed was 2-3 products every year coming through its pipeline which would generate more than \$ 500 million in sales, and the merger was going to do that within about 5 years. But not one has come through. So not only they have they not discovered 2-3 per year they have not discovered even 1 in seven years since the merger. And that's why share prices are crashing. Because the analysts cannot see where the new developments are coming from.

Can I take you back to Scotia, what went wrong there?

I had built Scotia up from nothing to 400 people. It was worth £500 million or something like that. But my interest since the 1970s has been psychiatry and neurology. So when I was 57, I thought I might have another 10 years of useful life and rather than running a large organisation with a diverse portfolio I decided to concentrate on psychiatry and neurology. So I brought the psychiatry and neurology out of Scotia and left as chief executive.

They brought in Robert Dow from Roche who was a complete disaster who didn't know how to manage anything. He lost most of his academic collaborations. He screwed up the nutritional business, which was a cash cow, bringing in money. He didn't want to be involved in that, so he got rid of it even though it was generating £150 million a year. He followed this new mantra of focus. We had had about 30 research projects and he announced with a big fanfare that he was cutting 25 of them. What he failed to say was that those 25 were only costing about a million pounds in total and they were the seed from which new things could develop. He decided instead to focus entirely on this phosgan photodynamic drug, but by this stage he had destroyed Scotia's relationships with academia because he cut off free supplies of the drug to clinical investigators around the world. He said we will only do trials under our control. As a result over 4 years, he spent £90 million but only got 200 patients into clinical trials, because he had to pay the earth to get academics, who had been doing huge amounts of work for us free. We had been just giving out the drug and saying try this. I think it will be eventually seen as a wonderful case history how not to do things.

One of the fascinating things about the biotech industry is this. Are they going to generate this wonderful flow of new products? Well the investment community you see thinks that scientists can't manage, so it says as soon as possible to any young biotech company that it has got to bring in management from the mainstream pharmaceutical industry. Now mainstream industry may be really good at selling and marketing, but what they are absolutely not good at is drug development.

I can see disaster after disaster happening in the biotech world because the managers they are bringing in from mainstream pharmaceutical companies actually don't know how to do anything, and in particular they don't know how to do anything on a shoe-string. They are used to huge budgets. Dow, for example, spent £90 million in 3 years and took the market capitalisation down from \$500 million to bankruptcy, and the number of employees from 450 to 8. One of the things you learn is that people from mainstream industry have never really managed anything because all they have done is worked their way up this leviathan, surrounded by vast networks and support systems, which are actually doing it. You put them in a tiny company, and they flounder.

Another problem with biotech is that there is almost no clinical input. They don't have clinicians. Not even practising clinicians but people with a feel for patients, and a feel for complexity. They should have a feel for clinical research. This is what the investment community should be saying - you've got to get those people in. But they are so molecular biology driven that they are completely bewildered when their clinical trials fail, and this is because they just don't know how damn complex this whole thing is.

Now in terms of the lipid story, as regards schizophrenia how does it look being faced with the monolith of the dopamine hypothesis, and the raft of orthodox views? Is there any way to break through this if you don't have a marketing department to sell lipids?

I think you just have to chip away. I think what's really going to bring about a breakthrough is depression not schizophrenia. EPA in schizophrenia has a modest effect in the same people who respond to clozapine. It roughly doubles the response rate, which is really important, but in depression the effect is magic. We have now got 4 trials for ethyl-EPA in depression. Bob Belmaker's one from Israel has only got 20 patients but it's significant at 0.001 level. We have a trial in Archives in July; again only 70 patients but again significant at 0.001. There are similar advantages from a trial from the Institute in bipolar depression with 75 patients and a Harvard group have done a trial in depression in borderlines and also found significant results. If you contrast this with the SSRIs where you need to do trials of several hundred patients to get a marginally significant result, I actually do think that EPA is going to transform the treatment of depression.

It is so safe and so effective that it will be an interesting to see what happens. The enthusiasm among the GPs and the psychiatrists who have been running the trials has been phenomenal. I really do think there is a revolution waiting in depression. The schizophrenia story is one of modest limited help, but I think it at least does show that here is another type of antipsychotic medicine and I think you can build on this and try to understand it.

One of the fascinating things about psychiatry is that it doesn't connect with the world of neuroscience. In the world of neuroscience, there is a huge literature out there looking at signal transduction processes after dopamine or serotonin arrives at a receptor and these signal transduction processes are all lipid related. It's hard therefore to understand why the industry has not gone beyond the cell membrane. The only thing that makes sense to me is your concept that industry wants a simple story to tell and so it won't look at things that won't fit with that simple marketing story.

Anyway we are not handing this over to any body else until we've actually got FDA approval. At that point we hold all the cards. A new drug with an entirely novel mode of action which at the lowest level is at least as good as existing antidepressants, but without argument has a side effect profile which is dramatically better. We hold a lot of cards there.

I am absolutely determined that I'm not going to employ large numbers of sales people but there are quite a lot of contract sales forces around. Basically you can set the marketing programme, give your drug to them and they take a 30% cut or whatever and market the thing. So we may actually not need to go through. In a funny sort of a way, the Forrest citalopram story indicates what can be done. Who would have predicted that a funny little generic company could make so much money.

Yes but they did it on the basis of old-style sales not because of the science. Are you prepared to get your hands dirty subverting science with sales?

Well what I would like to do is show you can do things in a different way. And a cascade of a billion dollars per year might just enable me to do that. I'd absolutely love to put say \$50 million a year into clinical research in Scotland. With no restrictions at all – so that everyone in an academic position in a Scottish medical school could have £200,000 a year to spend on what ever they like. I think the returns we would get from that would so far exceed any conventional research programme. I don't think you are going to change the way things are done by arguing. I think the only way you could change things is by a demonstration programme.

To come back to the marketing issue – are you not just selling fish oils and should we not try to tell people to eat more fish

We decided first all that there is not a hope in hell of getting a fish oil registered as a pharmaceutical. The controls make it impossible. So you have to develop a pure compound. Secondly fish oils are so variable in composition, and have so many agonists and antagonists, that if you try and work with an active product you are not actually going to get anywhere because you'll have no consistency in response, you won't know what dose to give because the fish have a different oil in September or August,

What we can legitimately say is that with straight fish you will actually not know what you are getting. I think it's a great idea to eat fish, but you actually will not know what dose to give etc. But most importantly, and this is where the stupidity arises, you won't get reimbursed. You have to have a regulated approved drug

Reimbursement for physicians?

No patients as well. No insurance company, or national reimbursement system will reimburse something that is not approved. So you have to get it approved. Looking at it from a slightly different point of view, if one believes that this is really is a new therapeutic modality, the fact is that you are never ever going to get it to most patients unless you treat as a standard pharmaceutical. Just as we found with folic acid. Why is folic acid not being given more widely - because the MCA and the FDA have not approved antidepressant claims for folic acid and nobody is marketing it.

So I do argue for nutrition, but if you take that route you are only ever going to get the benefits to maybe 5% of psychiatric patients in wards. The only way to bring it to most patients is to develop as a medicine.

How will a marketing department market EPA - a green medicine or rational engineering?

As penicillium mold I think. Yes it is a green medicine, and it doesn't have side effects but on the other hand its now completely quality controlled. The FDA has reviewed it and has approved the indication

I think this is the trump card against the mainstream industry. We can say OK just like you we have done all the controlled trials and toxicology studies and our manufacturing is just as tightly controlled as for sertraline or whatever. So we have a pure simple compound, but this pure single pharmaceutical compound is derived from a natural product and it doesn't have the side effect profile of standard drugs and so on. I'm reasonably confident because of the way the GPs are reacting

In terms of trying to market it would you feel you would have to go down the route of buying up satellite symposia at the CINP or do you feel that's all discredited?

I would really prefer not to. I would prefer to have official symposia at the CINP. I think the whole satellite symposium thing is just so discredited.

But to come back to the dopamine hypothesis. This dominates schizophrenia research so that anybody trying to say anything else is excluded essentially as unscientific. The niacin flush test is a good example. This is an easily demonstrable biological phenomenon, which enables you to define a subgroup of schizophrenia patients. Everybody who has looked at this, and there are now about 12 replications, has shown that it works. It varies between 30 and 60% of schizophrenic patients are abnormal. It seems to me absolute lunacy that there is so little interest in this because it is such an easily demonstrable phenomenon. It offers a beginning of a way out of the DSM IV morass of diagnostic categories that are clearly useless in terms of real patient care.

But I think the real challenge is that it challenges the idea that schizophrenia is a brain disease. And it challenges the dopamine-serotonin concepts of the illness and since almost everybody in schizophrenia research has built their careers on some form of variant of the dopamine hypothesis nobody wants to know.

It's slowly beginning to change. Pat McGorry for instance is getting enthusiastic about it because it helps him to make a sensible very early diagnosis of a large subgroup of schizophrenic patients. And what's fascinating is he's finding that it really helps to persuade patients to take treatment, because they can see that there is something wrong. And it's also a very attractive concept because they

can see this is like thyroid disease or Cushing Syndrome - a metabolic problem which has a cerebral consequence. And what's emerging partly as a result of Pat's efforts is that it is definitely associated with a deficit syndrome. So it concentrates deficit syndrome people and it does look as though it might be an indicator for people who will respond to clozapine.

Another interesting thing is this breath test. Basically a lot of the end products of cerebral metabolism are highly volatile, so they enter the blood in the brain and the first opportunity they get, they come out of solution, and they appear in the breath. So schizophrenic patients have a lot more butane and ethane in their breath than bipolars or others. I think this is also going to be a very interesting as a way of monitoring treatment, as a way of defining diagnostic groups, and so on.

But these things have been around for ages - 30, 40, 50 years, people have been saying patients who have schizophrenia smell different.

Absolutely. The smell thing in fact is very interesting because the people at Scripps have recently shown that there is a deficit of Apo D in the brain in schizophrenia and that clozapine specifically induces Apo D synthesis. Apo D happens to bind specifically with 3 methylhexanoic acid, which is the smell of schizophrenia. So there is beginning to be a biochemical rationale to all this. We all produce this stuff but schizophrenic patients have less Apo D, so more of it escapes and is volatile.

I think the biology is beginning to crack, partly under the weight of an absolute lack of clinical progress. Five or 6 years ago there was tremendous optimism about risperidone and olanzapine because they thought this was clozapine without agranulocytosis. But now certainly anybody with half a mind realises that if anything they are Haldol without EPS, but they are certainly not clozapine. And within the schizophrenia community there is a sense that the dopamine paradigm has failed.

What kind of response did you get to your book *The Madness of Adam and Eve*?

Bob Kendal wrote a very sympathetic review in the BJP. He said it may or may not be true, but what is certainly true is there hasn't been any progress and this offers a different approach. Paul Grof has just written a very sympathetic review in the Canadian Journal. And it's just been short listed as Science book of the year, for the Aventis Prize. But what's really interesting is how many patients have written in and have said look this book does more for stigma than all the anti-stigma programmes because it gives schizophrenic patients some reason to respect themselves, and respect their genes rather than thinking that it's a total disaster.