

THE HYPNOTIC BUSINESS

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So why a career in medicine?

I was influenced by a family acquaintance and also by the fact that at that time you either went straight into the army or you got deferment if you were a medical student. A senior boy at the school where I had been had set a precedent of going to Cambridge to study medicine and with him in mind I followed in his footsteps with a bonus of not having to go immediately and do one's National Service.

At what point did you think about doing psychiatry?

Because of this family acquaintance and conversations with him I'd always had the notion that what he called psychology was important. At that time at Cambridge you could either do what you might call your pre-medical years in two years, plus what was called a part 2 Tripos in some other subject, or in three years. Some of us covered the three year course in two years and that gave an extra year and I then went for what was called a Part 2 Tripos in Moral Sciences - Psychology. The year, after I completed it, it was changed from Moral Sciences to Natural Sciences. Desmond Pond, who had done the same, and I used to say to one another that we were the only first class moral scientists in psychiatry. Experimental psychology at Cambridge then was very unlike the sort of psychology that one had vaguely had in mind. It was really training in research methods - so that's how I got that particular interest.

After I qualified and was in the Air Force as a Medical Officer, I was just intending to work for an MRCP with no particular thoughts about psychiatry. But I was on a flying station which was a little boring and I heard of a vacancy coming up at the Neuropsychiatric Institute, as it was called, at Halton near Aylesbury at the Royal Air Force Hospital there. So I applied. As the vacancy was in the EEG department, with my background in psychology and the fact that the boss of psychiatry there was a Cambridge man who thought I must be a clever young man, he got me in to the Neuropsychiatric Institute. I worked hard and had really a very privileged position. I used to go up to London two days a week to the Central Medical Establishment, but I was able to spend time in the BMA Library and the British Museum Library and things like that. I had a lot of facilities and I used them for research at the Neuropsychiatric Institute. I'm afraid I conned the Air Force into thinking I could do something useful for them. I have to use that word because in the long run it wasn't of use. But I got a six month extension in the Air Force as a National Service Officer, by which time I'd got a BMA Research Scholarship which one used to be able to apply for and simply get in addition to one's salary. That helped because I also got what was called a Beit Memorial Fellowship in Medical Research - I think there was an Otto Beit who made a lot of money out of diamonds in South Africa or Rhodesia.

Which year was this?

That was 1957. I took up this research fellowship based at the Institute of Experimental Psychology in Oxford. So I was based there but in practice I went on using the research facilities of the Royal Air Force, driving over there a couple of days a week. I used to read their EEG records for them and in return they let me have facilities but in addition I got facilities in the University

Laboratory of Physiology at Oxford. I was at Oxford for a couple of years. I took this machine that I had designed while in the Air Force to a BMA meeting in Newcastle, I guess it must have been at the very beginning of 1959, and met Alexander Kennedy there, who was the Professor of Psychological Medicine in the University of Edinburgh. He was always very keen to fancy himself as a military man and he used to tell tall stories about his exploits when parachuted into Yugoslavia during the war. He came round the exhibition and was enthusiastic about this device of mine. Now it so happened that very shortly after that a Lectureship in Psychological Medicine was advertised at Edinburgh University. I had given talks to the EEG Society, including in Edinburgh not long before, where David Whitteridge, the Professor of Physiology, who was a leading light in the EEG Society had been in the Chair. With him on the selection committee along with Alexander Kennedy and one or two others who knew me, I got a Lectureship.

In those days, there was a bit of money about and the Department of Psychological Medicine was expanding. Alexander Kennedy persuaded the Faculty of Medicine to create not one but two Lectureships one for Dr Peter Fawcett, who had his DPM, and one for me. I had a degree of MD by this time from Cambridge for my research that I'd done whilst at Oxford but I didn't have a DPM. I had this entirely unorthodox background in psychology and my work at the Neuropsychiatric Institute but I was given an Honorary Senior Registrarship to go with my Lectureship, which would never happen today. I think it is a pity that someone with an unorthodox background shouldn't be able to get a job that would draw him into psychiatry, without having to take a drop in income.

OK so at Edinburgh at the time there was Alexander Kennedy and George Ashcroft had come as well and links with the department of pharmacology were opening up.

George Ashcroft as I recollect came on the scene a little bit later than me. He may already have been a Registrar up at Craig House as we used to call it, which was an almost separate section of the Royal Edinburgh Hospital. The MRC started the Brain Metabolism Unit there and he got a post of Senior Registrar status I would have said about 1961.

What were the interests in Edinburgh at that time? There appears from a historical point of view to have been strong biological tradition in Scotland but in Edinburgh in particular.

Well you see what happened was that Alexander Kennedy having been my boss for about a year suddenly died and Morris Carstairs was appointed to the Chair. His background was in Social Anthropology and a belief that social pressures through group therapy were the key to psychiatry. So I have to say that when he came my future looked bleak. About the beginning of 1963, he said to one of my friends, a Senior Registrar there, you must go in for the Gaskell Gold Medal and Prize - we in the University Department we'll pay your fare to London. So I said to Morris Carstairs, "Well, I'd like to be a candidate too, will you pay my fare?" "No", was the answer. I became a candidate, the other chap withdrew and I was awarded the Prize. Now that illustrates the kind of relationship between Morris Carstairs and me. In the same year I received the degree of Doctor of Science. I had as a member of staff been able to make application for this degree through the Faculty of Science and

not through the Faculty of Medicine which I very deliberately did to avoid the influence of Morris Carstairs. When Morris Carstairs found out that I was about to receive the degree, I'm afraid he did show himself to be not a little irritated. But that was how it was and there was really little future for me in the department, it seemed.

What drove the ideological rift - was it a matter of personality or was it to do with different understandings of psychiatry?

I don't think it was so much a clash of personalities. When Carstairs got the Chair, the other chief candidate had been John Smythies – J R Smythies – who had a very biological background. Having got the Chair, Carstairs invited Smythies to come and be a Reader. Having got him there, Morris Carstairs then got in Henry Walton, a group therapy man, and I would have to comment that in my opinion matters were so arranged that John Smythies could not but feel extremely humiliated. Things were later rigged by Carstairs so that a second Chair of Psychiatry was created and went to Henry Walton. Anyway as far as I personally was concerned I saw no future in Edinburgh so in 1964 I applied for the Chair of Psychiatry in the University of Western Australia - a very young medical school. It happened that their letter of offer got lost in the post. I got fed up with them but nevertheless I eventually flew out to Western Australia and looked around. I remember I took only my briefcase. I found that the wonderful new hospital that had been envisaged in the further particulars had been indefinitely postponed, though no one told me till on the last day of my visit I insisted on more details. With this slight disillusionment, I ended up saying that I would go there as a visiting professor for 2½ years, which seemed to me the minimum time to get a department of psychiatry launched. I had had a discussion with the Dean at Edinburgh before I left, who was a pharmacologist, and he very kindly agreed that I would go on leave and should I return I would get a Senior Lectureship. Edinburgh very decently agreed to pay the University contribution to my superannuation scheme while I was on leave. So I came back in December 1968 as a Senior Lecturer. Morris Carstairs later left and Bob Kendell came, whom we were very lucky to get. Later I became a Reader and then I received a Personal Chair.

Going back to 61, 62, 63, you say that Carstairs brought in Henry Walton who was into Group Therapy. The new drugs had all begun to come on stream at this point. There had to be some clash between views on the future of psychiatry between those who saw it being dominated by group therapy approaches versus those who would have had a more biological approach.

Yes. But that wasn't to say that those who believed in group therapy rejected the possibility of antidepressants having value or the phenothiazines in schizophrenia. The interest of Carstairs and Walton was in the personality disorders and the belief that these could be cured by many months of in-patient group therapy. There was one occasion when I went to the subsequent Dean with a party of slightly disgruntled psychiatrists and we pointed out that this approach involved a huge expense but although it was being undertaken by a University Department, no attempt had ever been made by the enthusiasts to set up any sort of evaluation of the effectiveness of their treatments.

At what point did you begin to actually work with the new agents - the antidepressants etc and when did you get interested in sleep?

When I was in the Air Force and being of an experimental bent, I was doing some research. Because of all the interest in the reticular activating system, at that time, I was doing experiments giving mild electric shocks to a volunteer aircraftman who was in our Neuropsychiatric Institute working as a medical orderly. I was trying to condition what are called K complexes in the EEG of sleep. To cut a long story short, one day he was awake and I made the shocks a little bit stronger, whereupon he promptly fell asleep. In due course, I read what Pavlov had written about his dogs - in his words, "the experimental sleep can be reproduced with the same exactitude as the reaction of a hungry dog to a piece of meat". He had described how his dogs fell asleep under similar sorts of circumstances. So I became interested in sleep. This was at a time when there was this intense interest in the reticular activating system. I came to Edinburgh having conducted research into sleep. My MD thesis which I wrote while I was at Oxford had the words anxiety and sleep in the title. I had wanted to continue something that Alexander Kennedy had been keen on and I set up a laboratory with sound proofing to do with what was called sensory deprivation - that was in fashion as a research topic at the time. Morris Carstairs came and refused to allow this. He wasn't interested in the EEG but there was an EEG machine in an out of the way part of the hospital and I continued to do research into sleep, doing my clinical and other work by day and research by night.

In order to get money, I thought of getting it from industry and I first got a grant from Slumberland Mattresses to compare sleep on three different mattresses. We found no differences between them. I realise now that the research did not have the power to show any differences with the small number of subjects we had but I didn't understand much about power then. I'm not sure how it happened but at that time one of the drug companies, Geigy, introduced a new barbiturate. I can't remember how I came into it - perhaps I approached them and asked them if they'd like some research done on it or they somehow got wind of me, I don't know. But that was how I first started doing any research with drugs and sleep.

I designed the research so that it was all in a nice balanced order, which included the sequence that some people were getting two nights of this barbiturate followed by a placebo. I naively supposed that a night of placebo would reflect their normal sleep. Now of course I realise that they would have had withdrawal symptoms after even two nights of the barbiturate. So that's how I got into that field. The next drug that I studied was dexamphetamine and drugs like it in patients who were addicted. Because in those days we had patients who were addicted to amphetamines, and we collected a few and Dr Vinod Thacore and I studied their sleep while we withdrew them from amphetamines and from Purple Hearts - a mixture of sodium amylobarbitone and dexamphetamine - over a period of weeks. We saw that there were things we could measure in the sleep of these people that betrayed an obvious withdrawal reaction which gradually resolved over a period of weeks.

The next thing was to look at sleep after barbiturates. I was really prompted to do this by Professor Ferguson Rodger, who was the Professor of Psychological Medicine at Glasgow. I had given a talk about this

amphetamine research at a meeting in Inverness and he said, look why don't you look at barbiturates to see if these withdrawal reactions occur. We did that as a cold experiment, getting money from Hoffman La Roche, who had a brand new sleeping pill, that they called Mogadon. We looked at that and at barbiturates. We gave them Mogadon for two weeks. Based on this Robert Priest and I published a paper in the BMJ in 1965 called "Five Weeks to Escape the Sleeping Pill Habit". In it we said, and I think we were among the first people to say so, that sleep was disturbed in various ways for a period of weeks after taking sleeping pills for as short a period as two weeks. So that's how I really got into the sleeping pill business.

As for the antidepressants that you mentioned, I had only used those in the treatment of patients, working as a psychiatrist by day and doing sleep research at night. Then I went off to Australia and there was not so much scope for research - I was busy setting up a teaching department. But we did a little bit of research, including a slimming drug called fenfluramine. When I came back, we got another tranche of money out of the manufacturers of fenfluramine and we reported that there were withdrawal effects from fenfluramine - that depression of mood was caused by it, which was maximal 4 days after stopping the drug. We reported this in the BMJ and I think to the great credit of the manufacturers they never complained or tried to get us to alter our results. In contrast, I have known a drug company, based in Spain, which got very nasty indeed, trying to get us to change our research results in later years, but we didn't. So it was fenfluramine that got me into the measuring of mood and sleep and dreams.

Mentioning dreams bring in the whole REM sleep issue and the effect of the antidepressants on this. At one stage it almost become compulsory for new antidepressants to be screened on sleep EEGs and most of the companies at one point must have beat a path to your door.

Yes, that's right. I used to say to them that as I saw it a drug company provides money for research and there are some research projects that they are interested in and we are not, and some that they are interested in and we find interesting also. And the third kind is the sort of research in which we are interested, and in which they have no interest, and the money we get from them for the first two kinds of research must pay for the third kind of research. So we did do a lot of what I would call pure research and research into dreams - waking people up in the night and that sort of thing, which was funded really by research money from drug companies.

You had an article in the early 1970s on the issue of why the antidepressants took so long to work.

Yes, it was purely a speculative kind of article, but I had been very impressed by the slowness of change of brain function that one could plot on a graph using sleep measures. I was at that time, and for 22 years, in charge of the psychiatric service to the Poison's Unit at the Royal Infirmary of Edinburgh. This gave access to people who'd taken overdoses of all kinds of drugs and it was possible to transfer some of them to my psychiatric ward on the grounds that they needed psychiatric help. With a little persuasion they agreed to have their sleep recorded at night. So one could see quite spectacular abnormalities in the first few days after the overdose that gradually declined, to what was obviously their normal pattern, over a period of weeks. So I had

been very interested in these slow changes in the brain. I remember giving a talk in 1966 at some meeting of the New York Academy of Sciences, while I was based in Australia, about slow shifts in brain functions based on the Mogadon and the dexamphetamine research.

I was always very interested in these changes and in the fact that the antidepressants like imipramine and amitriptyline did not bring obvious benefits until 10 or 14 days after people started them. In brief it's not everybody whose depression responds to mono-amine oxidase inhibitors but if they do respond, at the time when they respond there are quite spectacular changes in sleep with suppression of the rapid eye movement sleep as usually measured. This was in a paper with Des Dunleavy in the Archives of General Psychiatry 1973. The paper in the British Journal of Psychiatry to which you refer was a speculative paper, really just drawing attention to the fact that all these changes with the tricyclics or the monoamine-oxidase inhibitors that people were measuring in rats occurred at once, but the clinical improvement in depression took 10 or 14 days and there had to be some attempt to understand why that should be so. I don't think there ever has been an understanding of it but one ought to try.

Can I ask you something about that? If you look at the early CINP meetings, psychopharmacology, from the basic sciences point of view, was very electrophysiology oriented. Somewhere in the late 60s probably the early 70s things began to change and it became more molecular. They lost a molar view as it were and took a more molecular view. You could argue that taking this approach is more useful in terms of trying to generate new drugs but it seems to be less useful in terms of understanding what's going on at the level of the whole organism.

I totally agree with you. There are fashions in research as new techniques become available. Some new technique arrives and that's fashionable for a period and gradually knowledge advances and then the scope for the use of the technique becomes exhausted. Then some new technique starts a new fashion in research. The trouble is people tend to forget what was discovered with the earlier techniques and they should really go back to the library from time to time.

You could argue that scientific progress actually is driven by new techniques but you could also argue that what also happens is that we, rather magpie-like, go for the next bit of shining metal rather than try to answer issues that haven't been solved in the field. One of the things that the EEG story brings out is that in the 1960s withdrawal reactions to major tranquillisers and most psychiatric drugs were being described in terms of EEG patterns but with the eclipse of the EEG as a research focus, the awareness of withdrawal effects was also lost. It is perhaps of some interest that the people who brought the benzodiazepine withdrawal question to the forefront, like yourself and Malcolm Lader, had a background in EEG work

Yes, the usefulness of the EEG during sleep was in demonstrating that with clinical dosage you got obvious withdrawal features. It made it possible to actually measure something like that. It was only with time I think that people began using additional measuring instruments, like Malcolm Lader at the

Maudsley who became very interested in multiple measures of withdrawal from barbiturates and other hypnotic and anxiolytic drugs.

Were there any other people that you linked up with at this point in time – Turan Itil, Max Fink, Louis Lasagna?

Well I met people like Itil at conferences but he had his own language based upon some computer derived indices from EEG patterns of people awake. This made communication difficult. Certainly I had occasional friendly contact with Max Fink.

From your point of view when did the benzodiazepines or the problems of the dependence with them begin to emerge? Historically we can look back and say Leo Hollister did his trial in 1961 that showed withdrawal effects. You've also mentioned the report that you had in 1965. But clinically on the ground it seemed it was only somewhere around the late 1970s and early 80 when Peter Tyrer, Heather Ashton and Malcolm Lader began to question this - in some cases with people who had been very pro the benzodiazepines reversing their point of view.

Yes I would say it was in the early 1980s. I had certainly gone around the country throughout the 1970s giving talks emphasising that there were withdrawal features and that there was dependence. But let me say that I have always felt that the public reaction against benzodiazepines in the 1980s was over done and in many ways irrational. I think the benzodiazepines, and I'm not referring to the triazolobenzodiazepines with their very different chemical structure, are very useful drugs if used in a sensible manner, which means for brief periods. Perhaps for something like 10 nights, or in older people with perhaps physical disabilities in small doses for much longer periods. I think they are useful. I think that the litigation that began in this country, with people claiming all sorts of nonsensical symptoms with long lasting consequences because of having taken benzodiazepines, justifiably came to nothing. It was partly mismanaged by the lawyers, who duly made money for themselves from Legal Aid.

Were there any key points, key people?

I think Malcolm Lader's article in the BMJ in 1981 about withdrawal symptoms from benzodiazepines was a landmark. It got latched onto by the campaign group, TRANX. I had the misfortune to go once to the BBC TV studios in London. I was told that this was going to be a scientific discussion and that various other eminent scientists would be there. It turned out it was a trial run with a sort of compere who had no idea about the topic at all. They hadn't done any elementary work. They thought that Mogadon and nitrazepam were quite different substances. There were a small handful of us there who were pilloried by these hysterical people from TRANX, with stories about how their marriage broke down once they took this, that drug or the other, and, "I've been weeping ever since". But of course the obvious thing was that they were weeping because of the breakdown of their marriage. The programme was never broadcast. I thought that there was a lot of irrational blame placed on benzodiazepines taken in what had been recommended clinical dosages.

What then is different about the Halcion story?

I had been asked by Upjohn in 1971 to do research on their new drug, triazolam, and they told me it really was different. It was. I proposed studying

possible withdrawal effects and they decided not to proceed. Then in about 1980 I got some money from a drug company to study a new hypnotic loprazolam - to see the effects on sleep. Triazolam was seen by the company as the rival for the time when this new hypnotic would be launched. There were 21 insomniacs not taking prior drugs. Each person entering the study had two weeks on placebo, to get baseline EEG sleep data on their sleep, then 3 weeks on active drug and then a couple of weeks on placebo to get withdrawal features. Then after 4 weeks the whole thing was repeated but with cross-over of the drug. We were also measuring anxiety on visual analogue scales, which we used to do routinely and were very much surprised by the fact that while receiving triazolam people became more and more anxious, which didn't happen with the other drug. Anecdotally, there were some terrible experiences and when, the drug was withdrawn, on the first night they also had very broken nights. One woman only got 1½ hours sleep on the first withdrawal night after triazolam, 0.5mg, which let me add was a common dose around the world. We published this finding as a preliminary report in the British Medical Journal and came in for a great deal of flak, notably from, as he then was, Wing Commander A. Nicholson of the Royal Air Force. All this is in the public domain because it's all been gone over and read out in open court. What I didn't know was that he was being used by Upjohn to rubbish the research and that there was a special "strategy against Oswald", to use a phrase from an Upjohn document.

That sort of thing did increase my determination to try and find out the truth and we got some money from a German company, Schering AG of Berlin to investigate their sleeping drug lormetazepam, about which we published several papers. And then I put to them how about having a longer study purely of subjective data. We needed to use large numbers of people, if we were going to measure subjective data - you can't do that with the EEG it would be too expensive in the EEG lab. So we had 40 people on their drug, lormetazepam, we had 25 people on triazolam and 25 people on placebo throughout. The design was an initial period of placebo to get baseline data and a middle period on "drug" which in some cases of course was continued placebo and a final period on placebo. And then the question was, what is the difference between baseline placebo and continued placebo. Next, what is the difference between baseline placebo and lormetazepam for three weeks? What is the difference between baseline and triazolam continued for three weeks? Then are there differences among those three differences? And the answer was, yes. When the code was broken, we found that people on triazolam had become much more anxious particularly after about 10 days. They had a whole variety of nasty symptoms, weepings, quarrels and two became seriously paranoid. None of this happened among the 50 people who had had lormetazepam or the 40 people who had had placebo.

We sought to publish it in the Archives of General Psychiatry. It was turned down with some vitriolic reviews that I ultimately discovered - and all this is now in the public domain - were written either within the Upjohn company or by people who were funded by Upjohn. What we didn't know was that the then Editor of the Archives of General Psychiatry was funded by Upjohn and he had sent our paper to Upjohn to referee. As it appears in an internal Upjohn memo, after the paper had been turned down by another organ, the New England Journal of Medicine, as Upjohn put it - "so far we have been

successful in having it stopped". And I know that the sole referee for the New England Journal of Medicine article, a distinguished medical pharmacologist in the United States, was being funded by Upjohn at that time. Eventually we got it published in Pharmacopsychiatry but it took two years of delays. I didn't know that this delay was regarded as an achievement by Upjohn.

So you've referred to problems with Halcion and with Upjohn and you say the benzodiazepines were less hazardous compounds than triazolam but do you think all the companies behave in the same way as Upjohn did then?

I think that Upjohn were actually very unlucky. Here was a drug that was a variant of the benzodiazepines and they thought it was going to be just as safe as other benzodiazepines. It was short-acting, which seemed like a very good idea. As I've mentioned, I first got into the triazolam business at the invitation of Upjohn in 1971. They flew me to Kalamazoo and we had discussions about doing the research project in Edinburgh.

So you weren't a spurned suitor then?

Oh no, not at all. They sought me out at various later times and I'm quite sure that the Upjohn people in Britain had no idea of what had been in Upjohn's own original research trials in the USA. Nor did most of the people in Upjohn. The Upjohn findings were all on an Upjohn computer by 1983. And in the court case, in London, Upjohn were obliged to provide printouts from what had been on their own computer in 1983 as well as the original paperwork from the early 1970s. And it was immense labour, but from the printouts it was demonstrated that Upjohn, had with their own measure of what they called "restlessness/nervousness", had found the drug in their longer term clinical trials, that is over two weeks duration, to be a cause of anxiety. In court what Upjohn said was to the effect that they had never ran their computer to find out whether anxiety might be caused by triazolam in spite of the publications of people like Oswald because they held Oswald was not to be respected.

Is there a thing about these Drug Companies though - to an extent they have become vacuums it seems to me. There was a point when there were people in the companies that knew what was going on and could intervene if need be. But more and more as the companies get larger and larger, I end up having to introduce some people from a company to others from the same company and also very few people are with one company for long, so in a sense its perhaps not quite so surprising, at least now, that they may not know all the material that they have on their records and files.

I agree. In the case of Upjohn some of the original people were still there at the time of the court case to which I refer. I don't want to give the impression that I think all drug companies act behind the scenes to stop publications or to try and get you to change your results. I have a high regard, for example, for Schering of Berlin. In our first study for them, on lormetazepam, we reported this as a drug that causes people to lose weight and published that in the BMJ. But you know there was never any word of irritation or anything like that at all from Schering AG. They went on funding our research in several ways. I do believe that British companies have been less driven by their marketing people than has been the case with American companies. Where the making of profits has, as I see it, been paramount, regrettable things can arise. We

might take the example of Opren, manufactured by Eli Lilly. Eli Lilly in its original research trials discovered the very serious effects of that drug. But they still marketed it. Up to a very short time before it was banned in the United Kingdom, there was a Vice-President of the company writing in the BMJ to the effect that no such troubles had been found with the drug in their research. But they had been found.

There was nomifensine, the antidepressant, which had to be taken off the market and again it eventually came out that the trouble with nomifensine had cropped up before the drug was marketed. I think a lot of the problem has been because of a desire to save money at the FDA. The FDA's budget was cut in the Reagan era. Staff there are underpaid, their facilities are very poor. They don't have time to do a really detailed scrutiny of the original data of new drugs. They have to rely on summaries given to them by people at the drug companies. And the drug companies in the States make a practice of hiring people who have worked at the FDA. I certainly know it has been the case that somebody has been hired with the obvious object of knowing how to prepare a submission to the FDA that will paint the drug in a most favourable light. This is business. It's not surprising. It's just a fact that drug companies are there to make profits for their shareholders.

How compromised do you think the FDA is?

I think it does depend on the particular section of the FDA. It depends very much on who is the head of the division concerned – whether gastrointestinal or psychopharmacological. But there is a steady drain of people. One of the highest placed men in the FDA you know left to become a Director and Vice President of Upjohn, for example. I don't imply he acted dishonourably at any time. He actually resigned about the time that the court action against me was initiated. But it's inevitable that people like him have friends in the FDA - they're on first name terms and it must influence things. As far as triazolam is concerned I could also refer to the fact that of course it was the sleeping pill of President George Bush and thereby hangs quite a lengthy tale. I have a whole dossier on Bush-triazolam publicity prior to his failing to gain re-election. It's all public domain material.

You know there was the surprising arrival by air by George Bush early in his election campaign at Kalamazoo, where he was met among others by the Chief Executive of Upjohn. The FDA did not follow the CSM in banning triazolam. The head of the FDA at that time was Kessler. He is said in the obituary of Cooper, who was the Chief Executive of Upjohn, to have had a special meeting with Cooper over triazolam and the writer of the obituary says that Cooper persuaded him to allow triazolam to stay on the market. Now that's only what the writer of the obituary says. But the head of the FDA might well have thought, this is a sleeping drug, if we cut the dosage down any ill effects should be a lot less and the FDA did not ban triazolam, it simply cut the approved dose to a virtually ineffectual level.

Kessler, of course, had a much bigger object in his sights and that was tobacco. He was assailed from all sides by industry people being rude about him in the newspapers, writing to the President, making complaints on every score all across the pharmaceutical industry. He held his ground and he got tobacco in his sights. That was his big goal and he won. He got tobacco

recognised as an addictive drug and all credit to him – it was a much bigger goal than triazolam in small dosage.

So at the end of the day it comes down to politics.

Yes. In Britain, the Medicines Act, for instance, has a history of being influenced as it went through Parliament by the drug industry. They got into it a curious clause whereby after all the procedures have been put into effect to take a drug off the market, the drug company can request that there is a panel of people who are asked to reconsider the whole matter. Now the body concerned has no advisory powers under the Act. It can simply make a report. The drug company alone can make submissions, the drug company alone can decide whether the hearing is in private or in public. When this happened over triazolam, at the request of Upjohn the panel met in private. Curiously Upjohn is the only company ever to invoke this procedure, which it has done twice. Not only was I prevented from making any submission but so was the Medicines Control Agency. The only submissions made were made by Upjohn. I have read those submissions. Good earnest people were on it. George Ashcroft was one. But all they heard were Upjohn speakers and their comment was that the drug could be reinstated but in a dose, which was one half of the minimum 0.125mg dose that had earlier been allowed. Now this latter dose had not been demonstrated to be an effective sleeping drug let alone half of that. But my chief point in saying this is that here is this curious official procedure for a drug company to have a hearing when not even the Medicines Control Agency can make submissions.

Isn't this because the UK has been quite keen to be pharmaceutical sector friendly? It's been quite keen to build up the pharmaceutical sector in this country.

Well the Medicines Control Agency was, I think, a chief mover in getting the European drug scrutinising Agency set up in London and I must say that I'm much happier that it was set up in London than that it was set up anywhere else in Europe. The gentleman who was Chairman of the European body under the aegis of the European Union, Mr Poggiolini, was one of those who in a purge against corruption in Italy allowed himself to disappear. It was alleged, in the Spectator, that in his house was found an amazing quantity of valuables. It was implied that these were bribes. There is a convention recently instituted against bribery being allowed as a sort of tax rebate for European companies.

Some of the points you have made about how Upjohn handled you were echoed in the letter you wrote to the BMJ about fluoxetine. We both wrote in about the meta-analysis the company had conducted. It seems to me your point about companies having a management strategy for certain "scientific" issues is apposite to the fluoxetine case also

These people employ a whole lot of folks solely for public relations and for what appears as purposeful attempts to undermine the reputations of any one who has criticised one of their drugs.

How actively do you think they do that?

I think it's very active. I can think of a drug company associated with an Australian man who got into the news about 10 years ago because the drug company arranged all sorts of dirty tricks to undermine his reputation. One

has to wonder as well about Teicher in the case of fluoxetine. I've got a thick file of public domain material on the arrangements Eli Lilly put into train to undermine his reputation, as Upjohn did in my case.

So where does that leave anyone who wants to raise issues that may not suit the marketing department of the company?

It puts them in difficulties. One thing I have learned through having had access, through Court Orders in both the United States and the United Kingdom, is that there are a regrettable number of senior medical men and pharmacologists, who are very much in the pay of specific drug companies. They receive regular retainers under the title of advisors and they are willing to put their names to criticisms of the conclusions of anyone who's criticised the drug.

After Dr Van der Kroef in the Netherlands reported in the Lancet in 1979 that triazolam caused anxiety and other psychiatric symptoms, Louis Lasagna appeared as the author of a paper in the Lancet called Trial by Media quoting figures from Upjohn's own research to the effect that the ideas put forward by Van der Kroef were nonsense and based only upon a lot of publicity-seeking. Nothing like these adverse effects of triazolam had supposedly been found by Upjohn in its own clinical trials. Now I know, because it's in the public domain that Upjohn's own research had demonstrated what Van der Kroef had described but Upjohn had never communicated the relevant facts either to the FDA in the United States or to the CSM in Britain. When eventually, without breaking a court confidentiality order in the United States, I managed to tip off the Medicines Control Agency, the Agency acted very quickly and got some of the original documents from Upjohn. They looked at them instead of merely taking Upjohn's summary documents into consideration and the upshot was that in this country triazolam was quickly banned. There has been a court case about some of these issues where the learned judge said that the omission by Upjohn to provide the relevant information to bodies such as the CSM was a consequence of serious error. That is one way of putting it.

As long as you don't say things that are libellous, you can usually get your research published eventually. I think the British Medical Journal for example has instituted a good arrangement whereby they demand that people declare any conflict of interest. This showed up in my own case in the letters in the BMJ. But even this is a voluntary system, nobody at the BMJ is actually able to check on whether what is declared is the whole truth and because I have had access to Upjohn's own internal memoranda I know of one instance where, in the BMJ, a distinguished British psychiatrist was economical with the truth.

Where does that leave shall we say the truth? Is truth something that will emerge in the wash willy-nilly 10 - 15 years up the road when the drug goes off patent?

No I think the truth can be buried for ever. I think countries are increasingly run by big business particularly the United States. Congressmen depend financially upon big business. I think it's a matter of just being glad that we don't live in countries where we will get thrown into prison without trial or executed by death squads. All is not well in our own society but at least we are better off than many.

You reported on fenfluramine first of all in the early 1970s - that it both worked and caused weight loss but there were withdrawal effects to it. Now the issue of possible withdrawal effects from the SSRIs has become highly topical. Do you think these are linked potentially. I mean the SSRIs and fenfluramine are very similar compounds.

You know, I grew up in a medical profession that thought of drugs as having actions when you had just given them, and as long as you continued to give them, but had no concept of them having altered the organism so that there would be prolonged consequences when the drug was stopped. People understood on-effects but they didn't have any conception of off-effects. I think I was a pioneer in going round preaching that there were off-effects. They are much more recognised I think these days. They became recognised really in the 1980s but were really not recognised in the 1960s. In only a few of the people we dealt with, you know morphine addicts and the like, did we realise that there were withdrawal symptoms. Obviously there were odd case reports of withdrawal symptoms and delirium for barbiturates and so on but the majority of doctors simply didn't know about these or take any notice of them. I cannot comment specifically on withdrawal effects after SSRIs because they are really after my time.

With the SSRIs story today one of the interesting things about the discontinuation syndromes story is that these have been used to market an advantage. In this case Lilly are pushing out the boat saying that the other compounds have effects in this area that they don't. Whatever one believes of this, it's clear that the whole raising of the area is being done as part of company warfare shall we say. How much of the benzodiazepine controversy was, shall we say, engineered by people like Bristol Myers Squibb who were keen to break in on the benzodiazepine market with buspirone? Roche of course in turn essentially attacked the barbiturates in the 1960s in order to sell the first benzodiazepines.

The barbiturates of course were very dangerous in overdose and benzodiazepines were benign by comparison. Peter Tyrer might be someone who'd have more useful comments because he did work on buspirone. Buspirone was a drug that I never thought was going to be any good for anything. But of course the drug companies always say there are no withdrawal symptoms. They said that about sleeping drugs for instance. But I think there should be the assumption that any drug that acts on the central nervous system will lead to withdrawal phenomena as a fundamental. The nervous system is an adaptive organ; it's changing itself all the time, adapting to changing circumstances. If you suddenly take away a by now accustomed drug then trouble's going to flare up.

Absolutely but one of the interesting things here is that in the mid 1960s discontinuation syndromes to neuroleptics were quite clearly reported. At the same time WHO were defining drug dependence in terms of it will only happen with drugs that cause craving, that are nice, where the dosage escalation and that leads on to "addiction". In some sense, perhaps partly an accident of the historical process, they defined drug dependency in a way that meant we lost sight of the fact dependence syndromes that are not linked to addiction.

Yes, I agree, I used to criticise these changing definitions and the artificiality of the definitions. You're absolutely right that the definitions impeded understanding.

How do we disconnect processes that lead to you being an addict from the processes that lead to rebound which every drug that acts on the CNS must have? Can we disconnect these things?

Well I don't suppose that one can distinguish sharply. One gets into who are addicts and addicts are people who are rejected by society and who have rejected the norms of society and seek refuge in an altered mental state through drugs. One of the papers I published around 1971 was about withdrawal features that one could measure in the EEG in parallel with morphine products in the urine after I had been injected with heroin for 2 weeks. Well I've never been better pleased than when the damn stuff stopped. I never got any pleasure from it. I felt half-dead. It ruined my appreciation of the world and yet there were research folks in America who knew me who said they were terribly worried when they'd read this article and feared that I must be an addict. When I gave evidence in a murder trial in Missouri for the defence of a woman who had killed her children, (she had had Halcion for quite a time and she had become paranoid), Upjohn organised the prosecution with a whole lot of data. I was portrayed on two consecutive days in the local newspaper as a heroin taker with nothing at all adverse about the drug mentioned in the paper. Now I know that steps had been taken within Upjohn to get the proprietor of the newspaper on board before this trial started. So I got classed as a heroin taker in 1992 over some research that I published in 1971. But you see I wasn't someone who rejected society, I wasn't a drop out. I was ambitious and hard working and never liked the wretched drug. In the same murder trial the leading drug expert for the prosecution, brought in by Upjohn to rebut what I had said about triazolam's ill-effects, was none other than Dr Borison of Augusta, Georgia, whose true credentials have lately emerged as a sorry story in another court.

I think you've raised almost a key issue. A key stumbling block in the whole field is the use of drugs by people who reject society. I understand that in the Newcastle area there's even a street value for amitriptyline. This has to be because of the behavioural toxicity they can produce. Even frank dysphoria is preferable for some people to engaging in the world it seems.

Yes people have taken hyoscine for some dream inducing effects but you or I would find it unpleasant as most people do. I suppose amitriptyline induces a bit more in the way of sleepiness. Some people will take anything – petrol, anything.

So in a sense the question of being an addict can't be medically tied down – if one is operating from a purely physiological prospective.

No.

Your court trial was in 1994?

It was in 1994 yes. I was awarded in my counter-suit twice the damages that Upjohn was awarded.

I'm aware of that. But the point I was going to come to, the thing, which caught me by surprise, was this. At the time I was liaising very closely with Mike Bury, who was investigating the sociology of the minor tranquillisers in the media. Now he was particularly interested in your case because it seemed to sharpen the issues and I know that he went to court on a few occasions to hear what was going on. I know he has an article on the whole thing which went for publication to one of the Sociology journals but was scared off submitting it in the first instance for fear of what Upjohn's response might be.

Ah well, he's not medical, so he hasn't got a medical defence union behind him.

Good point but what I'm going to come to is this, shortly after the trial for whatever reason he was asked along to an Glaxo Advisory Panel for some sort of sleeping pill and found you there.

Yes. It was at the Le Manoir Aux Quatre Saisons near Oxford and we had some beautiful food. Yes.

I was actually surprised on two scores. First I would have thought the whole court thing would have scared the pharmaceutical industry off you but equally the other way around I would have thought that you'd have been so jaundiced about the industry that you wouldn't have taken it up.

Well I don't actually think the people who were organising this thing at Oxford were particularly aware of the court case. It was a very remote connection. The people were not really CNS people. One of their research workers who they'd supported had got some sort of preliminary data suggesting that their gastrointestinal drug might have an action on sleep and they wondered if they could exploit this. Being very wealthy they had the meeting at this shrine where my wife and I had stayed and eaten from time to time before. To get it all free was a lure. This is one way drug companies make friends. I remember being asked at the time, are you still doing research. I said no. All they got was a view about the nature of sleep and comments on the possibility raised at the meeting. I actually said to them that I thought it was worth following up but I don't think they did. I thought it was rather interesting. But no I'm not frightened of drug companies. I have been consulted by one or two others since the court case.

So they don't act together as one large group?

Oh no.

Have the companies changed over the years. You were involved with them during the 1960s when companies like Geigy and Roche were still small. Now you have these massive multi-national corporations. Have you been aware of much change in the character of these companies.

I can't say that I'm in a position to say anything on that. My belief would be that marketing experts must have gained a greater say but I think that's a general phenomenon in big businesses.

How about the sleep field? Have we actually made any advances at all over 30 odd years? We've got the latest benzodiazepine related drugs?

When you talk about advances in sleep, you're only thinking of drugs. But why do people complain about their sleep? They complain about their sleep because they are unhappy people. And the big market has been for people who are chronically unhappy, who shouldn't in my opinion be given these drugs except for brief periods of times of special crisis. Although I think it's entirely different when someone has had an operation or has really got flu and a bad cough, when to have a sleeping pill for two or three nights is useful.

How do you treat chronic low-grade unhappiness?

Well I think to start with you don't make them into drug dependent patients. The rest is a problem for you psychiatrists who have not yet retired. I don't think that in the long run the chronic unhappiness will be improved and certainly the individual's functional capacities will not be improved by giving them drugs that impair their capabilities and their decision-making. Anxiety drives us to decisions. I think there is rather more of a case for giving a benzodiazepine that would act chiefly during sleep than giving such a drug during the day when we ought to be alert and exercising our decision making and our full skills.

Well then do you have any comments on the kind of campaigns by the APA and Royal College of Psychiatrists to defeat depression which in effect have become something of a mass marketing of depression. These campaigns must have made the life of your average marketing manager rather easier than they had a right to expect.

I don't want to comment on that. Shortly after the end of that court case in 1994 I really set about genuinely retiring. While I occasionally look at the British Journal of Psychiatry, I have retired other than for a few medico-legal cases. So I don't want to comment on new movements in psychiatry. I retired from my University post when I was 60 having always intended to retire at 60 which was in 1989. I then worked more or less day and night on triazolam litigation documents. I had a quarter of a million sheets of paper obtained by court order. There wasn't a lot of time for reading other things in 90, 91 and 92 and 93. So I've not been keeping up with all contemporary trends.

Are there similarities between the way pharmaceutical companies operate and the major tobacco companies?

The big law firm in the United States that has acted for the tobacco manufacturers is Shook, Hardy and Bacon of Kansas City, Missouri. They acted for Upjohn and have acted for Eli Lilly. There is a book published by the University of California Press, The Cigarette Papers, which is very revealing on what law firms have been prepared to do for the tobacco companies. The book is about the tobacco industry based on those confidential memorandums that were smuggled out. It shows that Shook, Hardy and Bacon were acting directly in arranging financial or other benefits for people who would praise tobacco. The President of the American Cancer Society was in the pay of the tobacco industry. The tobacco industry, the book's authors argue, found long ago, back in the 1960s, that tobacco was a cause of heart disease and cancer but suppressed all this. They started working on a "safe" cigarette but their lawyers advised them they must stop because it implied that other cigarettes were unsafe and so on.

Now what happens when a law firm pays people to do things either in the nature of dirty tricks or to write laudatory articles that get planted in friendly journals is that when it comes to litigation, they invoke in court what is called attorney/client privilege whereby you cannot get the records. The court can order a tobacco company or drug company to produce relevant documents, although whether the company really does produce every one of them of course you don't know. A very large number that were ordered to be produced in the United States were not produced when they should have been, but turned up in my court case in London. What none of us knows is whether there might have been others that should have been produced that might have been incriminating and that were never produced. Nobody outside the company can know. But there were certain crunch points in my own case where we really wanted to know just what had been going on between Shook, Hardy and Bacon, Upjohn, and some of Upjohn's outside scientists. But the information was not accessible because it was held to be covered by attorney/client privilege. It is clear from the tobacco story that the law firms entered more than wholeheartedly into the struggle on behalf of the tobacco industry. What they may have been done over psychotropic drugs we shall never know.

I can understand that happening for the tobacco industry in a sense in that it's not a regulated industry but the pharmaceutical industry is. We, as medical prescribers and the pharmaceutical industry have a relationship that medical experts don't have with the tobacco industry. We are inextricably yoked together in a way that requires us to bring problems to the attention of the public in a way that medical experts don't have to do in quite the same way with the tobacco industry. This is because these drugs are only available on prescription. We therefore have a duty to keep an eye on what any emergent problems might be. The industry should be sensitive to our efforts to make the knowledge available in this area. They shouldn't be treating us the way that can, in a sense, justifiably treat medical experts when it comes to something like tobacco.

Yes. Some of them will certainly do anything to protect their billions of dollars a year income. Well almost anything. Don't go to drug conferences in Brazil. People get knifed on the street. One of the people from WHO, who was a witness for me, said he wouldn't go there for obvious reasons and that I shouldn't either.