PAUL LEBER

I probably thought I was going to be a physician early on. My father was a paediatrician and he had a practice in our home and I spent a good part of my early life being quiet in the afternoons after school so that I wouldn't disrupt office hours. My father lived in the days before medicine was reimbursed at a rate to make physicians wealthy. He spent his days literally in toil, rising early in the morning to go to the hospital for rounds, travelling throughout the city of Brooklyn in an unairconditioned car calling from one flat to another, walking upstairs giving shots of penicillin, coming back for office hours and making sure we all behaved. I think the image he gave of someone serving the community and the importance that he seemed to attach to the role of being a physician probably was impressed upon me early in my life and though I considered many other possible occupations, I probably knew in my heart fairly early on that I would become a physician without really having much understanding of what it meant to be a practitioner as distinct from someone who had the nominal title of physician. That's how I came to be a physician. I followed the usual course, thereafter - going to school, majoring in what I needed to get to medical school, getting to medical school..

Then into pathology

No, I first began in internal medicine. Actually I had taken something called a medical science's year between my third and fourth years in medical school. This was before the MD/PhD programs had been established. I had been captured by the bench researchers probably in my first and second years in medical school. I did some research and then applied for this special programme, which led to something called a Degree with Honours. I actually did work in enzyme biochemistry with a biochemist who was interested in active sites and so I was introduced to an equivalent of pharmacodynamic modelling early on. But I was persuaded by many people that if you got an MD Degree you belonged in medicine and so despite that period of time on the bench I went into the internal medicine, which was considered to be the area in which a young academic would have the most opportunity to do both. It was an age where I think we believed you could be both a clinician, a scientist and an investigator. Of course science was a lot simpler then. I got an internship in medicine, came back to Bellevue, where I had graduated from NY medical school, did a residency for one year in medicine and at that point decided that medicine didn't offer everything I thought it would offer. I had done a rotation of some months in pathology during my residency and I was impressed by the fact that many of the things I thought I could do in research, I could still do as a pathologist and so I decided to become a pathologist, although I must admit I had no intrinsic love of pathology per se. It was another way to continue the academic medicine life. I became a pathologist and for several years I wandered around interested in immunology and nephrology, before I decided that I needed a change of career and then probably 10 years out from the time I graduated from medical school I went into psychiatry.

In terms of what you have done since though, you talk about randomised controlled trial in terms of an assay system that works, that is sensitive to what you need to detect change, how much did your pathology training influence you to see things this way?

I think my pathology training didn't do much about trial design because pathologists aren't given to that. Assay sensitivity isn't my idea, that was Walter Modell and Raymond Hood but the notion that taxonomic diagnostic systems are authoritarian systems where people with declared positions of power say something is something because they say it - certainly pathology is rampant with that. A pathologist looking at a slide will say with great confidence but no evidence that the lymphocyte is travelling from one direction to the other in the lamina propria. There is no way to know that of course in a section of dead tissue but he feels quite confident that he can explain what he or she needs to explain that way. I think when I came to psychiatry I was struck by the fact that there was a shared similarity between the pronouncements of pathologists about tissues they knew little of but could describe fairly well and the psychiatrists looking at patients who they could describe very well but they could in no way explain what they

were doing. In the course then of working for an agency where you had to assess whether or not an expert reaching a conclusion about something has a basis to reach it, not that they have an opinion - that's understood, it became obvious that sometimes experts offer opinions like the pathologist and the lymphocytes. I think it's out of that that I became an enthusiast for structures of research and designs that provide the kind of evidence that would allow an expert, as we say in the language of the law, responsibly and fairly to conclude from the evidence that something is so or is not so. I distinguish that from simply associating some body of information with some conclusion and asserting there's a link. That's what assay sensitivity and such things have to do with. It is that your experiment is valid for the purpose for which you apply it. As someone who acts to make decisions in the area I would just as soon be able to say yes I can explain how I made my decision.

Why did you move then from pathology into psychiatry. Its an extraordinary jump.
I'm not so sure. Jokingly when one decides that they want to do something else, there are a number of options. I happen to have made this one. There were many reasons why I might have. I was teaching pathology and one of my other responsibilities, at the State University of New York in Buffalo, was to run the second year pre-clinical path course. Many of our students had difficulty and because at that time we were, as an institution, reimbursed by per capita graduation rates, there was great enthusiasm for promoting everybody and giving them Mds, and so we had psychiatrists around explaining why people failed to do what they should have done academically. In the course of dealing with such problem students, I often thought to myself that I could do as well with these students using what I thought was common sense. Of course I was wrong probably, in retrospect, but at the time it fooled me thinking that it was an attractive thing to do. That and the fact that my wife was a clinical psychologist. It seemed like a nice thing to do, get me back to clinical medicine.

Where did you go train?
I went to something called Bloomingdales, which was the Westchester division of New York Hospital, Cornell. It was a very nice 240 acre park institution, post civil war, beautiful grounds etc. It dealt with a very different type of patient population than one would expect to find in a modern day acute psychiatric hospital, state institution. But it had a major advantage in that it had a fairly cohesive faculty early on, all of whom had a shared interest in phenomenology, which for America was very unusual. That came about because a chap of the name McHugh, who for many years has been at Hopkins, had been at Cornell.

Who actually was Paul McHugh. His name has come up a few times.
He was a neurologist who agreed to become head of the psychiatric hospital in Bloomingales. He was there before I came and left by the time I came but he had left in place a series of people who were very intersted in his scheme which was basically to bring what he would call the Jasperian-Schneiderian German English school of Psychiatry to America to replace what he thought, I gather, was the almost religiously dominated analytical approach to psychiatry prevalent at the time. What was interesting about this was it produced a lot of shared experiences. We had a chance to assess patients in a group setting. The group consisted of other interviewers and clinicians who then after the interview would sit around and say " well did that patient really have gedankelautwerden or thought-broadcasting, or extra-campine hallucinosis, do you think they were bradyphrenic or not?". It was a very good training ground for phenomenology and clinical description. The only problem was, of course, that the language we were learning was totally orthogonal to the language of common use at the time in DSM II.

This was when
This was 74-77.

Had Wash U begun to have an impact by then with their neo-Kraepelinian program?

I certainly think it was going on pari passu with it. Everyone was aware of Sam Guze and the group at St Louis. There was a very complicated series of manouvers in New York City at the time, when the Chair at Cornell, in Psychiatry, became an analyst, which was highly unusual because Cornell up until that time had been a eclectic department of psychiatry, one of the exceptions. In the course of that shift the composition of the faculty of the Cornell Medical School, Department of Psychiatry changed or was modified and analysts began to come to the Westchester Division. The problem was that in the rest of the American world this German/English/Schneiderian/Kraepelinan language was foreign to everyone except us or so it seemed. When the analysts came they didn't know what we were talking about and they thought we were all some strange variety of unthinking automatons that for some reason didn't really understand that the patient had ego strength or ego weakness or projective identification or whatever they believed you could see. Whereas we were talking descriptively, they were talking deductively.

How did the whole DSM III process look to you from where you were at?
It clearly was very appealing at the time. Obviously there were the research diagnostic criteria that were available at time or at least their forerunners. We were also tied in with a group of people who were pushing things like the present state exam that Wing Sartorius and Cooper developed in Britain for one of the pilot studies of Schizophrenia, the World Health Organisation was doing. There was a commingling of standardising the objective interview, the collection of observations in systematic ways, using a defined glossary of terminology, training people in operational criteria etc. All of that was going and it all fit very nicely. Now in retrospect the system, even of Guze is no less taxonomic and in fact is more restrictive and in a way was just carving out those portions that they could allegedly easily replicate and reproduce. It didn't mean that they explained every psychiatric patient. The classic example is Briquet's syndrome being substituted for hysteria - it clearly is a much smaller portion of the broad space of hysteria. You can't substitute it for hysteria - its just one particular sub-group. Whether it even breeds true or not I don't know. But at the time that was very appealing because you had this phenomenological homogeneity which you hoped would produce a biological homogeneity and that would of course provide the basis for prediction. I still believe that if you could find homogeneous units, you are more likely to be able to predict things about them than if you were trying to make the prediction about a mixed group.

Westchester at this time was an interesting place to be, partly because you saw the transition and the struggle right up in your face between the analysts who were on their way out and the DSM III types who were coming in with their descriptive approach. Interestingly Spitzer was at Columbia which was the source of this transition that was taking place - that was an analytical place and yet they were supporting DSM III. There is a good paper by Mitchell Wilson that describes some of the political history of DSM III - that there were a group of people who shared interests who wanted to see this new diagnostic system. I was there when this was going on.

How do you read it. In terms of DSM III coming in there are a few different issues involved. One was the idea that yes if you had a more clearly defined phenotype we may be able to proceed further with our research. Then there was the personality aspect to it. There were the politicians - people like Klerman who were interested to push this forward. There was also the insurance industry and perhaps also the pharmaceutical/regulatory complex for whom more clearly defined entities would be useful.
Well I think that was Mitchell Wilson's point, never mine. In the article he made the point that there were a number of people who felt this dimensional declaration of pathology that you reach some point where you fell off some undefined norm, allowed everyone to treat everyone for everything and this was a bad state of affairs economically and in terms of reimbursement by the Government and third parties. They certainly had an interest but that remember is Wilson

imposing his explanation on a series of events that were going on pari passu and I have no idea how complex they really were. I just know that change that was going on and with the interests that I thought I had at the time, whether I had them or not, the change made much more sense to me. Taxonomic systems depend upon people who are in authority to say that's the way it is and this was unappealing when you're in an analytical training program and people are telling you, well you make counter-transference errors, I only have patients who have negative therapeutic reactions. It was appealing to me to be able to have a diagnosis to which one applies a treatment and then you get a result with a higher probability than if they didn't have the diagnosis. That's a very simplistic notion. When I was 25 years younger than I am now, I really did have much more hope for a diagnostic system that would allow predictions in terms of course and response of treatment than I do now. I see diagnosis today as much less likely to be able to do that. The complexity that has come out of neurosciences makes me think that things are unlikely to hang together quite as cleanly as we hoped they would.

So, at some point up the road, DSM V or VI could be quite different again to III/IV?
I think at this stage it would be hard to say. Maybe you'll have a sudden break in the course of science in the sense that Kuhn talks about and we'll move in a different direction. Maybe the neuro-anatomical concept of diagnosis which apparently drove this era is going to go away. Maybe we are not going to define a disease in terms of its pathophysiology or etiology and we'll talk about phenomena that we manage, that occur conditional upon certain sets of phenomena seen in the individual that we wouldn't think of as being diseased. I have no way of even hazarding a guess. But I think there is something unsatisfing in the diagnostic system now as there was then and I expect it to be unsatisfying for a long time because clearly the concept of diagnosis is almost a philosophical one. It began I guess centuries ago to explain things and there are few things that we ever explain that we explain well. You are lucky if these explanations work some of the time. I don't think I want to be as harsh as I might have been 20 years ago to say these diagnoses don't mean anything. They do mean something. They just don't mean as much as perhaps some of their proponents believe they mean. And if you actually read what they officially write, I think there are a lot of disclaimers about this. These are systems of diagnosis in evolution, put forward on the understanding they have to be modified, its an iterative process, something like fitting a hypothesis to evidence. It's not that you assume the opposite of what you want to prove, get evidence that shows the original assumption is untenable and reject it in favour of the alternative, its a much closer reductionism, where you have a hypothesis about the state of nature, you use it until such time the evidence causes you to modify it. You don't throw it away entirely, you change it, you accommodate the exception you have found. That's where diagnosis is going. It would be appealing for a lot of things I do now, if this was easy to do because it would solve a lot of workaday problems we have.

You also worked in Bellevue in the psychiatric service there at one point.
Not for very long. Less than a year. Actually it was what got me into the FDA. I left Bloomingdales which was a very interesting philosophical training program where I understood better perhaps than I ever did what the limitations of psychiatry might be and I was thrown into the real world of Bellevue where you really had sick patients. Bellevue at the time was undergoing a lot of stresses. There were days when the hospital filled its wards that were capped. I was given a job as head of a unit that could get filled beyond the cap. So we had an overflow of patients, perhaps say a bolus of extra patients admitted because legal charges were dropped against them and they moved from the forensic division to the public, non-criminal section and we might find 6 patients in the morning, unmedicated, undiagnosed, tied down to their beds. I had no staff and after trying to manage this with no resources, little support and less sympathy I think I decided that one part of the City Hospital system was not going to be fixed by me. I think that there are limitations to what the public will spend and very often our institutions are used in a way as a sop rather than a solution. So I was happy to leave. There were a lot of outstanding people working there under very difficult conditions, doing a

tremendous job, it was just not the kind of thing that appealed to me. I didn't think that the kind of things that were interesting to me was going to be acomplished in a setting where I was overwhelmed by a basically under-funded, under-supported system. I hadn't come there with a dedication to save mankind. Some people do, some people have a calling. They want to go into that. They like Bedlam. I didn't. I found it more in keeping with the way I think about things to want to have a larger scale of framing and thinking about things. It turned out the Food and Drug Administration had a program which I didn't know. I found out about it by accident. In fact, I read about it in an ad, probably in the New England Journal, and I enquired about it, met some people and I said hey this looks good.

What was the program.
It was a job in Neuropharmacology. They were looking for a psychiatrist and I thought it was very interesting because it appeared to have a mix of requirements that almost seemed to fit my helter-skelter background. A lot of it was trying to figure out what toxicology meant - my background as a pathologist was useful. Some of it had to do with trying to define what samples of patients were. We were doing a lot of work with DESI, the Drug Efficacy Supplement Implementation. America had a lot of drugs on the market after 1938 that had been approved because of safety. They were safe for use but their efficacy hadn't been established and in 1962 the US law was changed to demand that efficacy be shown for every drug that was marketed and so that there was a lot of retro-fitting. In the process you had to look at claims for drugs that had been marketed and diagnosis became importan. I recall one product had been advanced for apathetic and withdrawn senile behaviour. There would be other kinds of mixed opinion and description and the process of working through that was attractive. There were other things going on that had to do with medicine and the assessment of risks of drugs. It's not something that an analyst or psychiatrist would necessarily be skilled at and there was some advantage to me having had a background in internal medicine and pathology there. It was a place that could clearly make use of what I had and I liked the people and the job and it wasn't bedlam. It was fairly systematic, a chance to think and apply reason and do the right thing. So I took to it and I have been there ever since. That was 1978.

When did it hit you about the placebo controlled trial - the fact that the field at the time was for example using other antidepressants as a control for a new compound but the trial designs might not in actual fact be proving that either drug worked?
I had come to the FDA with no experience about clinical trials whatsoever. I had ideas but basically I wasn't a clinical triallist. If anything I had been a bench researcher, trying to induce models in experiments in rats. Those experiments might have been controlled, certainly we were aware of that, but we weren't doing randomisation of samples. We had inbred strains of rats - it was a different kind of problem. But in the course of trying to understand how we could reach conclusions, I was forced in a way to start afresh. What does anybody do in this situation - I began to read, look and try to understand how one could reach a conclusion. It was immediately apparent to me that if two things are the same, they may in fact be the same because they are the same or they may be the same because the test applied to them is incapable of discriminating that they are different. The FDA was characterised as a place that was out of the mainstream at the time, it was, but because it was out of the mainstream it had it's own sort of internal college of experts and many of these people contributed to my thinking. There was a chap who was actually trained by Ray Hood, at Cornell or Sloan Kettering, Bill Beaver who was a Professor of Pharmacology at the University of Georgetown. He had written the regulations for adequate well controlled trials for drugs that the FDA uses to this day. Bill was a consultant and I think I owe a lot to him because what I know about analgetic backgrounds in drug development, where most of the design structure comes from, came from the work that was done by guys like Modell and Hood and Henry Beecher and the like. They were the ones who worked out what you needed to do to show that 2 analgesics are different or that graded doses were different. What applied in analgesics clearly was going to apply to

antidepressants and it's that kind of cross fertilisation that happens almost accidentally in an enriched enviroment of people working with similar problems that made it possible.

Other people probably reached the same conclusion, independantly working on the same thing. They were dealing with different areas but with the same problem in form. We would meet and talk and there was a lot of fun. Just as we used to sit around in Westchester talking about phenomenology, the description of psychiatric signs and symptoms, so in the FDA in the early 80s we sat around talking about clinical trial design and the flaws and foibles of research models. I was exposed to mathematical statisticians. That was one great advantage we had. I think we were the first and only regulatory agency that I know of that could have a full mathematically trained statistician. They might not know much about controlled trials but the mixture of people coming together made it possible for people to start saying "gee how would I deal with this problem". While I have been there has been an appreciation of things that might have been known to people in statistics but if we hadn't all come together I think would not have moved as effectively as it did do into practice. Let's put it this way, any reasonable person wanting to do a credible job and not knowing what to do would probably have reached almost the same conclusions about these things given the nature of the law, the requirements, existing regs and applying them in their field, as I did.

How come the field took so long to come to that conclusion. They spent 20 years doing the wrong kind of trial.

I don't know that they did the wrong kind of trial, or a different kind of trial that served the purpose at the time. Remember it was not until 1962 in the States that you had to prove anything is effective. Then when you get into the issue of what efficacy means, you are thinking more in terms of the model of an antibiotic but the question is one of potency. How does this compare to penicillin because I don't want to treat my strep throat with anything less. This concept that you could look at the effectiveness of drugs is not being looked at in quite the same way when you deal with psychiatry. Luckily there were parallel groups there going on, I mean why did Max Hamilton write a paper in 1960 asking for an assessment instrument - for a Hamilton Scale for Depression. Certainly people had been playing around with factorial analsysis and other such things, but I think what happened was you were getting people doing trials who wanted to be able to measure effects. I don't know what Max actually did develop the HAMD for, was it a drug study, do you know?

I don't particularly think so. I think he had it before the first antidepressants came on stream and found to his pleasure and suprise that they seemed to fit hand in glove. In fact it did fit extremely well with the first tricyclics .

Yes I think that's true in other areas also. The scales that we have eventually used to track dementia were developed to measure the longitudinal progression of the illness without intervention. The fact that in a longitudinal study they were able to detect a difference then suggested that if you modify it it could be applied for looking at drugs. We have had a lot of problems with issues of how one assesses outcome. Luckily we didn't have it with depression or really with anxiety or the analgesics. In other areas we have had. But I think that what went on during that period of time is that people made a lot of assumptions that have been held throughout time - for instance the assumption that when one observes a change after one has applied a treatment, that the treatment accounts for the change, even though there were critics, probably in the mid-30s, who were clearly calling for the use of controls in the study of infectious disease. I am pretty sure that in Bradford Hills Textbook, which was the first clinical textbook of medical statistics from about 1937, issues of the design of experiments like this were understood. It was just that people in medicine were used to declaring that what they knew as a Professor was true. It was this authoritarian "I know - my experience teaches" and I guess it took examples. Certainly by the mid 50s in the States, there were all sorts of people who were crying for the need for controls to determine whether drugs worked. I can't know why psychiatry didn't pick it up right away. Maybe it did but maybe the people doing the drug trials

didn't because they served their end without ever needing to do them and it was really an accident waiting to happen. They were going to run into somebody some day who was going to say, "wait a mintue, this trial can't prove what you claim it proves". I just happened to be the realisation of that I think.

But that was in the early 80's,
Yes. I am talking about a drug trial and registering. If you can get your drug approved and if in all of the world people are saying, gee I used imipramine and this drug and I failed to distingush in a sample of 12, between the outcomes - that's great. Another part of this was that you happened to have things that fall into your lap. We had one drug which had been marketed in Europe and in the course of working it up in the States we happened to have a set of 3-way control trials - there was both placebo and an active control in that particular set of 6 trials. If you had only looked at the active control comparison, leaving placebo out, it would have shown in every case no difference between the drug and a standard which I believe was imipramine. But when you looked at the placebo results of that trial, you find that in only one of the 6 trials, were we able to discriminate between either of the 2 active drugs and placebo. It just so happens that even though drugs work, because of sampling issues you often fail to be able to show that the drug works and if that's the case, you can't rely on a finding no difference. You need to have a finding of a difference. I have probably said this a thousand times - these ideas of what you need to show something causal go back to discussions of John Stuart Mill in the 1840s in his discussions of methods of deduction and logic. He argued that the method of difference is far better than the method of agreement. Written 150 years ago, why didn't that get into the consciousness earlier, I don't know. I guess people didn't need to do it so they didn't bother.

Authority really was a big thing. Chatting to Michael Shepherd who was one of the first triallists in the field with his study on reserpine in people who were anxious and depressed, he said that no-one has paid any heed to the result and it wasn't because they published it in an obsure journal, like the Lancet, it was because they had tables and figures and methods and all that and as he put it the field was just not used to that. They were used to the expert saying "I gave this drug and I saw such and such ".
People have tended to diminish statistics. There has always been sort of a fear of it and at the same time a dismissal of it. People often celebrate what they call a difference between clinical significance and statistical significance, without knowing what they mean in either case. Certainly I take the point that one could, given enough size and luck with variance probably show a difference between two treatments that is so small that no-one could care from a clinical perspective and that's usually the case that marched out to say "ah ha, you can have statistical signicance and not clinical". On the other hand to say that you can have clinical without statistical is even more mystical because if the differences can't be known to differ from chance, how can the significance possibly be clinically important. That kind of inverse logic is the same as when people talk about life, they are functional or Bayesians but in our decision making for clinical trials we're frequentists. I think a lot of it has to do with what is the purpose for which an epistemological method is being applied, what do you need to do. If you go and secure approval of the drug, why would you chose a methodology which was doomed to failure and more demanding if you don't need to. So a lot of it depends upon people thinking it though.

Now if you go and look are our regs which were re-written in 1987, they spell out very clearly that the historical and active controlled trials are not particularly useful when they are intended to show similarity because you can't interpret that in conditions where the outcome being studied is variable, changing over time and unpredictable. If we were talking about anaesthesia and both drugs put both of us to sleep within a minute of the time we had it, we don't have a problem because the controll really is a historical control. You know from the result in the study that the outcome is different from what would have happened had no drugs been given. The problem in the antidepressant trial is that you don't know that and we have these counter-

examples that document you don't know. Several people have come at this now in arthritis, depression and neurology and it really has been changing although clinicians will still tell you, in diseases were, most people would recognise you can't ...

Take epilepsy where in fact the patient has a disease but most of the time they are not symptomatic and then at irregular intervals they emit an event called a seizure, sometimes not even a seizure but some behavior somebody calls a seizure. Somebody does an open study - Dilantin was discovered this way - and says "ah ha, the frequency of seizures I see now is reduced over what I saw before, therefore the drug works". Well everyone understands that this is such an unstable thing, how could you possibly reached that conclusion? I suppose if you had patients who were emitting seizures, every single hour, every single day, and you suddenly gave it them, and they had none, everyone would believe it. The problem is always the nature of the sample you are looking at. What works well at one time won't work well later. This is anecdotal but we saw something like this with Clomipramine and OCD. When we first did a trial with placebo in OCD, if I remember correctly the patients assigned the placebo, did not change - they didn't budge. But the people who got clomipramine - they weren't cured mind you, nothing cures it - were better and you could see the difference by eyeball. Now we have subsequently seen a lot of drugs developed for OCD and lo and behold, that placebo population no longer shows no response. To me that suggests some kind of diagnostic drift. I don't know whether it's a secular drift or a diagnostic criterion drift but they are not the same groups. I think that speaks to this issue, that when one makes assumptions about something being solidly proven and then relies on that proof as the basis for reaching an assumption, the drug may no longer be working in the same way in that sample. It all speaks to this issue of assay sensitivity. As I think everyone remarks in every field, something can be known in one area of science and it takes decades, sometimes centuries for a move from that to another field. Maybe its just the wrong people didn't talk to each other but someday somehow, somewhere, somebody recognises this and then of course - it's obvious. But I don't think any of these things are Kuhnian steps in science.

But this was extraordinarily obvious when you look back.
Well the equities were against it from the drug company, development, commercial perspective. It is a more demanding standard and I think that people who want to approve drugs rapidly clearly would find it an impediment. Not only that, it's also unfair. One of the things that industry complains about is that they initiate a program in good faith and half way through the game the rules are changed. Now I doubt whether they really had contracts with anybody even in the "symbolic" sense of the word but they may well have started studies in the mid 60s and early 70s and were finally bringing these studies forward at some point say in the late 70s. At that point someone brings up something up - well they can't be faulted in 1980 for what they did in say 1970. They may have been doing what was state of the art but by the time they got around to evaluating it, it was no longer state of the art, although I am sure that if you talk to people who were on the NIH side, they had controlled trials. In fact we used to go to them. That was another thing I should have mentioned, I had the advantage of having in the same building on the same floor, even though its a half a mile away almost, the somatic and treatment research branch of the NIMH. There was Nina Schooler and Jerry Levine, Bob Prien and other people. It was a good place to be because you had people with common interests and you could chat to them and they were very helpful to us.

Did the NCDEU program play a part in all this?
I think they certainly were a reservoir. Al Raskin for example was somebody who did a lot of consulting for us about the application of statistical principles to clinical trials and although I couldn't associate any one of these things with him when we had a factor analysis issue he would help. NCDEU didn't have any programs along these lines but the people in the field at the time were doing active control trials and I can't think of anyone I knew there who didn't say you have got to have an adequate control but I am not sure they drove it in that sense. On the

other hand, I think having a group like the somatic research and treatment branch at that time, Cole and Klerman's old unit, was very enriching. Having a lot of people in your area is like being in a good University where you have people around who are willing to talk about what they are doing. It was a pretty rich environment as my Division is now but for very different reasons. I want to be careful not to say that a lot of these things aren't just purely a function of the time. If you say it was me, I am not a psychopharmacologist. My business is to assess scientific evidence and the quality of the assessors. In fact I often think of myself now more as an expert in what experts can and can't do and what they can reliably testify to than in the details per se. This is part of what anybody at the FDA would be doing - when my expert tells me something, are they in a position to offer me a judgement that derives from a well thought through body of evidence or fact or are they, in fact, doing no more than offering an opinion from the top of their fantasies?

I wouldn't know one form of a receptor from another and I don't really care anymore, although I certainly would have gone through periods in my life when I cared vitally about allosteric hindrance and different forms of binding. Today that's a detail that is irrelevant to me although it might be very important in determining whether a drug is effective or not. It's not the level that I look at things or want to know. It's important in the sense if someone comes to you and says well this drug does such and such and I can ask them "how do you know" and if they give me an answer that seems to be inconsistent with the kind of reasoning that I expect to see in a qualified expert that would let me downrate their testimony. We recently had an interesting situation that involved a very difficult question of an anti-psychotic that produces a change in ECG records. I listened to experts on both sides of the aisle give me very different views about what significance those changes had and I was struck by the fact that none of the experts could do much more than offer guesses. What you do then is another type of decision but that's the classic example of where you're getting involved in an area that you can't possibly know as much as the experts but you listen to them and try to decide how do they claim they know what they know.

You have alluded to the industry having to shelve some trials. Do you think it had a big impact on them at the time ?

I have no way of knowing. I think there were many individuals who I am sure were frustrated by the fact that they had what they thought was a portfolio that should have been accepted as sufficient to bring about approval. They came in and they had this whippersnapper who doesn't know anything telling them that they couldn't get from there to here. I am sure it had an impact. Whether it's the one that was appropriate I don't know. I wasn't doing it to screw them over as they might have thought, to exercise power without limit. I recall I wrote a memo to the Center Director at the time announcing how crazy the situation was, and that we should do something about it. I didn't get an objection back so I thought that was license to do what we did. But, it was that kind of stuff - you never know. You might take the position and have someone say well we have a precedent for not doing that, you can't do that. Not every rational thing I wanted to do is instantaneously possible. I think it's very clear that there are many policies that I would love to see in place, but simply because I would love to see them they can't happen. We live in a time in which the level of regulation has to be adjusted to what the political support for it is. It's not just science logic. We have the people who believe we are not doing enough, attacking us because we are not stringent and demanding and the people who are saying "well you are just keeping off the market drugs that are going to save lives for the American public". These two complaints are incompatible with one another. You can't be proof positive without being slow and deliberate. Clearly the agency as a political unit is trying to respond and do everything, speed it up and do it better, and to the extent they succeed great. But I think there is a certain tension there. A lot of these questions are complex - the kind of thing that even if you are smart and you've been doing it for a long time, it pays to think about it and sleep on it and may be do it again and look at it in a different way.

One of the criticisms you were potentially open to and I am not sure how much you heard it, when you insisted on the placebo control trial was that it then became a means for companies to introduce an antidepressant that wasn't potentially as effective - that it could be superior to placebo but not necessarily as good as the old ones.
Well I don't think that's a fault that I would have. I would be the first one to say that the fact that you could distinguish yourself from placebo even on a measure alleged to be valid for the purpose for which it is put, such as testing an antidepressant effect, opens you up[to the possibility that what you detect is something that the scale registers rather a true antidepressant effect. If you couple that with the fact that you can "overpower" the study, you can put so many people in it that its a stable difference and the variance doesn't blow up by some accident, you can come up with a significant difference and on effect size that on the average is so small that it's not worth very much. The problem is that from my regulatory perspective nobody knows what is the minimum size effect. I suppose under the law because we are asked to rely on the judgement of experts about the quality of the evidence and what the evidence allows, they could say this amount of evidence does not allow someone to reach such a conclusion. I think the policy has long been that when a group really feels that way then they should look very carefully at the panoply of risks involved. If it's very risky you go along with it, but if it's marginally risky you say look, the way we calculate p values is based on some distributional assumptions that may not be true. Somebody out there might benefit from this drug and accordingly given the act of the law and even a small effect, if it's not risky and we can label its risks appropriately the drug should get out there.

The argument that we should always have an active control trial as a standard is something I'd love to see for the practice of medicine because I think there would be few of us whether we practiced medicine in the past or now, who wouldn't want to know in a fair way how 2 products perform, comparatively over their dose range. But if you think about the problem we are really talking about something that exists not only for the outcome measure in a particular frame in terms of benefit which can have several different dimensions, but the risk factors which are distributed over countless domains which we can't even enumerate. Not only that drugs differ in terms of their regimen as well as their dose and how long they are given and when you look. So you have this very very complex multiple domain problem in which you are trying to compare things. It is an almost impossible problem. It's one of the reasons why I feel strongly that comparative claims are dangerous. People often fix the conditions under which they make the comparison to make them look better. That's why we are sometimes more sceptical than companies like regarding claims made for some new generation drug - because they set them up in such a way that they have looked against people who fail on the old drug; they pick conditions that make the new drug look better. Now often they are right or they can't do the experiments that they would really need to do so in the real world you settle for a compromise.

The critics sometimes want us to show that the next drug is better, well on what dimension and under what conditions? If you think it takes a long time to get drugs approved now, if that there a pre-marketing requirement we would be here until the end of time because it would be very hard to do.

It may be in this age of managed care and economic concern that third party payers, insurers and governments are going to force this upon us and I am sure if we are forced to do it, the agency or some other group who gets charged with it, in France they already have it, is going to look at the drug and says "yes effective but not marketable". We can't pay that much for this effect size on average. Costs too much. Take Clozaril and the no blood no drug policy in terms of its distribution in the States. There have been a lot of economic arguments that have been made; you could say "look, you're saving lives on what we know about the cohort has been followed, we've reduced the incidence of case-fatality from agranulocytosis but if you go through the usual pharmaco-economic calculations, the cost of saving a life here is astronomically high, therefore it's not a good bet". You could provide the drug to people without

this no blood no drug policy and you would do away with that problem, so why are you doing it, it's not cost effective. Well cost effectiveness isn't only measured in the economic domain. It might be measured in the public confidence domain. If we put a drug out that caused a lot of absolute cases of death etc, it might be damaging to the confidence of the public. I think you can rationalise these things any way you want but I don't think they are a single dimension problem and that's why they are so hard to solve. What's a good solution for the regulator is something which is consistent with the law and is one of many solutions that is acceptable. It doesn't have to be the perfect solution, no such thing exists. There might be other ways to do the same thing who knows but I don't think you'll ever really have a way unless the drug is clearly better to be able to say that with great confidence, or make it a requirement of approval under current rules.

In terms of fast-tracking the registration of drugs and of challenges to the placebo controlled trial, the whole AIDS thing blew up a few years after a requirement for placbeo controlled trials were introduced and all of a sudden the ethical aspects of it all came on the agenda again.

I think the AIDS thing is related to denying people immediate access to drugs they need to save their life. Somebody who wants to make that argument then goes and pulls out the declaration of Helsinki and they say look it says that in research with human patients, no subject should be denied equivalent or immediate access to the treatment that is thought best for him and that includes the control. If that's true, you can't do any research, so there is a certain incoherence and inconsistency here. The problem I think you have is that everyone in drug regulation politics is trying to scare the public about the consequences of the current system. When the FDA wants to gain an authority it has long said look how dangerous it is. If you are going to put out dangerous drugs that are going to kill people, you might be about to waste your money on ineffective drugs with false claims. The counter-argument is that may be true but you are much more likely to deny people access to drugs that save their lives. They go out and they look at beta-blockers in which the FDA took a very stringent stance that was eventually overturned. At the time, people said look at all the lives that were lost because American's couldn't have it and we got the pharmacoeconomic argument.

You can play this game anyway you want but I think what came along with AIDS was the idea that there should be no delay. It wasn't just an attack on placebo controls, it was attack on the efficacy stance. I think the placebo control is a stalking horse people use. You could use a graded dose response, you could use an active control - the goal is to show a difference, it's not to beat placebo. It so happens the ethicists who are often no better than the "scoundrels" in this are pushing some vision they have about why its important to do something they call protecting the interests and autonomy of the individual patient, which I celebrate as much as them, except I don't think they are doing it the right way. One of things I think they are doing wrong is to go after placebo because they can invoke this image of someone not caring about the patient but yet they are willing to let patients be exposed to drugs that have never been tested and that are not known to be effective. The idea that we need placebo isn't the point. What we need is an assay sensitive trial and the fight with AIDS was that we don't want a test of efficacy. If anything will work give to me, I have got nothing to lose.

We see that in ALS. Now it so happens in the States there is tremendous pressure to say "look, ALS is such a devastating disease, with such a predictable and miserable progression that if a drug has a slightest suggestion that it may work, it should be available no matter how little you know about it". You have to admit there is some appeal to this and yet it's interesting over here, the Motor Neurone Society had a different view. They said "it is important to think not only about curing patients but patients yet to be". That's a utilitarian view not this principalist deontological position. They said that we as a society advocate fully controlled trials so that in the future we will know whether our treatments work or not because the worse thing that can happen is to flood the armamentarium with products none of which works. What AIDS did was it made people scared that lives would be lost because of a delay to immediate access. The

placebo was sort of an innocent by-stander that got beat up because it was a prominent example. The real issue is do you need an efficacy standard. That's the fighting going on in the States right now. You really have some anti-regulatory forces who say "look, let the market place sort it out, as long as the drug isn't manifestly unsafe in the way the famous elixir of sulphanilamide was, it's okay. "

The attackers of the randomised control trial sometimes point to outcomes research. Where did all that come from, who were the key players?
I don't know who the key players were. All I know is that it appeared pari passu with this business of AIDS. When somebody says we can't afford to wait for you to do epistemologically valid research, give it to us now, we'll figure it out in some other way, they sometimes add if the drug really doesn't work we'll pick it out in outcomes research. There are other people involved in outcomes research for other reasons. They say look there's a difference between efficacy and effectiveness. A drug may work in a test-tube but we want to know if it gets matched with the people that need it. That's a legitimate question but I don't think it answers the question about whether or not drugs work, which is what I want to know. I don't think you could know that from an outcome. This I think was something being sold by people who were stepping into a place where there's a demand to get us these drugs faster and get it quick. I like to use as an analogy here a television program called Name that Tune from many years ago. Contestants would bid how many bars of music they would need to identify the tune. They would be given a little hint and then the contestant would say "I could name that tune in 5 notes", someone else would say "no 3 notes or 2 notes". Somebody even said "no notes" - that was from someone who understood from the clue what the answer is likely to be. Well a lot of this business with drug approval is getting that way. You say gee you can't really have valid evidence, I wonder if therefore we can use a lesser standard. Finally you'll have no standard at all, you'll have a theory - yes it does bind to the third lymphocyte from the Sun ergo it must work because I have this model in which it will work.

That's surrogacy. Now we have recognised surrogates but they are used in a peculiar kind of way by some people and legitimately by others. You have to be careful because its not a direct method of inference. You are taking something that stands for what you are interested in. There may be a reason to do it but it might mislead. Everytime you make one of these exceptions you increase the risk that you will falsely say the drug works when it doesn't. Is that terrible, well if you think the big risk is missing effective drugs, and denying people access to them, I guess not. But my view is that the past showed us, although the past is not a perfect experiment, that if you didn't take care you got an armamentarium filled with junk. People will say "ah that was the past, now reductionist science has advanced so far, it's not going to happen anymore". Well is that true? My experience of seeing new drugs being developed in the last 10 years is that we have loads of miracles, advanced in every corner of modern science, they get into clinical trials and no-one can show they have an effect. I think many things born of a rational scientific logic simply don't turn out because we don't understand enough or we are just dead wrong. The model isn't applicable. If we believe every risk seen in animals prevented drug development in humans we wouldn't have any drug development. We let loads of drugs go with the philosophy that changes in an animals organs mean this simply is a target organ to worry about not a proven risk. Risk comes from people with one or two exceptions. The same thing goes on the efficacy side. Someone might have a wonderful model for changing the behaviour after a stroke where they tie off every vessel going to the head of a gerbil and they give the drug half an hour before the gerbil gets his vessles tied but that doesn't necessarily convince me that they have a stroke drug. Sometimes they will but I think the venue for deciding whether it works still ought to be humans in a controlled setting.

I think people have a right to take placebo with informed consent. I have concerns about doing research with people who don't give informed consent, although we recently allowed that in the States in people with head trauma. If you say that everyone ought to always be given the best

treatment because somebody after World War II was very upset about the behaviour of Nazi's, that necessarily today translates into stopping valid research. Then I think we have a problem. I am referring to the things like the Rothlin and Michael's piece in the New England Journal a couple of years ago in which a broad side is launched against the use of placebo that shows the people who wrote it don't even understand why placebos are being used and yet they are saying it is unethical.

The randomised control trial is clearly a powerful means to produce evidence that things work but its also extremely costly means to produce evidence and the problem with all of that is that powerful interests will tend to be the only people who can produce the evidence. So you are forcing a certain corporate development on the field.
No, I'm not. If the drug effects are large and really major breakthroughs you don't need a large trial. The reason we need large trials is the drug companies are trying to produce and sell drugs that have relatively modest effects, relative to the size of the variation in the phenomena they are trying to treat. If we had a drug that truely was a major breakthrough, how big a study would you have to do? It would be done easily by the academic single investigator. I think the problem is that a lot of the drug effects we are trying to sell are fairly modest. I would say big deal. You are not going miss the miracle, you are not going to miss the big effect. The other side of the coin is that you are going to have to wait for the evolution of science to the point where you really have the more homogenous units that we were talking about earlier, where the homogeneity relates to the ability to respond to treatment. I am convinced that everyone of our homogenous samples, as much as we try to enrich it with potential responders, actually is a mix of indviduals who can respond to drugs and those who can't or who respond only slightly. Clearly if you want to do an experiment that really shows you whether the drug works or not in the explanatory sense, you want to find a way to test it in the circumstances where you really decide that question very officially. You have got to find the tools to find a pure set. The question after that is what fraction of the population posesses this trait. There outcomes research and other epidemiologic techniques might be wonderful.

Within subject designs is another possibility. If you really want to prove a drug works, it is in theory possible to prove it will work within a single individual. The problem would be what fraction of the population that applied to. The Act doesn't deal with fractions of the population. And I suppose you wouldn't have answered questions such as how risky is the drug. I don't have the answers to these things but I think that a lot of people are interested in them and it's the debate that may be useful. Because as these things get kicked back and forth, you have the need, you have the objection to the solution, you have a new solution to the objection and you iterate toward something that will do a better job. Along the way the job people like me should be doing is saying "well just look at the price you are paying for this if you do it by cutting back on epistemological validity". Maybe we ought to go back to a safety-only standard if such a thing is possible, without considering the context of use but I think the system of having efficacy established as a "proof of principle" is fine. This is what I call it because I would agree with the people who criticise us that the estimates we get from clinical trials don't really tell us what the distribution of effect is going to be in the population. If you want to find that out you have got to go and find out what the homogenous units are in the population that control response.

You think that pharmaco-genetics will play a part here in due course?
Pharmaco-genetics is being used here as a code, as a means of finding those predictors. Yes, if that were the source of it - it could be some mixture. To the extent that you could identify all factors controlling response, then you would be able to say that here is an individual that has 50,000 of the 150,000 factors, therefore we can predict this kind of response. I don't know that that will happen, but it is theoretically possible. With some dimensional reduction maybe you will need only 10 factors to tell you everything.

At a BAP meeting 3 years ago you said that your job is to act as a lens focusing debate.
Well basically what we apply is the result of a lot of different forces that act upon us and we come out at some equilibrium position. I think the debate is where we play a role. But only one part of it. In the sense of lens, we take societies' inputs and project them out to the world. If a body of experts who advise us and everybody I deal with doesn't agree with us, there's nothing that I could do ever that is going to be sustained. I may want to influence people or argue with them but you really have to be consistent with your time. You are like a lawyer, you go to court, you think you make your case but you don't necessarily win every case you believe in. I think people attach in an ad hominem way to individuals decisions and actions that really are institutional ones. Anti-dementia drugs are an example where the institution is doing what it wants, it's not an individual thing. We are the one nation now that I think has a drug approved for dementia and we have just approved another. Its fascinating how standards change - here we are the obstructionists in the States but we have moved ahead on this one.

On the dementia guidelines issue, let us come back to a point you were making there. You were saying about that at one point that really what you do is you get the field to come to a consensus but people on the outside often see it as your business to lay down the law which is not what you are saying you do.
Actually, what we are supposed to do is very clear. The process by which the law, usually written in terms of what Congress wants, is construed is through a process of regulation making or rule writing. What happens is that there is a prescribed process, where the agency proposes a set of regulations, sends them out for comments, adjusts the regulations allowing that way, supposedly, everybody affected by regulations to have some input. The FDA is never expected to lay down the law. It's supposed to, in good faith, interpret the requirements of Congress, which are often fairly vague. We do the same thing in each expanding level in this hierarchy. So when somebody has a regulation I try to interpret it. We have 5 different types of adequate and well controlled trials that we recognise, I try to look and see which of those apply in the various areas. We entertain the possibility all the time that a historical control might be okay in ALS for instance. There are people who believe subject's-own control should do - fine if you get a big enough change in slope. So you just don't come out and apply this - it is all iterative but what you don't want to do is change the principles - that's what I'm trying to fight against.

In 62, people moved towards encouraging the industry to develop drugs for disease entities. They wanted to move away from the idea of non-specific compounds, such as tonics...
Well, let me make a point. Under the definitions of a drug in the act, it is either something named in one of the pharmacopoeia officially, or its something which makes a claim to have an effect on the structure, function or body of man or appears to do that. There are some exceptions to that now, in the sense that we have this law 94 which allows claims that aren't quite drug claims to be made for functional things - such as helps the colon, improves well being. Those are close to your tonic claims. They are not given the strength of drug claims. I am not even sure how they are being handled but they come about because Congress in its wisdom said American's shall be allowed the benefits of vitamins for example and so on. Under the Act, if you have a symptom that is legitimately recognised in the community, you can have a drug for that. You could have a drug for acute anxiety. You don't have to call it generalised anxiety disorder. I would admit it makes it easier for us in terms of identifying appropriate samples to have a more elaborate structure and call it a diagnosis. Pain drugs are a classical example, in which general pain claims are given, usually evaluated in several pain models and yet we also have specific pain, we have migraine. Well how did migraine get separated out, perhaps because they think it has a distinct pathophysiology as compared to other pain. But generally speaking there are people who will tell you that NSAIDS and opiates work fine in migraine and a good fraction of migraines may in fact be tension headaches and for all I know a good fraction of tension headaches may respond to 5HT1-D agonists.

It's very hard to know but the law is very forgiving unless the claim is so vague as to be seen as false and misleading. I mean apathetic and withdrawn senile behaviour, I have no idea what that is, its in the eye of the beholder. On the other hand, age associated memory impairment, was one we toyed with for a while. If you have a symptom or sign or use that was legitimatised that's okay but we are going to have trouble with the feel good or do better claims not because of the drug claims but because of the attitude people will have about their risk benefit. This is like short stature use of growth hormone. Its not clear whether it works, maybe it works in a small fraction of kids with short stature but should society approve that use? It's a major fight. We allowed it. There are others. What about performance on exams? We might say "gee amphetamines really do improve performance". Probably some evidence they do. Why couldn't you get approval? The risk will be cited but what if you said you want to make a new one that releases dopamine that isn't dangerous. If you then had this drug that improves the exam performance, I can't think of a reason to disapprove it except for the fact that the risk it might impose is too great to tolerate such a trivial gain.

So, let me come back. Some of the antidepressants for instance then could have been developed as a tonic. Has the industry made a mistake ? You see at the moment we have got very bad compliance with antidepressants, it would seem, is this because compared to compounds like St John's wort in Germany, which is a problem of living compound, a pick me up, a tonic and people say "yeh you know, I'm under stress, I need a tonic" , but in contrast with the antidepressants, for you to get one you have got to be sold a disease as well.

Well if you believe depression is a disease and not a collection of phenomena ranging from disease at one end.... It goes back to this argument, what's a disease. In a taxonomic system it's hard to know. We would probably take anybody's homeopathic or over the counter medicine and subject it to a standard test but you still have to have the population suffer from something that can be identified fairly reliably. Now the minute you get into something like apathetic dejection or some quasi-description judgemental thing, it's very hard to do.

Sure but would there be anything to stop someone like Bristol Myers Squibb at the moment for instance calling nefazodone a tonic?

Yes. Probably because we would think that is false and misleading. Which is a requirement of the Act. Because I don't know what a tonic is. What would it be promoted as?

It improves sleep, it improves appetite ..

Then why don't you make those claims. Each one of those claims is obtainable. If you really do improve sleep. You can show that. If you really do improve appetite, maybe you could show that. But what is improved appetite? I like my food more, I have a zest for eating or I gain weight. It becomes more difficult to assess it. We have people who want us to approve drugs for aggression..

Wouldn't it be easier to assess improved appetite or sleep or reduced aggression that to assess improvement in a disease state?

Well improved sleep, I think that would have difficulty because the question is what happens if you have no change in total sleep time? What's improved sleep. If the idea was that people more often said they had improved sleep, it would be a tough call because you wouldn't know what you're dealing with. In theory before the fact, it would be very hard to know how to approach any of these except in an open mind. We are not there to say that people can't make claims but you don't want them to make claims that are subject to misrepresentation. Somebody who wants to say a drug works in a particular disease where some phenomenon is troubling and yet they just picked it out of many diseases where it is troubling poses a problem. We have a lot of people who want to push antipsychotic drugs in the mentally retarded who are behaviourally aggressive. Now is that really a diagnosis. Or is that a recommendation for a sub-group use in which they think they can promote a drug. It's somewhat misleading because

it sounds a little specific. It's like me saying "oh yeh use this drug for anxiety in New Jersey housewives".

I am not saying that we've nailed this all down. What are the interests to the public, how much do you want accuracy and truth in labelling. There's a whole movement that says "look labelling is like free speech, how dare you impose any limitations". Then why do we controlled advertising, why do we care about false and misleading advertising, why don't we let people go back and sell snake-oil? Clearly society decided to limit free speech in some areas, especially in economic areas. You can't say your lard which comes from hogs is butter, by adding yellow to it - why? Free speech you know! It comes out of that kind of heritage. I don't know where we'll end up.

Coming back to the improved sleep front. Janssen some years ago had a 5HT2 blocker, ritanserin, which as it turns out now, you could argue is a therapeutic principle in schizophrenia - when you add in 5HT2 blockade into a D2 blockade you seem to produce something useful.
You have to prove that...

Well that's the way the clinical trials seem to come out at the moment.
It so happens that drugs with those 2 properties have but then again they have a lot of other things that we don't know anything about. Certainly this current generation of anti-psychotics has been pushed becuase of that combination that it, of ligand affinities but that doesn't mean that it has anything to do with what they are really doing. Its a good bet but if you really wanted to prove that, then you could do a combination study of a pure D2, a 5HT2 and a combination and show that .

But aren't we stuck with a problem here which is when they had their 5HT2 blocker in the first instance, which I think was actually developed for use in schizophrenia because LSD acts on the 5HT2 receptor but it turned out not to be useful as a single free standing agent for schizophrenia. Arguably added in to say Haldol decanoate it would have been extremely good but who was going to do that kind of trial.
Well they could have done a fixed combination product and proved that it worked.

Are fixed combinations still legit...
Well they would have done is the combination, the 2 components and placebo and then you look in a factorial design and see whether or not each element makes a contribution. If you find out that the antipsychotic does as well as the combination then it means that the 5HT2 makes no contribution and you forget about it. They could have done that.

Isn’t that what happened to Limbitrol where it had been shown to be superior to the individual component but the ...
Only unfortunately early on. You see there's an example of how well do you have to study a drug to make it an antidepressant effect. Limbitrol’s difference between Chlordiazepoxide and I guess Amitriptyline alone, was in about 2 weeks. They were supposed to look late at about 4 weeks, to see whether or not they came together because people at that time were concerned that a benzo might in fact show some symptomatic improvement and there was concern that it had a differential effect at an earlier time point. However, that's another can of worms. But I think the idea would be that any product could be fixed combination. There are products where people could make 2 drug products and probably demonstrate in a combined way that the drugs in fact had a combined effect and you could probably celebrate that in the literature. To what extent you could get that in the labeling of a single drug is interesting. Perhaps in the controlled trial section of the description, because it would be looked upon as contributing to the efficacy of the drug and you can describe things that will modify the efficacy of the drug in labelling. It's a legal question that we would have to address at the time.

I think this is going to happen more often because I think people may want to be able to use combination therapies especially in areas where multi-factorial diseases are involved. Its certainly coming up in ALS, where you appear to have drugs working by different mechanisms perhaps and you might want to use them in a combination. How do you do that? Do you do a joint trial and both drugs get the credit or does only one get the credit? These are hypotheticals that have to be decided on an ad hoc basis but I don't think the agency or any other sensible group of people charged with this would ever want to keep information that's truthful or not misleading away from anybody. Whether we can promote is another story. I am not responsible for, nor can regulation be, for the economic incentives. If society wants incentives, its the old business called subsidy. You could do it by supporting research and you can do it by direct grants in aid.