

## **MANAGING UNCERTAINTY**

### **PAUL LEBER**

#### **Why did you choose to become a physician?**

MY father had a lot to do with my choice of career, although not because he ever directly encouraged me to become a doctor. A paediatrician, he practised in the days before medicine was reimbursed at a rate to make physicians wealthy. In retrospect, little about his work-a-day way of life seems especially appealing, let alone glamorous. To the contrary, his practice was extremely busy. He worked terribly long hours, and I remember him being more often than not, on the verge of literal physical exhaustion. Yet, his way of life brought him an abundance of respect and admiration, and, as a child, I suppose that was what most impressed me. As far back as I can remember, when anyone, be it a patient, colleague, or tradesman learned that I was my father's son, they invariably seemed compelled to tell me, in glowing terms, just how wonderful he was - competent, reliable, dedicated etc.

Early on in life, I resolved, as so many others have done, to be like, even better, than my father. And so, not too surprisingly I suppose, I set out to become a physician. Once the choice was made, all that followed was derivative - going to a "good" liberal arts college, majoring in chemistry, a "tough" major for a pre-med, getting the grades to gain acceptance to a "good" medical school...etc.

#### **Then into pathology ?**

No, immediately after medical school my post-graduate clinical training was in internal medicine. But the story of my peripatetic medical career begins even earlier. I first wandered from the ordinary path of training while I was a medical student. Between my third and fourth years, I competed for, and was awarded, a Medical Sciences Year Fellowship in enzyme kinetics. A fore-runner of the now prevalent MD/PhD training programs, the fellowship program was intended to foster the development of a cadre of physician-scientists who would pursue full time careers in academic medicine and research. It may seem somewhat odd that someone who had presumably entered medicine to become a clinician - to follow in his father's footsteps, so to speak - would take such a step, but, in light of the environment prevailing at NYU at the time, it is readily understandable.

At NYU, perhaps more than at other American medical schools at the time, the prestigious members of the faculty were known for their academic and research accomplishments, not their clinical skills or acumen. Numbered among the faculty were world renowned luminaries in science and medicine, among them Severo Ochoa who won the Nobel Prize in biochemistry while I was a student, Lewis Thomas, Chair of the Department of Medicine, who, incidentally, although a medical essayist nonpareil, was anything but a skilled clinician, Homer Smith, the famed renal physiologist, Otto Loewi, yet another Nobel Laureate, as well as yet to be acclaimed innovators in the field of immunology such as Baruch Bannacere. Thus, by the time I had completed my second year at NYU, my interest in clinical care had waned, replaced by hopes of a career in academic medicine and research. No doubt my "conversion" was assisted by the discovery during my third year that, unlike my father, I had no "calling" for the practice of clinical medicine.

In any event, based on the work I did during my fellowship on the modification of enzyme active sites, I earned an "MD with Honours in physiology." I enjoyed working in the lab and I gave serious thought to foregoing further clinical training and pursuing a full time career in bench research, but I was strongly counselled by my advisors that an MD, even one with a seemingly hot hand at the bench, needed clinical skills if he was to pursue a career in academic medicine. And so, heeding their advice, I went off for clinical training in internal medicine. Following an internship in medicine at the Johns Hopkins in

Baltimore, I returned to New York City, serving for a year as a resident on NYU's medical service at Bellevue Hospital. My experiences as a medical intern and resident persuaded me, however, that the day to day life of the medical practitioner was demanding and it would be exceedingly difficult, therefore, to be simultaneously both a good clinical internist and a productive bench investigator. That judgement is primarily responsible for my decision to train in pathology, a field in which I concluded teaching and research could more readily be pursued simultaneously.

My decision to become a pathologist proved short-sighted, however, because, I suspect, it was driven too much by reason and too little by enthusiasm for the substance of the field. Although the intellectual content of pathology is extremely interesting and basically one and the same as that of medicine, I found the day to day chores that constitute the actual practice of anatomical and surgical pathology only marginally tolerable. My lack of intrinsic enthusiasm for the practice of service pathology notwithstanding, I completed residency training, gained Board Certification in Anatomical and Clinical Pathology, and, subsequently held academic positions in the Pathology Departments of 3 medical schools. During my years as an academic pathologist, I taught - an activity that I truly enjoyed - and pursued a number of research projects in renal pathophysiology and immunopathology.

### **Why did you move then from pathology into psychiatry. Its an extraordinary jump**

As the years passed, I was forced to accept the fact that success in research requires more than clever ideas, hard work, and long hours at the bench. Perhaps, if I had truly enjoyed the day to day practice of pathology, I might, as have so many other fledgling academics whose careers begin to stall, gradually shifted more and more from bench research to the service side of pathology. But, for me, even the thought of such a move was intolerable. And so, some 10 years out from medical school, I resolved to change course and become the clinician I had once intended to be.

Doing so by becoming a psychiatrist, albeit a seemingly extraordinary jump, as you put it, actually made considerable sense at the time. it allowed me to make a clean and complete break, to go in a single step from a field engaged entirely in the reductionistic explanation of pathophysiologic mechanisms to one devoted to an understanding of the mind of man in global and empathic way. On a more mundane and practical level, I wouldn't have made the change, if I had not also thought that I'd be a good therapist. I had the hubris to believe that I actually knew something about the field, my wife being a clinical psychologist. Perhaps more important, I thought, incorrectly it turns out, that I had had a good grasp of what psychiatrists actually did, having, during my time teaching pathology, worked with psychiatrists in efforts to help "troubled" students "make it through" medical school.

### **Where did you train?**

I went to the Westchester Division of New York Hospital-Cornell from 74 to 77, a large private psychiatric hospital situated on a park like campus in White Plains, New York, commonly known as Bloomingdale's. The hospital, by dint of its private nature, had a somewhat more manageable psychiatric patient mix than the typical city or state institution of the time. It also had a largely non-analytic eclectic orientation, and a clinical staff that, for the most part, shared an interest in phenomenology. In the United States, at the time, this was decidedly unusual. The hospital's unique orientation had come about in part as a result of its affiliation with Cornell, long a bastion of anti-analytic persuasion, and in part, as a result of the singular efforts of Paul McHugh who had been in charge of the Westchester division shortly before I became a resident there.

### **Who was Paul McHugh?**

Paul McHugh, originally trained as a neurologist, is now Chief of Psychiatry at Johns Hopkins. I know him entirely by reputation, but he was largely responsible for the Jasperian-Schneiderian German English approach to psychiatry that was being taught by the Westchester division faculty when I first began there as a resident. While clearly at odds with the analytically styled training offered by most other major university affiliated training programs of the time, the phenomenological approach taught at Bloomingdale's provided residents with an observational "set" and descriptive tools that I am convinced prepared them to deal with the revolution that subsequently took place in the field of psychiatry far better than analytical mumbo-jumbo being taught elsewhere.

Newly admitted patients were regularly assessed in group settings and, afterwards, faculty and residents reviewed, together, what had been observed. Whether, for example, there was evidence, and if so, what it was, that a patient had experienced thought-broadcasting, had auditory hallucinations, or exhibited bradyphrenia. The systems of description and classification employed were at odds with those employed by the majority of the profession, however, and this proved to be somewhat of a problem.

Nonetheless, to this day, I am thankful that I had the opportunity, if only for a year or two, to observe highly competent and experienced medically oriented psychiatrists and psychologists evaluate and describe the form of the psychopathology exhibited by a wide variety and kind of acutely and chronically ill psychiatric patients. Regrettably, in the midst of my residency, the new chair of the Department of Psychiatry at Cornell, Bob Michels, began to recruit increasing numbers of analytically trained psychiatrists to the Westchester faculty. It was not long, therefore, before the objective eclecticism that had made the residency so fascinating and instructive gave way to a pedantic orthodoxy of the most oppressive kind. What the analytically styled faculty advanced as "training" was all too often little more than a homiletic indoctrination into the rituals of their cult. There was little, if any, tolerance for disagreement between teacher and student. Appeals to evidence and reason, even clinical training and experience deriving from sources external to the analytical system of belief, were not only deemed irrelevant, but treated as a threat to the very survival of analytical psychiatry.

Residents were expected to accept, without question or reservation, virtually every silly pronouncement of every petty analytic acolyte who had been recruited to the department. It was mind-boggling. Untestable speculations about the origins of putatively dysfunctional operations of each patient's internal object relations were the focus of virtually every supervisory session. Worse, it was not only the patient, but the resident who became the target of such gratuitous speculations. Why I might have elected to stand up and open the door for a female patient entering my office, I recall, became the focus of several hours of inquiry and speculation by one especially silly supervisor.

### **Did all your analytical supervisors behave that way?**

No! And I'm glad you asked. First, not every supervisor who was analytically trained behaved as I have described. To the contrary, several to whom I was assigned were highly skilled and competent psychiatrists who provided invaluable advice and counsel. Moreover, one must take care to distinguish between the teacher of a subject and its value. The teachings of analytical psychiatry, while largely irrelevant to the treatment of individuals who suffer from the majority of the major psychiatric conditions, do provide invaluable insights into the motivations that drive much of human behaviour. In sum, although I found analytically styled supervision a dysphoric experience, analytical theory was not entirely without value.

Fortunately, analytically styled supervision that focused on the details of the therapeutic process had little effect on the actual medical and psychiatric care given to my patients. While supervisors held forth in analytic "metaspeak" on matters such as projective

identification and narcissistic rage, I comforted and supported each of my patients as best I could, prescribing, when required, tricyclics, phenothiazines, lithium and benzodiazepines in accord with the recommendations of the biological psychiatric literature of the time.

I must admit that I felt somewhat vindicated, when, in the waning days of my residency, one supervisor, a prominent analyst who had obvious difficulties in dealing with his personal ambivalence towards me, confessed that he, along with many of the analytic faculty, found me a “perplexing” fellow. They could not figure out, since I did everything so “wrong” in delivering therapy, why all my patients had done so well.

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

Those who were among the phenomenological oriented faculty at the Westchester Division regularly cited the work of Sam Guze and his group at St Louis; in fact, much of what I to this day hold true about psychiatric nosology is put forth in the 1974 monograph, Psychiatric Diagnosis, that Guze co-authored with Woodruff and Goodwin.

### **How did the DSM III process look to you from where you were at?**

The coming of DSM-III was anticipated with considerable enthusiasm by those with biological and/or phenomenological orientations. DSM-III's approach to psychiatric classification dovetailed with the research being done by several on the faculty who had been recruited by McHugh. For them phenomenological homogeneity was a necessary first step to a nosology based on biological homogeneity, and with that, a system of psychiatric diagnosis that could reliably predict both treatment and outcome.

Because of the influx of the analysts, there was an opportunity to witness, up close and personal as they say, the impact of DSM-III on the struggle between the analysts, who largely seemed to prefer a dimensional approach to diagnosis, and the proponents of the new nosology who saw it as the way to bring psychiatry back into the fold of medical subspecialties.

Interestingly, Bob Spitzer, who led the fight for DSM-III's adoption was on the faculty at Columbia, the source of many of the analysts that had just come to Westchester. Incidentally, there is a very good and interesting account of DSM-III's role in the transformation of American Psychiatry by Mitchell Wilson (AM J Psych. 150:399-410, 1993). Wilson provides an interesting political and social account of the struggle, part of which I witnessed from the perspective of a resident in training.

**In terms of DSM III coming in there are a few different issues involved. One was the idea that if you had more clearly defined phenotypes we may be able to proceed further with our research. Then there was the personality aspect to it - the politicians - people like Klerman who were interested to push this forward. There was also the insurance industry and the pharmaceutical/regulatory complex for whom more clearly defined entities would be useful.**

Well, those are all points made by Mitchell Wilson. I recall that he also emphasised that some of the opposition to the dimensional diagnostic approach reflected concerns about cost. A dimensional diagnostic system allows virtually everyone to be classified as suffering from a psychiatric disorder and this obliges government and other third party payers to spend more than they intend on reimbursement for psychiatric services. Accordingly, such groups favoured the adoption of DSM-III because it seemed likely to reduce the prevalence of individuals carrying psychiatric diagnoses.

In any event, I hardly have a systematic understanding of the forces and interests involved. As noted earlier, the classification of psychiatric illness offered in draft versions of DSM-III were clearly attractive to what remained of Westchester's biologically oriented

faculty. DSM-III was also attractive to residents like myself because it provided a basis to challenge the capricious, and often bizarre, labels applied to our patients by some of the analytical faculty. From their perspective, diagnostic classification was largely a nuisance, paper work that was required for reimbursement from third party payers. Their attitude, given their perspective, is understandable - if all who appear receive an identical treatment in form at least, there is little, if any, need for diagnosis at the categorical level.

In any case, at the time, I was certain that a diagnostic system based on unique biological entities could be developed. I am far less convinced of that today. Indeed, the complexity that has been revealed by research in the neurosciences persuades me that nature will not be divided quite so cleanly and easily as I once hoped it would.

### **So, DSM V could be quite different again to III/IV?**

Perhaps, there will be a sudden break in the way we conceive of psychiatric illness in the sense that Kuhn has written about and we'll move to an entirely new system of classification. Perhaps, the neuro-anatomical basis of diagnosis, the model from which the Kraepelinian approach to psychiatric illness derives, will prove untenable. Perhaps, the field will find it more useful to define psychiatric behavioural impairments in terms of specific symptoms, signs, and phenomena that can be relieved with specific treatments. Whatever the future may hold, the current diagnostic system is not ideal. It remains little more than a set of tentatively held hypotheses in need of modification and revision. In short, I expect that the psychiatric nosology will continue to evolve as new evidence about the causes of psychiatric illness and disturbed behaviour emerge.

### **You also worked in the psychiatric service at Bellevue at one point.**

Not for very long. Less than a year. Actually it was my experience at Bellevue that got me to the FDA. After completing my training at the Westchester Division, I obtained a position on the faculty of NYU's Department of Psychiatry. I had yet to decide precisely how I would earn a living in psychiatry, but, I had some hope of working as a liaisonist on the medical service, developing a small private practice, and becoming involved, part time, in some form of clinical research. This was not to be.

Bellevue at the time was undergoing a number of changes. I had taken a position there with the understanding that I would serve as one of several attendings on the residency teaching service, but I was, instead, assigned to head a unit that served as the ward that admitted patients only when the rest of the psychiatric hospital was filled to capacity. In theory, this "overflow" condition would occur only infrequently, and I would have time, therefore, because of the unit's low census, to pursue my interests in liaison and clinical research, etc. Unfortunately, the psychiatric hospital was regularly filled to capacity, and, as a result, my unit was not only very busy, but was regularly filled with especially difficult cases.

For example, if charges against a prisoner with a psychiatric diagnosis being held in the hospital's forensic unit were suddenly dropped, the individual would be transferred to my ward. On a given morning, as a result, I might arrive to find as many as half a dozen new patients, undiagnosed, in restraints, unmedicated, awaiting evaluation and disposition. The ward had only part-time psychiatric staff assigned to it, no permanent head nurse and no established nursing team. It took me relatively little time to recognise that protests about the conditions extant were not going to affect the resources available to support the unit. Having reached that conclusion, I decided to leave Bellevue. I looked at a number of different opportunities. Among those available, a position as a "Medical Officer" in the Division of Neuropharmacological Drug Products at FDA's Headquarters' in Rockville, Maryland, was uniquely attractive.

**Before moving onto the FDA, can I ask you did your pathology training influence your outlook in psychiatry and your subsequent outlook in regulatory affairs?**

Well 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. It's that experience which has led me to become an enthusiast for experimental 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. As someone who acts to make decisions in the area I would just as soon be able to say I can explain how I made my decision.

**What did a medical officer in the FDA do?**

FDA Medical Officers served as leaders of multi-disciplinary review teams responsible for evaluating INDs and NDAs. The job, accordingly, seemed ideally suited for someone with my background and experience in medicine, pathology and psychiatry.

At the time I joined the Division, the agency was still enmeshed in the Drug Efficacy Supplement Implementation project known commonly as, DESI. It was intended to deal with the fact that all drugs marketed in the United States in the period between 1938 and 1963 had been evaluated only for "safety." With the passage of the 1962 amendments to the Federal Food, Drug and Cosmetic Act, drug products could only be legally marketed if they were determined, upon assessment, to be effective in use. The DESI project was the program under which that assessment was being conducted.

Thus, I cut my proverbial teeth as a clinical reviewer evaluating clinical trial reports put forward by sponsors to meet the DESI requirements. My task was to determine whether or not the evidence presented had been adduced in adequate and well controlled clinical trials, and, if so, whether it provided valid support for the claims for which the DESI drug product was being marketed.

**When did it hit you about the placebo controlled trial - the fact that the field at the time was using other antidepressants as a control for new compounds but the trial designs might not in actual fact be proving that either drug worked?**

I had come to the FDA with no experience whatsoever in clinical trials, and little, if any, familiarity with the methods used in their analysis. I did, of course, have a clear enough understanding of the need for controls in research, but experiments of the sort I had conducted with laboratory animals did not ordinarily require randomised assignment or employ statistical assessment. The lesions I sought to induce in animals were of a kind unexpected in the inbred strains with which I worked. Accordingly, the success of any given line of investigation turned on the demonstration that a given intervention induced, in one repetition of the experiment after another, a characteristic lesion in experimental animals and not in the vehicle treated controls.

In short, I came to the FDA with much to learn about how clinical trial data were evaluated. Aware of my near total ignorance, I began to read avidly and to seek the counsel of experts, many of whom were but a few steps from my office in the Pharmacologic and Somatic Treatments Branch of the NIMH. Several experts from academia also contributed to my education. Among the many who offered insights and counsel, none was more helpful than Bill Beaver, a physician and Professor of Pharmacology at Georgetown, who served as a consultant to the Division on analgesic drug assessment. The agency's regulations detailing the attributes of adequate and well controlled clinical investigations (now appearing at 21 CFR 314.126) were largely a product of his work. Also of note is the fact that he had been trained by and worked with Raymond Houde, a prominent clinical pharmacologist and clinical investigator. This link is especially important because Houde and Walter Modell, another famous pharmacologist, were champions of the notion that experiments with drugs, whether conducted with animals or humans, must have "assay sensitivity," to be interpretable.

### **What is meant by assay sensitivity?**

An experimental trial has assay sensitivity if it can distinguish an active treatment from an inert control, and better still, can discriminate one level of the active treatment from another. Clinical trials of analgesics were regularly designed to have assay sensitivity. It made considerable sense to me that a principle that applied regularly to the assessment of analgesic drug efficacy should apply with equal force to almost every class of therapeutic drug products used in psychiatry and neurology.

### **Were you alone in taking this view?**

Hardly, other clinicians and scientists working at the FDA reached very similar conclusions about design and interpretation of clinical trials. Indeed, during the late 1970s and early 1980s, most of the methods and strategies now accepted as routine regulatory practice, were being developed by FDA staff.

### **How come the field took so long to recognise the importance of assay sensitivity. They spent 20 years doing the wrong kind of trial.**

I don't know if that's entirely fair. Remember, it was not until 1962 that marketed drugs in the United States had to be shown to be effective in use. Only then was serious consideration given to the question of what would constitute valid experimental evidence of a drug's efficacy in depression. Indeed, the tools for measuring the effects of drugs on the signs and symptoms of depressive illness were not widely available until the 1960's. Didn't Max Hamilton develop his scale to assess the effects of drug treatment's on depression?

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

In any case, despite the theoretical justification for demanding that evidence of antidepressant efficacy turn on the showing of a difference, a policy enforcing that standard might have met far more resistance had it not been for a set of data presented in an NDA submitted in the early 1980's for an antidepressant drug product that, at the time, had already been marketed in Europe for several years.

Among the controlled studies submitted were a set of 6, identically designed, 3-way, parallel, controlled trials - that is, each of the 6 trials had both a placebo and an active control arm. Had the analyses of the results of these 6 trials been restricted to a comparison of the investigational drug and the active control, we would, in the fashion of the time, have reached a conclusion that the new drug was equivalent to the active control, imipramine. However, in 5 of these 6 studies, because of the placebo arm, it

could be determined that neither the new drug nor imipramine had exerted any therapeutic effect whatsoever.

This set of studies demonstrated unequivocally why it was so critical for the agency to insist that studies of antidepressants be designed to rely on the showing a difference to establish efficacy. The epistemological desirability of relying on the demonstration of a difference, incidentally, was recognised long before Modell and Houde described the principle in terms of “assay sensitivity;” it was advanced as the preferred path to inference by John Stuart Mill in his writings in the 1840s on the scientific method.

**Authority seems to have been a really big thing in the early days. Chatting to Michael Shepherd who was one of the first trialists in the field with his study on reserpine in depressives, he said that no-one paid any heed to the result 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”.**

It is not uncommon for clinicians to disparage the value of statistics. There has always been an unreasoned fear that it can be used to mislead - for example, the quote that there are lies, damned lies, and statistics. Much is also made of the supposed distinction between clinical significance and statistical significance. That observation, however, is, more often than not, off point.

Certainly, given sufficient sample size, it is possible to declare a clinically unimportant between treatment difference statistically significant. In such circumstances, it is not unreasonable to opine that the result, although not likely to be explained by chance, is of little importance. To claim, however, that there can be clinical without statistical significance is completely illogical. How can a difference that may reflect no more than the operation of chance be acclaimed as meaningful?

**Must every probative result derive from a difference shown in placebo-controlled experiment?**

No. The agency’s regulations make clear that in some, very limited, circumstances active and historical controlled trials may adduce probative evidence of a drug’s efficacy. To illustrate, a concurrent control for an anaesthetic that induces its effects within minutes of administration is hardly necessary; the reason is that the outcome observed is almost unimaginable in the absence of treatment.

An historical control trial, or an active controlled trial that fails to show a difference - they are much the same - provide little useful information, however, when the course of the disease involved is highly variable. In such circumstances, only a between treatment difference can be unambiguously interpreted.

**But this was extraordinarily obvious when you look back.**

Perhaps, but the insight was hardly welcomed by the drug industry. By requiring sponsors to establish efficacy by the showing of a difference, we were establishing a much more demanding standard than that required elsewhere in the world.

Not only that, the imposition of the standard, logical and defensible as it may now seem, was probably viewed at the time as unfair. One of the things that industry has regularly complained about is that after they, “in good faith,” initiate a drug development program, the FDA comes along and changes the rules. My refusal to interpret a failure to find a difference in an active control trial as evidence of efficacy is likely an example of what they have in mind.

**Did the NIMH provide support for the agency’s approach?**



Some certainly did. I mentioned earlier that a number of individuals on the extramural side of the NIMH were quite helpful to me when I first came to the FDA; they continued to help after I became a group leader for Psychopharmacology and, subsequently, Director of the Division. Nina Schooler, Jerry Levine, Bob Prien and Alan Raskin were especially helpful in psychopharmacology and Tom Crook did much to help in the dementia area.

**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 legitimate criticism at all. Commercial drug developers did not design their clinical trials to demonstrate the superiority of their new drug products to the standard treatment being used as a control, but to fail to find a difference between the treatments compared. Such designs, therefore, not only are uninterpretable vis a vis inferences about efficacy, but provide no information whatsoever about comparative performance.

Importantly, too, no company has ever been told that it would be unacceptable to document the effectiveness of their product by demonstrating its superiority to an established drug used as an active control. The problem with such an approach is that a study designed to show a new drug's superiority to a standard control must ordinarily be much, much larger than a placebo controlled trial. From a sponsor's perspective, that is unattractive, especially because a finding of superiority in such a study cannot logically be advanced as evidence of superiority in general.

Thus, although the argument that new drugs should always be compared with already marketed drugs is appealing on face, it is not very practical. Moreover, those who advocate it fail to consider the difficulty of making truly valid comparisons among drug products.

**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 placebo controlled trials were introduced and all of a sudden the ethical aspects of placebos came on the agenda again.**

The AIDS epidemic has forced everyone to recognise that government programs intended to control the quality of the drug supply impose a variety of costs and limitations. If new drugs are required to be assessed for safety and efficacy prior to their marketing, individuals who seek access to them before the assessment process is complete can be claimed, at least arguably, to be adversely affected. Not unexpectedly, opponents of drug regulation make much of this libertarian point.

Opponents of drug regulation also find common cause with those who believe, as a matter of ethical doctrine, that society has no right to pursue its collective interests at the expense of its individual citizens. For those who take this view, randomisation is an anathema because it requires that individuals be assigned to treatments, not in accord with their immediate individual interests, but in regard to those of society. Indeed, their position would seem to be entirely in keeping with the tenets of the Declaration of Helsinki that hold that in experiments with medical patients, every subject, including those assigned to the control treatment, should receive the best available treatment.

While I personally find this facet of the demands of the Helsinki Declaration illogical, and, if taken literally, one that would require virtually all randomised clinical research to end once a nominally effective treatment became available, the issue is a serious one. Just who is to pay the human costs of new drug development? The issues are vexing and

terribly complex. Nonetheless, I tend to believe that the placebo control serves largely as a stalking horse for those with other agendas. No one is compelled to employ a placebo control; there are alternative ways to show a difference - graded dose designs, in particular, provide a highly satisfactory alternative.

**The attackers of the randomised control trial sometimes point to outcomes research. Where did all that come from, who were the key players?**

I'm less familiar with the issues here; no one has yet, to my knowledge, submitted an NDA that relies upon evidence developed in an outcomes assessment database.

It could happen, of course, although I doubt it would succeed; it's hardly the kind of evidence that could meet the Act's substantial evidence requirement. I've heard some proponents of outcomes research suggest that it could be, but I find their arguments unpersuasive. indeed, the oft cited assertion that outcomes research can, in contrast to randomised controlled trials, generate results with external validity seems to border on the paralogical. How can evidence that has no internal validity have external validity? To be clear, I am among the first to acknowledge that the external validity of the results of typical randomised trial used to assess the efficacy of a new drug is limited, but the results are at least internally valid, and, as such, are a source of proof, in principle, that the drug has the effect claimed for it.

**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.**

Perhaps, but there may be no alternative if society wants to have new drugs marketed that have relatively modest treatment effects. The effort required to develop a new drug with a truly substantial treatment effect would, of course, require far less effort. The reason large trials are required is the fact that sponsors are attempting to market products that have relatively modest effects relative to the degree of the variation present in the population of patients being treated. Of course, in the future, as our systems of diagnosis become more biologically homogenous, variation will be reduced, and relatively small studies may be all that is required to show the efficacy of a new drug.

**Do you think that pharmacogenetics will play a part here in due course?**

Possibly, if by pharmacogenetics you mean efforts that facilitate the identification and selection of biologically homogenous samples.

**At a BAP meeting 3 years ago you said that your job is to act as a lens focusing debate.**

Well, I'm not sure if the metaphor is perfect, but regulators do try to operate in a way that takes into consideration the diversity of scientific and political views extant in society. I believe I made the point that even if I wanted to advance a particular point of view, I could not succeed in doing so without the agreement and support of the physicians and scientists who serve as the agency's advisors. Anti-dementia drugs are an example where the FDA has not done what I would have preferred personally, but what those who served as our expert consultants thought best.

**Well on the dementia guidelines issue, 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 is construed is known as notice and comment Rule making. The agency proposes a set of

regulations by publishing them for comment in the Federal Register. The agency considers these comments, amends its proposal as its policy makers and legal counsel conclude is necessary, and publishes the rule in final form. Thus, the FDA is not the source of the law, but a good faith interpreter of what Congress intended the law to do.

The Federal Food, Drug and Cosmetic Act, for example, instructs the agency to disapprove an NDA unless there is evidence, adduced in adequate and well controlled investigations, that the drug will perform as claimed. It was the agency's task to interpret what Congress meant, but it did not create the standard.

**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, I'm not so sure of that. Among the definitions given in the Act, a drug is a substance claimed to have an effect on the structure, function or body of many. Accordingly, nothing in the Act precludes the development of tonics, per se. As a matter of practical enforcement, however, it is much easier to develop a drug for a defined disease entity, and that is why, I believe, you may have inferred what you have.

**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, which is a problem-of-living compound, a pick me up, a tonic and people say "yeh, 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 is depression a disease or a symptom? Indeed, what's a disease? In a taxonomic system it's entirely arbitrary. A homeopathic medicine, as much as any other, can be subjected to test in controlled trials. If its efficacy were established, and its safety shown, it could be legally marketed.

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

Yes. We would probably argue that such a claim is potentially "misleading," and, on those grounds, reject it. We could take such a position because the concept of a tonic is so vague that we could not write adequate directions for its use. For example, to whom and under what labelling would it be promoted?

**It improves sleep, it improves appetite.**

Then why not make those specific actions claims in their own right? If a treatment improves sleep, it could be marketed for the purpose, provided, of course, one can define what it means to "improve" the sleep of someone who is sleeping normally. A claim for improving appetite might be somewhat more difficult because it is uncertain when and in whom a product stimulating appetite provides a benefit. It's difficult to assess it. Similar concerns affect claims for drugs with putative anti aggression effects.

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

Well improved sleep, perhaps, but even there I 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, after treatment than before, said they had improved sleep, it would still be a tough call because you wouldn't know what the effect you were you're dealing with actually was. It's rather hard to answer these kinds of questions definitively; the only way to approach them is with an open mind. the agency is not tasked to prevent sponsors from developing medications that provide meaningful benefit,

but it is obliged to prevent the marketing of products that carry false and misleading claims.

I am not saying that any of this is readily nailed down. It is not always obvious where the interests of the public reside. At some point, government control over the accuracy and truth of drug product labelling can become excessive.

**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**

It so happens that some drugs with antipsychotic activity exhibit those 2 properties, but, that might not be what determines their effectiveness.

**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 might have, but I'm not sure of the point you make. A sponsor is always free to develop a fixed combination product. As long as the evidence adduced shows that each component makes a contribution to the efficacy of the combination, its legitimate. Of course, if it turns out that the combination is no better than one of its components, the combination is irrational and will not be approved.

**Nearly twenty years have passed since you joined the FDA in 1978. During that time you and your colleagues have had to face and resolve a variety of vexing issues affecting the fate of a number of psychotropic drugs. How do you manage? Clearly you can't possibly know enough in detail and depth on each and every medical/psychiatric and statistical issue that comes before you or can you?**

Of course, you're right, but I'm not expected to be a technical expert. To the contrary my business is to assess the quality of scientific evidence and the quality of those who assess it. 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 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. We recently had an interesting situation regarding anti-psychotics and changes in ECG records. I listened to experts on both sides of the aisle give me very different views about what significance those changes had. 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.

Decisions about the marketing of drugs are invariably made on the basis of incomplete and imperfect knowledge. Anyone who is involved in the drug development and approval process must, therefore, find their own approach to dealing with the uncertainties that affect all but the most routine regulatory decisions. I cannot claim to have found an ideal approach, indeed, I doubt that one exists. I do believe that drug regulators are paid to be

skeptical about claims advanced for new drugs. Public health decisions should not be made on the basis of hopeful expectations and sanguine theories, but upon facts and findings that are robust enough to withstand careful, thorough, and thoughtful examination and challenge. Extrapolations from evidence should be reasonably circumspect where effectiveness claims are concerned and rather more liberal where drug associated risk is involved. This asymmetric approach is sometimes characterized as being unreasonably risk averse but I am convinced that it remains, in the vast majority of instances, the preferred approach when decisions are being taken in the face of uncertainty.