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Can we learn anything from the past?

One hopes that there are some lessons. At a meeting several years ago at the ACNP, a man responsible for CNS drug development at Merck bemoaned the fact that animal models were not terribly helpful in predicting what a drug was going to be good for and he couldn't afford to do endless randomised controlled clinical trials so what should he do? Some of us old timers said "well is it possible that you could do what they used to do in the old days which was to go to some skilled psychiatrists and say here's a drug - we think it may be good for this or that but we don't know for sure. Try it out and see what you find". And he said "oh no we have been led up so many false paths with unbridled enthusiasm etc". I'm not sure that he is right because to me what he was describing was a philosophy of despair - we don't know where the hell we're going, we don't know how to pick drugs and then we are stuck with spending a lot of money doing things that may turn out to be negative but falsely negative just because we have studied the wrong patients.

My own contributions to the field were really mostly in the field of analgesics, although I watched other drugs develop and was responsible for selling, in the early 1950s, the concept of controlled clinical trials which had started with Bradford Hill and the streptomycin study back in the 40s but which took a little while to be transferred over here. There was a double problem with selling people on the notion of controlled trials. One problem was selling people on a seemingly artificial way of studying drugs - different at least from what they had been doing for years. The other was convincing them that subjective responses could be studied in a valid fashion.

When the analgesic work first started, people said you can't find out whether people are in pain or not - I mean this is within their head. How can you ever get any insight into it? And the answer was well if you structure your questions in a certain way or use visual analogue scales or whatever and do it properly with attempts to eliminate bias and use controls and so forth, by God it can make sense and one can get dose-response curves and so forth. So the analgesic research in a way opened up the whole field of subjective responses and brought into the tent of science if you will the measurement of anxiety and depression.

When was all this - when did Beecher and Gold start?

Beecher started I would have guessed in 1950 or thereabouts as far as his clinical trials were concerned. He made the observation during the war on the Anzio beachhead that soldiers suffering wounds at least as grievous as those suffered by civilians seemed not to demand as much in the way of analgesic medication as did the civilian patients with whom he had had experience prior to the war and he concluded that this was because there was a neurophysiological component to pain and then an emotional response to the stimuli being perceived which allowed the meaning of pain if you will to get into the act. His suggestion for the difference that he observed was that in civilian life grievous wounds were ordinarily a tragedy but on a battle field it might be a blessing because it got you at least away from the front lines to a base hospital and maybe out of the war completely. Who knows whether that was the correct explanation or not but that is what got him started.

When exactly the analgesic research started I don't know except I joined him in 1952 and it had been going for a couple of years before that. He had an internist with him called Jane Denton and a man named Arthur Keats who had been a classmate of mine in High School and College. I first got into it by meeting Keats on the Atlantic City boardwalk at one of the so called clinical meetings and having him tell me about this new research they were doing. And it sounded so exciting to me that when the time came for me to pay my time back to the armed forces for having paid for part of my way through medical school, I eagerly acceded to Beecher's request to come and join him.

He pulled strings. I had been in the Navy and then was transferred to the Public Health Service. I actually got paid by the US Army because Beecher had an army grant to study psychotomimetic drugs. He came back from a trip to Europe with this lurid story about how the Russians were building not one but two factories beyond the Ural mountains to make LSD which they would drop into the drinks of diplomats or generals to get secrets from them and so forth. So he got me assigned to work on this top secret project. I had to be screened for top secret level believability and so did Beecher. We passed that. A psychologist of the name of von Felsinger with whom I worked refused to go through this because he thought this was McCarthyism and Beecher's secretary who typed all the reports refused to be screened - so we had this mixed security. The reports would go back to the Pentagon by an armed courier with a briefcase manacled to his wrist. And I know at least once they called up and wanted another copy and Beecher said well you told us to destroy everything after we sent it to you, what happened to the first one? The answer was - it's lost in the Pentagon somewhere.

After I left Beecher and came back to Johns Hopkins to start the first division of clinical pharmacology, I couldn't help but be interested in the new developments that were occurring in this field and couldn't help but be impressed by the fact that indeed most of the early discoveries were serendipitous. They weren't science marching down a pathway in a straight line but lucky observations by people in studies where the controls were really historical controls and not randomised controlled trials. Meprobamate came along that way, as did the benzodiazepines, imipramine, chlorpromazine and the monoamine-oxidase inhibitors. So here I was on the one hand saying well once you identify a compound if you want to persuade people that it works you really ought to do controlled trials but having to face the fact that the breakthroughs were not achieved in that way. So it is interesting that so much of that was serendipitous and maybe will continue to be that way.

In the field of analgesics for example we are a lot better at identifying new receptors than we are at figuring out what to do with them. My major contribution in terms of drug discovery I would say was the discovery that nalorphine, which was given to us as a pure antagonist, was in fact a mixed agonist/antagonist. The way we stumbled on that again was serendipitous. Beecher and I had this funny idea that if we combined in some magical ratio nalorphine, allegedly a pure antagonist, plus morphine we might get rid of some of the bad things that morphine did. We were willing to settle for whatever God sent our way in the way of losses of bad things - less nausea, less vomiting, less constipation, less addiction, whatever. So we had a couple of ratios and I, in my obsessive-compulsive way, said well we really ought to have a nalorphine control just for the hell of it and to our surprise it turned out to be effective as an analgesic. So that opened up pharmaceutical research which was pursued in part by Arthur Keats, whom I mentioned earlier who had left Beecher to go to a chair in anesthesia in Texas but mostly by the Sterling-Winthrop company. They looked and looked and ultimately a number of mixed agonist/antagonists made it to the market but not nalorphine because they thought it had too many hallucinatory potentials. I'm not sure that any of them has been a major contribution to the search that started in the 1930s to come up with a non-addictive substitute for morphine.

My training was as a physician internist. Then I had a post-doctoral experience in the pharmacology department at the Johns Hopkins School of Medicine where I did primarily laboratory work and published several papers. Beecher sold me to the army as someone who was uniquely qualified to pursue these problems - he couldn't imagine anyone in the world better than me to do this. It was hilarious to me at the time. In addition to the episode I told you about the lost Pentagon paper, I got a call from a General from a base in the United States asking me whether I would be willing to work on this top secret

project. I said well I would love to go to the Massachusetts's General Hospital to do it but what is the project? He said I can't tell you, it's too secret. So I took it feeling fairly certain that whatever else I did there for the army I would be doing something interesting and I did the first controlled trial on hypnotic drugs whilst I was there.

Which ones were they?

Chloral hydrate and a barbiturate. What we did was to study several hypnotic drugs and we had a placebo group. It was the only trial that I have ever done that had a no-nothing group - a group that got neither placebo nor an active drug. I often refer to that because it is the only trial I've ever done where I could with some certainty decide how much of the placebo response was due to suggestibility and how much was due to spontaneous change. Using a very crude endpoint - of falling asleep in less than an hour as success - 65% of the placebo group did so but the no nothing group was also about 65% so we were just studying the relative ease with which people admitted for elective surgery fell asleep. I had thought they would have a terrible time being anxious about the next day. This is the only time I ever did that and I doubt that many people have done it - the end result is that you get a lot of crazy talk about placebo responsiveness.

Beecher, by the way, was responsible for people going around for years - to this day - saying that about a third of people respond to a placebo. He took a bunch of published articles ranging all over the place and he averaged them up and the average was about 35% or so. But the average, as usual, hid a lot of variability and to this day some people still refer to the magic third but more sophisticated people realise that if you ask a stupid question like will a placebo prevent you from dying from the common cold you get a 100% success rate which has nothing to do with the placebo talking you out of dying.

One of my contributions was convincing people that you can study sleep. This was prior to the sleep lab days when people moved over from just the subjective responses or the evaluation of night nurses or technicians trying to see whether people were awake or asleep to using electroencephalograms. In a way I think it is a pity that so much stress is placed on the sleep lab and so little on clinical studies because the sleep lab is a highly artificial hot-house - wires on your head and so on.

Can I ask you some more about Harry Beecher. Who was he, where did he come from?

He was a very complicated man. His name probably wasn't Beecher. He was born in Kansas and if you look at some of his early publications and some of the books that he had in his library, you saw two middle initials K and U - Henry K. U. Beecher. The U as far as I was able to tell stood for Unangst.

An appropriate name.

Exactly. My guess is if anything maybe his mother was a Beecher. He later took great pride in attending Beecher family reunions and so on but I have a feeling that his paternal name was probably Unangst. He went to school in Kansas but then came to Harvard Medical School, started off to be a surgeon, went off to work with a Nobellist called Krogh and I think while there they asked him whether he would like to come back and be Professor of Anesthesia in the Massachusetts's General Hospital. I forget what he did to train himself as an anesthesiologist but he came back and chaired this department. He always spent a lot of time travelling, around Europe especially, recruiting a lot of very talented Europeans to come to work at the Mass General for a year or two.

He was a very dramatic figure in many ways. I always dreaded writing papers with him because he would always insist on the introduction referring to the previous stuff from his lab and then ending with rather more dramatic conclusions than I would have wanted. He engaged in a number of controversies. He did a study on curare, for instance, implicating

it as a bad performer in anesthesia. People who thought it was perfectly safe to use it if you used it properly took umbrage at that report. But he was clearly a leader in American anesthesiology and maybe beyond America; he was well known in Europe. He had a very good clinical department. He supported investigators who were not anesthesiologists, like me for example. He had a woman named Mary Brazier, a Brit, who was an EEG person and he supported her research. He had a couple of young men who were neuro-pharmacologists or neurophysiologists I guess you could call them. He let people do whatever they wanted to. He was very supportive but a complicated man. Very few people felt neutral about him - they either liked him a lot or disliked him a lot.

He wanted me to stay on and succeed him as Professor of Anesthesia. I said Harry there are two problems with that: one is that I don't really want to be an anaesthesiologist and the second is what makes you think you will be able to pick your successor - it's not exactly a hereditary post. I enjoyed thoroughly my two years with him. It was a lot of fun. He enjoyed the fact that von Felsinger and I were interested in the placebo response.

We published a paper in which we attempted to see what predisposed people to respond positively to placebo. In retrospect it was a bit naive because while I do believe that some people are more suggestible than others and more influenced by their feelings about the medical profession and pharmaceutical substances, there are so many things that specifically will affect the placebo response given the situation, person, the physician and so forth that it is probably silly to think about placebo reactors and placebo non-reactors. Probably none of us are consistently placebo reactors or non-reactors.

Is there any way then to evaluate the placebo response? Is it in essence the question about how do you evaluate psychotherapy?

There was a paper published by my two of my colleagues at Hopkins, Park and Covi. They took a small number of neurotic out-patients and they said "We are going to give you a placebo. Do you know what a placebo is? A placebo is a non-active medication but it helps some people or it has been known to help". To their great surprise many of these people said it was wonderful; some said it was the best thing they had ever had; some of them disbelieved that it was really lacking in medication. They published it as an example of how for some people their attitude towards medications or physician gestures, which I guess the placebo is, make it impossible to eliminate suggestibility and anticipation of a good effect. Obviously you could also anticipate a bad effect. You could be a sort of negative placebo reactor, dislike doctors or nurses and hospitals and so forth or be fearful of medication.

Today, I think if you do a crossover trial where patients are given both the active treatment and the placebo, then in fact those patients unable to distinguish between a placebo and an active treatment are useless and the only differentials that come out of it are in those patients who respond to one treatment and not the other.

These days the placebo is being clobbered by certain bio-ethicists who believe that the Helsinki Declaration doesn't allow placebos. In fact it doesn't but it doesn't allow a lot of other things. It was put out in the 70s and modified once or twice. One of the modifications says that every patient in the trial including those in the control group should be guaranteed access to the best treatment available. Now that means that not only will you have trouble doing a placebo-control but how would you ever study a new medication unless you were treating a disease for which nothing existed? I think the Helsinki Declaration was written by people who really didn't understand what research was about.

I'm not saying there aren't ethical problems. The FDA in this country really insists most of the time on placebo controls. The reason they do is that they know that at least with

some therapeutic areas it is quite possible to do a study comparing say a standard antidepressant with placebo and have the two come out no different because the population just couldn't discriminate - depression being a remitting disease you can see why that would happen. So in a sort of statistical morality sense FDA staff feel that if the FDA lets a compound get on the market because there has been no difference demonstrated between it and the standard drug in a couple of trials, it may be doing terrible harm to thousands and thousands of patients by subjecting them to something that really is ineffective or poorly effective, which you would find out if you really studied the right population.

My own view is that one can defend that although I think there are other ways to handle the problem. For example in the analgesic game we do dose-response relationships with the standard drug and the new drug and if you get those then you come up with a therapeutic ratio for the two preparations and pretty reliable conclusions about how many mgs of this is equivalent to 10mgs of Morphine. So I think in situations like that or situations where you are comparing a mixture of two or three drugs against individual drugs, if the mixture turns out to be better than any of the individual drugs I can't understand why you need a placebo arm.

Do you think trial design possibly by virtue of the 1962 amendments of the Food and Drugs Act has become a very rigid thing. There are other things that we could do like a multiple-baseline design where you could in essence give all the people involved an active drug but you begin at the point at which they begin the active compound in a staggered way.

A man named Walter Modell and I were really responsible for the demand for well-controlled trials being in those amendments. The reason we did it was because in the bad old days, while occasionally physicians would come to the truth - morphine, digitalis, aspirin - there were also other medicines which were ineffective but were used for years. So I still believe that the randomised controlled trial is a hell of a good way of persuading people that you have something. But in contrast to my role in the 1950s which was trying to convince people to do controlled trials, now I find myself telling people that it's not the only way to truth.

My favourite quotation was taken from Austin Bradford Hill's Heberden Lecture, this was probably 30 years ago, and in it he said "If one came to the conclusion that the only way to find out the truth about a medication was to use a controlled clinical trial, it would mean not that the pendulum had swung too far but that it had come completely off its hook". And this is from someone who might be called the father of the controlled trial. In another part of the paper he comes up with something else that I have been trying to sell to people with not an awful lot of luck. What he said was that a controlled trial does not tell the physician what he would like to know which is how do I know in advance without engaging in trial and error which antidepressant is better for Mr Jones or Mrs Smith. That's what doctors and patients would like to know. We don't do that.

To get a drug on the market in the United States and in the most other jurisdictions all you need to do is show that on average when a group of people are untreated they would do less well than a group of people that are treated. That is enough to get a drug on the market. And if you look back at your trials retrospectively saying it looks like left-handed Lithuanian women did better or middle aged Mexicans did worse you are accused of data dredging. It's really silly because any scientist worth a damn would look at his or her data to see what clues are there, not necessarily convincing you because we know that occasionally by chance you come up with correlations that are meaningless. For instance, Richard Peto had a trial that shows that people born under a certain zodiac sign did a lot worse than everybody else. But why shouldn't one be looking at whether Ashkenazy Jews get more agranulocytosis on clozapine or not. If one had been able to

predict who is going to get agranulocytosis from clozapine, it would have made the marketing in this country completely different. Clozapine would have got on the market a lot sooner, would not have had requirements for doing white blood cell counts periodically and so forth.

Some people won't even buy the fact that you can do case control studies or pharmaco-epidemiologic studies to get some feeling for what is really there. I think that's a pity because the controlled trial world is really a very hot-house world. Not every patient qualifies and you tend to have patients that are not complicated. It's a pity that we have got so rigid about it.

Another craziness, which used to be just an American disease but is spreading like a virus to other parts of the world is the so-called intent to treat analysis. The notion that even if people don't take a drug they ought to be counted as if they had is bizarre. I can understand people saying you have got to watch these scurvy knaves in the pharmaceutical industry, they'll discard patients that fail, to make the drug look good and that is a problem. I remember one time talking to an anesthesiologist and he said you know it's not true that morphine's effect peaks in about an hour, it peaks much later and it lasts for a long time. I said really? Then he showed me his data - what he had done was eliminate everybody that dropped by the wayside so by the time he got to the 12th hour all the failures had disappeared. He was only counting the happy subjects who have gotten pain relief and that's it. You can't do that. So yes you can't ignore drop outs and the best thing to do with drop outs is not to have them. You can't ignore them but while it is perfectly legitimate to ask the question if I took 100 people and told them to take the drug this way and some of them took it this way and some of them didn't and some didn't take it at all, what would happen - not a bad question to ask; a real life question - but it's different from "what would happen if 100 people took the drug as told?". They are two completely different questions and why one shouldn't be interested in compliance as a determinant of effect I don't know, especially these days where we don't have to rely just on pill counts or an occasional blood or urine specimen which have been shown to be not very good because people can throw pills away and a specimen about once a month tells you something about what has been going on in the recent past but not for the whole month. Now there are these little electronic monitors where you can at least see whether the patient opened the container or not. If the container has been unopened for a month you can be relatively certain that anything that is happening to the patient, either benefit or harm, is not due to the medicine. It is a pity that we get so bogged down in these rigid, inflexible ways of doing things.

Is one of the other things that has come out of the controlled trial the idea that there is a single right dose for a drug. It seems to me that before we went down the RCT road, with drugs like digitalis, for instance, you would titrate the dose for each person but in order to run trials you had to have a fixed dose. What comes out of the trial then is the recommendation that if you want to treat people who are depressed this is the dose you should give. A dose that may be great in the mean but extremely poor for some people and too high for others.

In the psychotropic area you have trials that sometimes do involve titration - antidepressants that start low and work their way up. One trouble with that approach is that it's wonderful for coming up with a false U-shaped dose response curve because the ones that are doomed never to respond, maybe because they don't have the disease you are studying, are going to be in the group that got the highest doses. Sometimes there is a legitimate U-shaped curve as is true with certain antidepressants and certain antipsychotic drugs but the only way you can pick that up reliably is to do a standard fixed dose for each subject with some people getting one dose and some getting another and then if a high dose produces a less good response than an intermediate dose you can argue that there is a therapeutic window and that is important.

Yes but it seems to me that the problem is we don't actually go back to the patient - and this is perhaps true more for the neuroleptics than the antidepressants - and ask their verdict of whether they are on the right dose. We aren't prepared to begin low and work our way slowly in a particular person after the drug has been licensed.

You know another consequence of ignoring compliance is that you end up with doses that are too high for the obsessive-compulsive patient that follows directions. You conclude that 60mgs is the best dose because you get as good an effect as you are ever going to get benefit-wise with little toxicity but that is only because some of your patients are taking less than 60 and maybe the best dose is really 40 mg. So if you are marketing it at 60, the obsessive compulsive patient who takes the drug religiously will not be at this nice point on the dose-response curve. They will be getting more toxicity than they need.

The dose-response relationship is the only thing that differentiates pharmacology from the other basic sciences. Its very hard to think of many things that are just pharmacology's domain and it's amazing how little attempt is made to be sophisticated about that.

In the cardiovascular area, for example, in the treatment of hypertension the original approved dose for hydrochlorothiazide was 200mgs. If you look at the standard textbook on hypertension, this is what you find in the first edition. Second edition it's 100mgs. Third edition it's 50mgs. Fourth edition it's 25mgs. And the last one I think was 12½mgs. Now it's shameful to have been that wrong in recommending the optimal dose. You can see how it happens. If you're a pharmaceutical company spending a lot of money on these trials you're not going to try and shave it so close to an ineffective dose that you have a good chance of coming up with a negative result. But that's for convincing everybody that you have got a drug, the fine tuning which is what seems to be the ultimate goal for medicine shouldn't then be ignored. This is too bad.

Did Harry Beecher know or have any contact with Harry Gold at all because he was also using placebos

Gold as far as I can tell probably coined the term double-blind. I tried to pin him down on this one time and he more or less said he thinks he was responsible. He was doing studies on ether, as I remember. He did believe in controls and in placebos. And actually he used to edit a series called The Cornell Conferences on Therapy. That is where I first got turned on to both pharmacology and placebos. He would have a session on placebos and would tape what people said and then edit it and publish it in a book. Harry Gold probably deserves credit for the concept, but when exactly he did that I'm not sure - it was probably in the 40's.

Who was Harry Gold?

He was a cardiologist in practice in Manhattan, on the staff of the Cornell Medical College but never a fully legitimate academic because he was in practice earning money. He earned quite a bit of money because he was a very good cardiologist and had a wealthy clientele. I met him on a few occasions and liked him. He was an interesting figure. He never got academic recognition because he was not a full time academic. But he was very interested in how to study drugs properly and very interested in studying humans as opposed to animals although he did do some animal work too as I remember. He had a bio-assay for standardising the potency of digitalis glycosides that utilised EKG changes. Beecher did know Gold but not terribly well I think. He met him on one or two occasions and he may have corresponded with him but I don't think they were bosom buddies.

So they both came to their ideas very much independently of each other. Was there anything else back behind them? Were there any other figures before either Gold or Beecher?

Bradford Hill but I'm pretty sure the original streptomycin trials didn't employ placebo. They thought it was unethical to stick people on placebo. As far as placebos go, I think Gold probably deserves credit for being the first man in the territory.

You pick Bradford Hill as the person who actually created the RCT. What was the chain of events that led from Bradford Hill to here.

I'm guessing because I can't trace it with certain accuracy but the streptomycin trial got a lot of play over here plus Harry Gold had begun to plant the idea of the controlled trial. Then Beecher came along and there was an increasing awareness of placebo effect and the ability of physicians in the past to be misled about medications by reason of not having done proper controlled trials. I guess that is the way it happened. I am not really sure exactly what raised the level of attention. I'm trying to think what was the first trial. Some of the things that came along about that time were deemed to be effective without the need for randomised controls. I'm thinking of penicillin for subacute bacterial endocarditis and so forth. In the case of the blood pressure lowering agents, they weren't satisfied with surrogates for those until finally somebody came along to do the first controlled trials showing that there were benefits in terms of prevention of cardiovascular catastrophies of one sort or another. Maybe there was no big leap, maybe it was a trickle down thing because you know at those hearings of Kefauver's, Walter Modell and I were the only people who addressed the clinical trial issue. Other people talked about prices and profits and generic labelling and so forth. Kefauver's original orientation was an economic one, it wasn't the quality of research etc.

This was in 1959/60.

It started in December of 1959 and it went through until 1962. So it was about two years worth of hearings in the House under a man named Blatnik and in the Senate under Kefauver. No one expected it to happen because Kefauver had a history of looking into things and then no legislation appearing so the pharmaceutical industry were not too worried because they thought this would fail too. And were it not for thalidomide the legislation would have failed.

The hearing was more about excess profitability. An economist would get up and say now 20mgs cost how much to make and the box costs 2 pennies, ignoring the investment that had produced these, the sort of thing that one hears today also. And then there was a flap about medical advertising being unmonitored and unvetted.

The idea that if articles were inimical to a companies interest they might pull the advertising out of the journals...

There were those threats. I don't know if they were real. I testified in a weird way. I was a consultant to the committee but one day they had a man named Mark Nickerson who was supposed to testify. He had been in Michigan but he was living in Canada and during one of the breaks one of the staff people of Kefauver's committee asked did I think he was going to be a good witness? I said jokingly that he should be because he had appeared before the House Unamerican Activities Committee. For what? He was and may still be a card carrying Communist, I said. Well that was all they needed to hear. They whisked him out immediately lest that come out and the testimony would be tarnished by this anti-capitalist tone and in a moment of madness I agreed to go on unprepared as a witness in his place. That is how I got to testify.

Originally I was just there to answer questions like what does this term mean and what does that term mean. I tried to help them on medical advertising. The man after whom this building is named, Arthur Sackler, was the inventor of the multiple-page, multiple-colour spread ad in medical journals and Kefauver wanted to subpoena him to testify. I said if you want real information from Sackler why don't you meet him in camera. You may get more that way than if you have him on the stand and he refuses to answer

questions because it is embarrassing. To my great surprise Kefauver did this and they got along splendidly. But nevertheless all of that would have gone down the tubes if thalidomide hadn't come along. While it had nothing to do with the bill as it was written, it nevertheless turned the Congress's attitude around and we have been living with it ever since, both the good and the bad effects.

At a Congressional committee meeting earlier this year I was asked by the chairman of one sub-committee why we couldn't pass a law that you only had to study 84 patients to get a drug on the market. I thought oh my god how am I going to communicate to him that this isn't really the way to do it. But then even worse than that was his saying "why can't we go back to before 1962, make sure that safety isn't an issue and let the market place decide if the drug is effective or not?". I had to disagree with him because I don't really think anybody wants that. If I were the Commissioner and I was told that I no longer had the authority to approve a drug when I was convinced on the basis of the evidence available at that point that if the drug were used as labelled it would do a hell of a lot more good than harm I would resign. You should handle it differently if you are dealing with a life saving drug for a disease for which nothing exists as opposed to the 45th clone of an anti-inflammatory. So one hears of occasional luddites willing to take us back to before 1962 but I am sure that isn't going to happen.

To chase the placebo further, Michael Shepherd was one of the people who took the controlled trial furthest, at least in the mental health arena, but he ended up it seems to me deriving the conclusion from it that the placebo was almost the thing that was actually discovered by the RCT in a sense. Obviously when people got well on things before the RCT which we now know weren't effective there must have been a placebo component to it. But what the RCT did quite clearly was to dissect out a specific placebo in a sense - a placebo that was totally different to anything that ever went before.

When I was referring earlier to certain bioethicist complaints about placebo, another reason they object to approving a drug on the basis of superiority over placebo is that they quite rightly point out that for the practising physician and for the patient you really want to know how a new drug stacks up against what is already available. That is really more important than is it better than suggestibility or spontaneous change.

It has gotten so complicated in some areas. I am interested in obesity management. In the old days, trials would compare an appetite suppressant against a placebo but today it is an appetite suppressant against dietary advice, exercise advice and sometimes behaviour modification therapy. Now those things are hardly suggestibility controls. They really put it to you to top off what is perfectly fine medical practice but it is such a far cry from what used to be the placebo. The placebo in the old days was just giving people a tablet and really seeing whether the appetite suppressant worked better than that.

This is the point that interested Michael Shepherd. When they did the NIMH studies of placebo versus cognitive therapy versus inter-personal therapy versus antidepressant they figured that they could not have a no- nothing kind of placebo they had to have the best possible clinical management to compare with the other so called specific treatments. And it turned out to be extremely powerful in its own right.

You know when you finally get a drug on the market the benefit it provides is obviously a combination of the placebo effect plus whatever pharmaco-therapeutic benefit is derived and in a way it is strange to compare it against a placebo tablet or capsule because in real life unless you prescribe something you don't get that therapeutic gesture if you will with whatever it connotes because doctors don't these days at least in the United States often prescribe placebos purposely. They may be prescribing drugs which are ineffective, like giving vitamin B12 for weakness or something like that. That is a therapeutic gesture

made by the physician who is hoping that it will work but at the very least there is going to be a demonstration of his intent to do something for the patient.

I don't take care of the sick any more but when I used to I invariably was able to think of something that might help the complaints of a patient that I was seeing, although I couldn't guarantee it. I never prescribed placebos and I think most doctors don't. In order to capture the placebo benefits you have got to write a prescription for something. That is what I think doctors do. With all the criticisms about doctors maltreating patients it is unfair to accuse them of often purposely giving patients placebos just to cater to their whims.

I suppose you could say that if you are giving penicillin for a sore throat that you feel pretty sure isn't streptococcal in origin, that's giving a placebo. But I think most physicians would probably say they are doing it not because if they don't do so the individual will go down the street to see another physician but because it is damned hard to be sure that it's not streptococcal and penicillin is cheap, its pretty damned safe and if it's streptococcal it's important to give it. It's interesting that with the so called abuse of antibiotics over the last 40 years, there has been a decline in rheumatic fever and rheumatic heart disease, which I think is probably most easily explained by the promiscuous prescribing of penicillin to a lot of people who didn't need it but to some who did.

In 1969 you had an article that has always appealed to me, where you gave volunteers some instructions on the side-effects of a drug they were scheduled to take and found that many of them were unwilling to on the basis of side-effects take what later turned out to be aspirin. At the same time what they now knew about aspirin didn't affect their willingness to take it outside the experimental setting. So much for informed consent!

I serve on a local institutional review board, what you would call an ethics committee, and I keep pointing out to them that first of all we should pay attention to the language that we use and I am not just talking about saying baldness instead of alopecia. A lot of patients don't understand some other language like maybe they don't know what a protocol is. And there are some shocking misinterpretations of words like "orally" in New Haven, which was described by many people as meaning how often you would take it - not that you would take it by mouth. Whether they were hearing it as hourly I don't know. The second problem is if you are obsessive-compulsive about putting everything in, then you should face up to the possibility of information overload and should ask whether you are getting the major messages across. What our study showed was that if you had the same information but more and more embroidery that you will get fewer subjects and some of the ones that you do get will miss very important information.

What was also interesting I thought was the fact that they were told about all the risks of this drug and said no we are not going to have it but when they went home they had it. It is a completely different thing between risks that are ones you know how to live with and risks you are having to process cognitively but you have not had to live with as it were. It is curious isn't it?.

It is the fear of the unknown. We once studied obstetrical pain experiences and I was convinced at the end that for women who have never had a baby before but whose exposure to the procedure was in movies where invariably the woman was having a dreadful time this was hardly conducive to peace and tranquillity as you were awaiting the experience yourself. Once you had it you were sort of prepared for the next one however bad it had been. By the way in that study you might be amused that we asked the women who delivered babies and their obstetricians how effective the control of pain had been. About 20% of the time they agreed pretty well but 80% of the time they disagreed. Almost invariably these women said they had had a harder time of it than their physicians

said they had had. It is easy to explain why that might be. First of all physicians don't like to think they are doing a bad job of controlling pain but also the typical experience in the United States is for the obstetrician to come in, and using a base ball term, signal for a fair catch but not having been there during the hours that the woman was groaning and moaning and asking for help.

I delivered two of my own babies in our car because we didn't make it to the Johns Hopkins Hospital in time. The first time it happened was the first time that I had ever seen a baby born of an unmedicated mother. In the old days they used a lot of medication, including opioids. Out came this baby, ready to go. I had only seen sleepy babies and I thought that the normal status for a newborn was to be sleepy, not realising until that moment that it was because I had never seen a baby born from an unседated mother. I think one of the reasons that doctors decided to make the procedure less unpleasant for the patient was that these patients would then go to their friends and say oh you ought to go and see Dr so and so if you are pregnant. These days they have a different attitude about the hazards of doing this and the desire of many women and their spouses to be together going through the process and not expecting it is going to be dreadful.

Whilst I was at Hopkins we had some Australian midwives training there and they were the most popular health practitioners because they spent a lot of time with the women during their visits prior to the delivery, explaining to them and diminishing their fears and anxieties to a certain degree, being with them throughout the whole delivery, rubbing their backs and answering the questions that were often not answered by nurses in other situations.

Let me take you to the 1956 conference which was organised on the back of the monies that Nate Kline and others got out of Congress to fund the evaluation of psychotropic agents. It seems awfully curious for a start that the key people behind it were yourself, Ralph Gerard, Seymour Kety, Joe Brady - hardly a single psychiatrist there. It was a bunch of non-psychiatrists who put this thing together which.....

Well you know I can't remember the organisation of that meeting. Nate Kline was of course always angry that academia did not give him the credits that he thought he deserved for his role in the monoamine oxidase story.

He pitches it in the press as being that he did not want to get tied down with professorial jobs - he wanted to be a free spirit. He doesn't pitch it in terms of being disappointed.

He won any number of awards for his contribution to the field. He created an institute, he had battles with some of his colleagues. He was a complicated man. But Heinz Lehmann and Fritz Freyhan also did a lot of the seminal work on neuroleptics and they never got academic recognition. Working in Montreal the Royal Victoria was the most elegant place to be and Heinz was at the Verdun Protestant. Freyhan was at the Delaware Hospital in Maryland. So you have Kline and Freyhan and Lehmann who were important figures but never made it academically in this country. But Kety did make it and Brady did too.

Michael Shepherd said he sat in on a few of the meetings with yourself, Kety, Gerard and Jon Cole who all tried to organise what were the issues - how do you actually structure up this meeting, what should we be doing etc. There was a feeling that the whole thing was about trying to contain Kline.

Well Kline got the money appropriated by Congress for the Psycho-pharmacology Service Center and he was very bitter because he had wanted the money to come to him to do a trial comparing reserpine and chlorpromazine. He had done this study on reserpine and with huge numbers showed a statistically but almost biologically

insignificant difference between reserpine and placebo. Then he and this journalist from the Mid-west, Mike Gorman, and Mary Lasker, had an enormous impact on Congress because they were smart and articulate. The Psychopharmacology Service Centre was started in large part because of Gorman and Kline's testimony.

Then there was a committee for doling out the money and oh the early applications were pitiful in quality. I remember asking the the Head of the NIMH at one point - Bob Felix - what do we do if we don't have anybody that we want to give the money to. And he said the money will be spent. Under no circumstances was money to go back to Congress. So in those days in contrast to today when terrific researchers have a hell of a time getting funded it was almost too easy to get money.

But there was this desire on the part of people like Kety and Gerard who were sort of super-academics to have a discipline and rigour and to avoid both the hucksterish folks, in which category they would put Kline or people who just did it the old fashioned way like Frank Ayd, people who treated patients and reported anecdotally that they all got better. They had a scornful attitude towards these Johnny-come-latelies, who professed to be scientists but who in the minds of the super-academics were not. Some of the criticism was deserved but some of it was unfair.

On that point reading through the volume that came out of the meeting, there was a point where Kline at one point on the issue of rating scales and end points and things like that the risk was that really all they would do would be to put the rabbit into the hat and then think they had done something wonderful when they pulled it out again. That what we should be doing is looking at endpoints like discharge from hospital or moving from the backward to one of the open wards. Anything else is a con job. No-one actually took the message on board - they went ahead and they created all sorts of rating scales but in many ways this surrogate endpoint is a tricky thing isn't it.

I remember when Cade came up with lithium, what was persuasive was that the first patient had been on the back ward for so many years and everybody had given up hope. It's what I call the Lazarus phenomenon. It isn't quite bringing the dead back to life like Jesus did with that leper but it's analogous to it and its damned impressive when it happens. Unfortunately it doesn't happen all that often. Jesus only did it once, as I recall.

A lot of folks these days are very critical about things like the Hamilton scales for example they say well they are not all that great - just because we have got used to them we think they are wonderful. People who know more about them than I do go through a list of criticisms to show how you can get misled by it. It is probably a tribute to our willingness to keep doing things because they are acknowledged by the gurus to be what you should do instead of thinking how could we make it better, how do we measure meaningfulness.

I know when I started in the analgesic game there was a man in Britain whose name I can't remember who had a way of calculating analgesic performance where you got points for pain relief and you took points away for side-effects. I remember thinking that's dreadful because a patient could end up with zero score and it might mean no relief and no toxicity but it might mean significant benefit and significant toxicity the two neutralising each other.

An early cost-utility approach?

Yes but I changed my mind with the passage of time because now I think the most important question you can ask about a drug like an analgesic is what did you think about that drug? Was it good, terrific, moderate, trivial, terrible? You should ask subjects about benefit and harm separately so you can analyse them properly but ultimately it's this

weighing of the good and the bad by the patient which determines whether you would want to have it again. And this is an important question to ask. When I was doing hypnotic trials, for example, at first I was amazed that somebody who had got a dose of secobarbital fell asleep quickly and slept soundly all night through, when asked how it was would say terrible. Why? "Well, because I felt sort of raped by the drug. I was no longer in control of my brain. It's yielding to a chemical Svengali". Well that's an interesting reaction and it's a very important question because if you have a lot of people who feel that way you have either got the wrong dose or the wrong drug.

You appear to me to be entering into an area there that we have completely neglected for 30 - 40 years which is the whole area of self-assessment of drugs. We don't let the patient make assessments. Have we made a mistake?

It's a terrible mistake. There is a wonderful article in a British journal by a man named Jachuk from Newcastle who did a study on hypertensive patients on medication and their relatives. He asked the doctors and the doctors all thought it was splendid because they were studying the manometer. He asked the patients and some of them were positive and some were negative. But the relatives to a man and woman thought that the medications were terrible. They had had no trouble with Dad before he was on this medication - he was behaving perfectly alright and what did they know about his hypertension; it wasn't affecting anything. Dad was not sick until he started taking these pills but now he's a hypochondriac. He's a pain to have around and he is muddled. Three quite different answers - each of them right and wrong in its own way. But if you don't ask them all, you get a bizzare version of the truth or at least only a piece of the truth.

But the pharmaceutical industry are not into that are they? And no one else has the resources to run the studies.

Now they are into a different ball game in this country and in Australia. Now you have got to do pharmacoeconomic studies to get a drug successfully on the market and that is because third party payers whether they are HMOs or Health Insurance Plans with the Government or what have you are asking of a new medication, in what way is this better than what I have been using? Why should I use your drug at all, let alone at the price you are asking for it? So the essence now is comparative performance against what is already available. The problem is that we are not very good at doing these studies yet and we are not as sophisticated as we need to be in trying to evaluate benefit or harm.

A colleague at MIT here in Boston says that outcomes research is like teenage sex - everybody talks about it, a few people are doing it but no one is doing it well. There is a certain truth in that because there this great impetus to do something. At launch you must have these studies available and because you have done them prior to launch they have to go to the FDA as part of your new drug application and because of that you have the FDA wandering into the economics of reimbursement which they are not supposed to do legislatively. But if your economic claims are based on science, the FDA is perfectly competent to evaluate that. If you want to claim that your drug is better in some way then you will have to show it to the FDA's satisfaction. So we are probably going to move more in this direction as people get more sophisticated and they realise what are the important questions to ask. Up until now we have not often been asking these questions.

Let me chase thalidomide - you were involved in trials for it weren't you?

I only did one study with thalidomide as a hypnotic and concluded that it was an effective hypnotic and thank God said something like we don't know enough about safety.. This was before 1962.

Did it actually send people to sleep?

Oh yes. It was an effective drug and you couldn't kill an animal with it unless you covered the animal with enough powder to keep it from breathing. It was clearly an effective hypnotic.

In Germany at the time it was sold over the counter. Now before 62 rules there was certain pressure building up as I understand it to reverse the idea that these new drugs should be on prescription only the 51 Humphrey-Durham Amendments to the 1938 Act.

Prior to thalidomide there was a push to have over the counter anything that could be used safely by individuals if they paid attention to the labelling. So if the consumer could make a judgement about the indication and the treatment it should be available over the counter. But in fact I can't think of any drugs at least in my life time that have been approved for over the counter sales that weren't first prescription drugs.

No but if Thalidomide hadn't happened...

Would they have gone more in that direction? I don't know. Thalidomide was what made the 1962 amendments possible because those amendments were dead as a door nail until Dr Helen Taussig testified showing pictures of deformed babies. All of a sudden you had both houses of Congress unanimously passing this bill. They hardly ever pass anything unanimously and it was peculiar in that the bill had nothing to do with thalidomide babies. It had to do with all sorts of things like getting the FDA into the act earlier and what you needed to document benefit. Safety had been part of the earlier 1938 Act.

Of course some companies had been doing teratogenicity testing before thalidomide but it was not part of the mystique to do it and prior to that time people interested in teratology were folks who used drugs in animals as methods of producing abnormalities and studying how the abnormalities were produced without worrying about clinical usage. But I am not sure that today we couldn't have another thalidomide. I am sure that the tests we do on animals are not perfect for predicting harm. You occasionally get a drug killed because of the animal findings without knowing whether it would be a problem in humans. By the way thalidomide is likely to come back on the market because it works for leprosy and a number of other diseases - graft-host disease and so forth. I think the drug could be used safely with proper attention to avoiding its use in pregnant women.

We have a compound on the market in this country, Accutane, which is supposed to be used only for severe acne but I am sure it is used for less than severe acne at times and it is clearly a teratogen. To get it a physician has to go through an extensive informed consent procedure having people sign off and so forth. I mention it because acne strikes me as a less bad disease than some of the things thalidomide is now acknowledged to be useful for. So if you say well it can't be on the market because it is capable of being a teratogen then what about Accutane? If we are rational we will allow it on the market will all sorts of warnings. If you are a male it is hard to say that you should not have thalidomide if you have got diseases that would benefit. If you are a post-menopausal woman, likewise. And for pregnant women or women with the potential for pregnancy it is going to be a warning problem. By the way it is bizarre to me that we are now hearing we *must* study new drugs in women of childbearing potential because it's their civil right to be studied because otherwise you won't know how to label the drug for them.

This is tremendously risky.

Well I think it is. The Institute of Medicine has come out for this; the FDA has too and I keep wondering are they going to be co-litigants, when some woman who has a deformed baby - and we know that 1-3% of babies are born deformed in some way anyway - says post-hoc ergo propter hoc, I want \$10 million now. Who is going to foot the bill for that - not the FDA; they would say we are part of the Government, so you can't

sue us. And then there is this question that you must study children, you must study blacks, you must study Hispanics, there is no end to it. I am not saying that one should not try to study these subpopulations at least pharmaco-epidemiologically after the drug is on the market. You can't study everything. We know in the UK 4% of approved drugs are withdrawn from the market for previously unsuspected toxicity. In this country, cautious as the FDA is, slow as the FDA is allowing time for trouble to surface in other countries first, 3% of our drugs are withdrawn from the market for such toxicity. So we ought to be studying drugs in the real world after registration because that is the way you stumble on the pleasant surprises as well as the unpleasant surprises.

By the way I should have mentioned something about Beecher. You know he is the father of the informed consent movement in this country with an article he wrote in the 1960s. He sent me the manuscript to read before he submitted it. He had asked me for examples from the literature and I sent them to him not knowing what he wanted. I said Harry you know we never got consent when I was working with you. And he said I didn't say I was without sin. Well but you don't have anything in here about the fact that in your own laboratory you never got consent from subjects. And I said you know it also hasn't been traditional to mention these things in scientific publications. It is conceivable to me, not likely perhaps but conceivable, that some of these investigators got consent but didn't put it in the paper. He said no if they got consent and didn't put it in the paper it's as bad as if they did not get consent at all. Now I cite this one as an example of Harry not wanting fact to interfere with drama. I think most people would have said that if they got consent the fact that they didn't put it in the paper wasn't an indictment against them.

Now if you ask why weren't we getting consent, it wasn't that we were Nazis saying well if we ask for consent we are going to lose some subjects and it is going to be harder for us to do our research. We were so ethically insensitive that it never occurred to us that we should get consent. If you had asked us how these people were benefiting, we could have said truthfully that the patients we studied were interviewed by a technician every hour and if they were not doing well they could get something else which is more than you could say for people not in our study who might be lying in bed for hours having received no benefit from the first dose of morphine and having to wait four hours for the next dose.

When I had a haemorrhoidectomy at Hopkins I came roaring out of anesthesia with the worst pain I ever had in my life. They gave me a shot of pethidine but it didn't work so I said I need another shot but they said no you've got to wait 3 - 4 hours. I said go and get one of your bosses and tell him that I know about analgesics and if I haven't got pain relief by now I am not going to get it in the next 3 hours and so they acceded to my request but ordinarily you would have to live with it. So there were some benefits from being in our studies but also we trampled on the rights of people who didn't know they were in a study. We never asked whether they were willing to participate or not. That is another thing that makes Harry Beecher controversial to me.

When you said he was the father of the informed consent movement... what did you mean?

He wrote an article pointing out that people were not getting it and that this was not right. Now later on it's interesting - having started this revolution in a sense by this article - he then went on to say that the principal, the true safeguard for an experimental subject was an ethical investigator. Consent forms notwithstanding, if you had an unethical investigator that was bad. But he did start the revolution and deserves great credit for it.

It seems to me that we just have not paid enough attention to how well or bad we are doing this and the bioethicists are right in a way when they say it is imperfect but what the hell is perfect in this world? Those ethicists who say that informed consent is a sham

should be ashamed of themselves because I feel much better about research that is being done today than I did before. Yes it is imperfect but at least our patients or our healthy volunteers who are approached are being told that this is a research project, laying out the risks and benefits, which often are minimal so in a sense people are sort of sacrificing themselves for the benefit of science or other people. They are told they don't have to participate and if they do participate they are told how they will be compensated. There is at least an attempt to level with people and I find that so much better than what we did back in the 1950s. What's the alternative - not to do any research at all?

When Hopkins set up its first institutional review board, we met with the lawyers to the hospital who said it's very easy we just won't do any human research. We said no, that is not an option. So they retreated and we set up these safeguards. We don't approve everything. We usually re-write the consent form. We sometimes will be attacked by angry investigators who say they are part of a multi-clinic study and everybody else has approved already and yet the review board wants to change it and we say well that's too bad if other people have approved it, it's not good enough for us. There was one investigator whom we approved a few years ago but because we did not trust him to get consent honestly we insisted that the consent must always be obtained with another person present. So we do try our best to do it more ethically than has been the case in the past.

You mentioned the issue of the pain you had after an operation and being in a sense able to prescribe for yourself which brings me back to the 1962 amendments which copper-fastened in place the idea that these drugs were going to be by prescription only. One of.....

The prescription only came about in the 1940s. The FDA was responsible for that really because they had a problem getting the information out to patients. They felt that if there was a learned intermediary then we wouldn't have to worry about putting all sorts of things on the label because there would be this learned intermediary that would intervene between the patient and the medication.

But of course it means that the average patient has not got the advantages that you had when you are there in the bed in pain and you can say look to hell with this if I actually have to prescribe this myself I will do it. There was a case that was in the news lately - Mahlon Johnson, a physician who has Aids who claimed to have cured himself because he tried all sorts of combinations of cocktails which of course he was able to do because he was able to get access to these things which the average person can't do.

I chaired a committee that got to be known as the Lasagna committee because people could not remember its long name and we were addressing the issue of how to speed the approval of drugs for cancer and AIDS and possibly other life threatening illnesses. The AIDS advocates were the most effective advocates I have ever seen in my life - articulate, impassioned, well informed, willing to be obnoxious if necessary. When we were having the hearings their general attitude was we want access to anything that surfaces anywhere on the globe that is possibly beneficial.

An AIDS activist named Martin Delaney said being an AIDS patient is like being on an aeroplane, the engines have knocked out, you are plummeting to earth, there is a parachute on the seat next to you, you put it on and somebody from the Government taps you on the shoulder and says by the way that has not been fully tested yet or approved - the response is well I'm going to take my chances because I am facing death. Our interviews with AIDS and cancer patients show that most patients with lethal diseases know that they have got a bad disease and are willing to take risks. But what we were hearing at the hearings was more or less let's have access to everything. Now we've got surrogates - you get a drug approved on the basis of a good effect on CD4 lymphocyte

counts without any proof that that makes a clinical difference and now at least some Aids patients are beginning to say gee I think we were wrong. We should have some evidence of clinical benefit and some knowledge about safety and toxicity or otherwise we may not be doing ourselves a favour. That fits in with my own philosophy as well.

When I chaired this committee we had a member named Thomas Merigan, an infectious disease expert from Stanford, and he and I sat down one evening and asked "what if we were God or we were commissioner of the FDA, which is more important than being God, what would we demand of an anti-AIDS drug? And we concluded that we would like a good impact on a surrogate like CD4 lymphocytes or circulating antigen *plus* something clinically beneficial - like feeling better, requiring fewer transfusions or having fewer infectious diseases. Something which might or might not be a surrogate for survival but which would be a good end in itself. I still think that is the way to do it because if you approve a compound on the basis of surrogate endpoint only and it turns out to be not beneficial and even worse not beneficial and toxic, you embarrass the agency, you embarrass the manufacturer and you get a hell of a lot of patients who are angry with you. There has been a turn in sentiment there.

With anti-cancer drugs there is a move towards what the oncologists have been recommending for a long time, namely use of a surrogate endpoint such as tumour burden because in general compounds that diminish tumour size do turn out to have potential for benefit. Its a tricky business this use of surrogates but clearly if there are short cuts to approval then we ought to be using them provided we are doing the right thing.

You were obviously one of the people who pushed hard for the 1962 amendments taking the shape that they did. Peter Temin in his book put you down as one of the people who changed their view as to whether the 1962 amendments were a good thing or not. Your view in the early 1960s was that the whole field of medicine has got so complicated that the average doctor can't really know what to do and has to be told by the expert.

Its not really reneging on my conviction about controlled trials, its just that I think we have gone overboard with believing that it is the only way to come up with any useful information. My feeling is that Bradford Hill was right about that and that we should not be ignoring other ways of getting useful information. I am just asking for a sort of broadening of the evidence required to get a drug on the market. I also think that the process has gotten enormously complicated because the FDA is now in the act all the way through from the request to go into humans to the very end. This has to do not just with clinical trials but with pre-clinical toxicology and so forth. It is now taking 10 - 15 years from discovery to marketing and costs hundreds of millions of dollars - the number keeps going up every year.

Our figure in 1987 dollars was \$ 231 million. Half of that was out of pocket expenses, the other half was what they call the cost of money - what you could have got if you had invested the money and it was paying a reasonable return. We have gotten to the point where a company might well say what the hell are we in this business for. These days a me-too drug is not going to sell at all - in the old days we could make a little bit of money at least by having a compound that was no worse than those already on the market - but those days are gone. The generic industry is out there bigger every year. How can we justify to our stockholders looking for cures for Alzheimer's disease and all the other things that are badly treated.

By the way, everybody says you only need two trials to get a drug on the market, in fact the average number now completed before filing an application is 60 or more. Some of that is looking at children and what have you and some of it is pharmaco-economics but I

can't believe that all of those trials are necessary. What I have been saying now for about 3 years is why can't we have early and continuing collegial relations between the FDA and the sponsors plus an appeal mechanism in case there is disagreement where the sponsor would have a chance of winning were he or she in the right, so that when you get to the new drug application it is self reviewing because you have asked and answered all the appropriate questions and not asked and answered inappropriate questions. Because I am sure that some of what is being done now and contributing to the cost and the time are either unreasonable demands by the Agency or mistaken perceptions by the sponsor of what the agency will ultimately require. We shouldn't put up with that. I am not talking about cutting corners I am talking about asking is this trip necessary every time we are considering doing something. I think that would serve the public well, would serve the industry well and serve the FDA well too because their mission is to protect the public health which means worrying about frauds and crooks and poor quality drugs but also promoting the public health - that's another dimension and that has to do with getting drugs on the market.

I guess the current climate in the public is that you don't actually promote health by getting drugs on the market....

It depends who you talk to - if you talk to cancer and AIDS patients - they are dying for new drugs to get on the market. The public doesn't want the agency to shirk on protecting the public - they want to be protected from frauds. In fact one of the first things the present commissioner did when he took over was to try and get over the shame of the generic drug scandals where some of these generic companies were paying off with trivial amounts of money FDA employees to give their compounds preferential treatment in the process and filing fraudulent data. The agency lost some of its reputation because of this bad publicity.

When was that?

That was 6 or 7 years ago. There were a few instances of shameful behavior by generic companies. There was one company who took a SmithKline and French compound and instead of comparing it with their generic version compared it with the SKF compound in another capsule. I am not sure if there is any evidence that the public was ever harmed by this but it made it look as if the agency had people that could be bought. And the first thing the commissioner did was to apply a cops and robbers approach with massive crackdowns, having inspectors going to visit plants with pistols - a little bit hammy but it worked and the FDA now is back in good odour.

I don't want to diminish that and I don't want the agency to stop looking for crooks and frauds but up until AIDS by the large the agency was only accused by the Congress of poor performance if they approved a drug that later on caused trouble that nobody predicted. Until AIDS they weren't besieged by pressures from Congress - why aren't you getting drugs on the market sooner? And the agency to this day I am afraid still think that type 1 errors are worse than type 2 errors and that the worst that they can do is to allow a drug on the market that doesn't deserve to be on the market - refusing a drug access to the market that deserves to be on the market or slowing it down is less important.

That's always the bureaucrat's response really isn't it?

There was a former Assistant Secretary in the Dept of Health Education and Welfare, as the department was called in those days, who said that if you're a bureaucrat you find that you're like the whale - if you don't surface you don't get harpooned. So stay below the surface of the water. This is true for University bureaucrats too. It isn't just the regulatory agencies.

The 1962 amendments said that drugs would remain prescription only and they said that we want to evaluate the drugs in the way that the experts say they should

be evaluated which was the randomised controlled trials but they also said we don't want drugs that are non-specific - we want drugs for indications that experts say we should have drugs for. In other words for a disease entity. We want to do away with drugs for halitosis and tonics and things like that. Was that a mistake because you could arguably re-classify all of the antidepressants as tonics but called tonics they might have been a lot more acceptable to people than antidepressants - a disease indication can be problematic with the public.

I don't think it has actually been a problem. It's true that you are in bad shape if you go to the agency with trials where you say well we had multiple endpoints. They want you to pick a primary endpoint that you have settled on in advance of doing the trial. They look at other endpoints as a way of compensating for failure by coming up with something totally different.

But there are an awful lot of people out there - 10-15% of the population who have a generalised anxiety depression type of thing - they've fatigue and nervousness and it was okay during the 1960s to take a drug to the FDA which was going to be an anxiolytic. You can't do that now because of the benzodiazepines. So these people have all of a sudden become depressed and we are doing trials with antidepressants which involves a certain fraudulence...

There is a problem because as you were just saying in real life these things don't exist in pure form and you ought to face up to the fact that they don't exist in pure form.

But the 1962 amendments at least for psychiatry don't do that.

I think you're right. I had not thought of it that way but I think that's right. And it's again part of this desire to keep things as clean as possible which is not a stupid experimental approach when you do experiments in the laboratory. You want to have the variables under your control - if you use rats of different strains and dogs of different strains you just make it a bit more difficult and so I can see why you would want to study - if you could - pure anxiety or pure depression. On the other hand if you do studies of those patients it seems to me the very least you have got to worry about is will these findings also apply to impure anxiety and impure depression.

It seems to me that the clinical trial process for neuroleptics would be so much easier if the FDA were prepared to accept tranquillization as an indication. But say we want a drug for schizophrenia, whereas in actual fact its quite clear that the drugs we use for schizophrenia are relatively non-specific to schizophrenia. They will treat any psychosis, they will even treat people who are depressed or anxious. What these cases all have in common is some form of tranquillization which we have not looked closely enough at because of the fact that we have been focused at the disease endpoint the whole time.

At one point there were ads run by I forget which company for a major tranquilliser which had elderly patients kicking chairs - obstreperous, cantankerous you know. And that got into bad odour because if you have elderly patients come in and you ask what's bothering you, they don't say I'm cantankerous. I know myself, having worked in hospitals, that if you have a patient especially if he is across the hall from the Nurses Station who every 15 seconds is bellowing, after a while there is a desire to write a tranquillization order. Who is being treated in that case - is it the nurse being treated or the other patients? It's a real life problem but if you demand evidence that that tranquillisation benefits the patient then that's a lot harder than is it benefiting the nurses for example or the other patients on the ward who finally have a chance to sleep at night. That has been part of the problem.

Sure but the way the amendments have gone again at least in psychiatry has been to say well we want drugs for schizophrenia. This is the indication the experts say we should be trying to develop drugs for. And we end up with the idea that these

drugs are anti-schizophrenic in some sense whereas in actual fact what we have at best is a therapeutic principle that may be useful in schizophrenia. Have the amendments forced us too far down the road of an illusory therapeutic specificity?

Yes it is probably what Alfred North Whitehead, the philosopher, called mis-placed concreteness. Probably the psychiatric profession are accomplices of this by their use of scales and what have you.

We want to be part of real medicine. Can I hop to another theme. You took up the first Chair in pharmacology in Johns Hopkins .

The first division of clinical pharmacology in this country anyway. A group of people devoted entirely to the study of drugs in humans, sometimes going to animals, but always with a focus on humans. That was 1954.

Were there any other clinical pharmacologists in the country then?

There were, here and there, and shortly thereafter other groups formed. There were some leaders - a man named Leon Goldberg who used to be at Emory and moved to the University of Chicago. A man named John Oates who ultimately became head of the department of medicine in Vanderbilt. A man named Daniel Azarnoff who was the group leader in Kansas City. So there were a few of us early in the game who were charismatic leaders who got training programmes started. We got training funds from the National Heart Institute, because a man named Bob Grant there thought that clinical pharmacology was a good thing even if it wasn't entirely cardiovascular.

So we got off to a good start but I have been disappointed in the evolution of clinical pharmacology. I think the Swedes and the Brits have done it better. You have Chairs in Great Britain. The Swedes have Chairs and infra-structural support for a unit in every one of the Swedish Medical Schools. In this country we haven't achieved that. My guess is that in Britain and Sweden if one of the leaders of one of these units or the occupants of a Chair died or retired they wouldn't hesitate for a moment to replace that person. In this country not infrequently what has happened is if the charismatic leader leaves - had he been a haematologist or a cardiologist the academic leadership would say well we have got to have a haematologist, we have got to have a cardiologist but they don't say that about clinical pharmacology. Partly I think it is because clinical pharmacology is a generalist speciality or can be unless you focus on just one kind of drug and the other specialities say who are these guys who know everything about everything. They must be dilettantes at best.

It has been disappointing to me especially because I would have thought that in the year 1996, every hospital of any size would want a staff clinical pharmacologist who might on the one hand be a therapeutic conscience for the institution and on the other hand help to make cost-benefit judgements. It is true we do have doctors of pharmacy in this country - PharmDs - I don't know whether you have them in Britain or not - and they sometimes play that role in hospitals and I am not decrying their use but it seems to me that having a medical degree ought to augment the ability to do that provided you don't lack the proper training in pharmacology. So I can't say I feel happy about what has happened to clinical pharmacology in this country. I am sometimes called the Father of Clinical Pharmacology but I don't feel as if I've spawned a discipline that is properly appreciated.

In this country a clinical pharmacologist has more of a future in government - the FDA - or in industry neither which would dream of trying to function without clinical pharmacological expertise. Now it is true that if you are an MD or PhD or a PharmD or anything you are poorly prepared for a career in drug development and drug regulation. You have to do things that you have not learned in the process of getting those degrees. But once you have learned them you will be very useful in the FDA and in a drug

company, whereas in academia there are plenty of institutions who say we can get along without a clinical pharmacologist. To me that's a pity.

One of the awfully curious things at times is when you go along to an ACNP or BAP meetings which are supposedly for pharmacologists is that you find anything from 300 to 1000 clinical psychiatrists or behavioural biologists and you can probably count the number of actual proper card carrying pharmacologists on the fingers of two hands.

I think you're right. A lot of the sessions are rather esoteric for many of the people who go to the meetings - and lots of people don't go. The ACNP prides itself on having good scientists be they biologists or epidemiologists or clinicians or what have you. But in fact over the years it is fair to say that some of the folks who got in early in the game wouldn't get in today - they would be seen as "just clinicians". Frank Ayd who was president of ACNP at one point would probably not get in today.

Is it a problem that groups like ACNP are becoming almost neuroscience societies?

You are right. I don't go to the neurosciences meetings but my guess is that you can overlap them with ACNP without any trouble at all. Part of the trouble is that - Einstein used to worry about this - as science gets more and more complicated it's hard for the human brain to cover a lot of territory. If you get a research grant in this country from the NIH, God forbid that you should strike out in a whole new direction that isn't well circumscribed. That is part of the problem - how do you avoid the specialist versus generalist tension. And there is no doubt in my mind that for certain kinds of molecular biology, you damned well better not be a dilettante. Do it well or don't do it at all. We have always had this need for something that over-arches and brings people together but how we achieve that linkage I don't know.

One hears a lot of talk these days about cytobiology and molecular biology and receptorology and computer assisted design and whatever, as if ultimately you didn't need whole animal research and whole human research in order to see how things work out. No matter what the 3D configuration looks like if the molecule doesn't get into the brain it is not going to have any effect. Sooner or later you have got to move away from cells and molecules to the big picture.

I heard that put awfully well by Silvio Garattini who said you have all these people arguing that we should not be doing work with animals because it is so far away from man but he said the same people then say that we should be doing work with cells which is even further away.

Well that's right. Would to God we had good models for the Merck man that I mentioned earlier. He would love it if somebody had an animal or a cellular model that worked. That to me has always been the definition of a useful model. I have a slide of this beast, that I call the Hound of the Baskervilles, straining on a leash and the next picture is of him tranquillized by amphetamine. I don't care whether this dog is the canine analogue of clinical hyperactivity and attention deficit disorder, if it predicts efficacy in attention deficit disorder it is a good model regardless. I am not going to go around looking for schizophrenic mice because I don't know that I can find them even if they exist. So I am left with models that are usually chosen on the basis of something that has been stumbled upon serendipitously in the past. Then the question is whether this model is only going to allow you to predict more things like what led to this model whereas what you may want is something quite different.

In the field of analgesia my nalorphine experiment wasn't predictable in animals and to this day wouldn't be. There are no good animal models for the agonist antagonist analgesics or for the non-steroidals. I remember one time going to Upjohn and they'd had

for years a screening programme going to come up with a substitute for aspirin. They said one problem is we can't pick up aspirin in this screen. So I asked said well what are you using it for then? And they said, the girls are terribly good at running these assays.

One is left with a desperate where the hell are we. We can't just pick compounds off the shelf. You have got to pick them for some clinical trial somehow. We do the best we can and the trouble is we are not terribly good at it. Some things we are better at than others but in the field of oncology, which I have been forced to get into for a variety of reasons, for the traditional cytotoxic drugs we have models that are not so bad but if you come up with new things - anti-angiogenesis factors or whatever - things that don't affect a tumour but affect the spread, those are different models that will have to be tested empirically. It's a constant challenge - how the hell do we use theory or serendipity or common sense to allow us to pick candidates, knowing that thousands of chemicals are synthesised for every one that goes into humans and of the ones that go into humans only 20% or 25% ever make it to market. So it is a risky inefficient business but what else can we do? I wish I knew.

Can you account for the explosion in health care that has happened post-World War II and perhaps in this country more than any other country in the world, there has been an exponentially rising number of general physicians, surgeons as well as psychiatrists.

Well, medicine has always been a good profession to go into even today when people say we ought to close every 5th medical school and cut the class sizes and so forth. Yet there are more applicants this year than we have ever had. I think it is because they say well compared to what is medicine bad. We have had the greying of the population which means more people needing medical care. We have had explosions of transplants, new hips, new knees, new CAT scanners, new MRI machines, new drugs, new surgical procedures. Science has come up with a lot of things that could be delivered to the public if society is willing to pay enough for them. So our health care expenses are up to 14% of our gross national product at the moment which is pretty high. A lot of people are saying "that's enough".

Now my prediction is as follows: we will go through a period, which we have already entered, where there will be strong attempts to cut the fat out of the system. Knock out the prescribing of unnecessary drugs, unnecessary surgery, unnecessary CAT scans, MRI's and what have you. This is a finite move pitted against the infinite ability of science, unless we stop supporting research, to come up with all sorts of ways of spending money. Now some of those ways will actually save money - for example now that we know that peptic ulcers are caused by *Helicobacter pylori*, we can cure it and I am sure that the ledgers will look good. But for many things you are not going to save money. You are going to make people feel better. If you have got a painful hip and you get a new one, you feel a lot better and you are more mobile but economically it may not mean all that much. So what does that mean? I think it means rationing but a different kind of rationing from what we have always had.

First of all there is the rationing in war time on the battle field or in floods, earthquake, typhoon, where you triage. If I take care of those two dreadfully sick people I can't save 20 less dreadfully sick people. And that engages us in a statistical morality. But today we are facing something quite different. We are now talking not about our ability to deliver but whether we can afford it. That to me means that we are probably going to keep the safety net where it is so that there are certain things that everybody is going to have access to and then other things that not everybody will. There are two determinants of access which I have seen in every country. One is geography. If you are an Eskimo on the shores of Hudson Bay you don't get the same kind of treatment as if you were living in Toronto. The other determinant is personal wealth. If you are wealthy enough,

you don't have to wait in line to have your cataract operated on. You go to another city, another hospital or another country. Now is that anti-egalitarian? You're goddamned right it is.

But lots of things in this world aren't egalitarian. We don't all live in the same size houses or drive the same cars or have the same boats or what have you. You might say that health is different from having a car. Yes it is and no it isn't. So I see an increasingly painful scenario at least for the older docs who grew up in the days when you did what was best for the patient. Early in my career I worked in hospitals where we undercharged the poor or charged them nothing and overcharged the rich - if you want you can call it the Robin Hood School of Medical Economics. At the end of the year if the hospital had a deficit you passed the hat in the community and raised the difference. It worked pretty well actually but that isn't the situation any more.

Now we have managed care which some people have said is really managed cost not managed care where we have outrageous guidelines such as you are entitled to two days of hospitalisation, if you come in with pyogenic meningitis. That's ridiculous, after two days to go home with a serious illness like that. That should never have been allowed. Now they do say "use your judgement, if a patient needs more than two days" but then you may not get reimbursed for the extra stay. It is a gloomy scenario that I see ahead of us. But if our society insists on capping the percentage of GNP spent on health I don't see any alternatives.

In Oregon 5 years or so ago Medicaid had just so much money to pay for the health of the indigent - most of whom were women and children - and they decided that they wouldn't do any liver transplants on chronic alcoholics because they're expensive and the money for one liver transplant could vaccinate a thousand children, a socially more justifiable use of the money. Now that is reasonable enough unless you are the alcoholic needing a liver transplant. It is very tricky. But the one good thing that is happening is that people are beginning to talk about it as rationing. For quite a while nobody talked about rationing. The R word was a bad word because it connoted war time, petrol, etc.

You have been looking at the psychiatric business from right at the start - the 1956 conference - where you were able to look at this bunch of people trying to work out their problems. Who has impressed you in US or world psychiatry as a real player, people who have actually contributed anything substantial or has there been anything substantial? We've got the trappings of being part of medicine now but has there really been anything....

I would give credit to people like Delay and Deniker, Lehmann and Freyhan, and Nathan Kline and Frank Ayd and Cade and Schou - the people who opened up the field. I would give Jonathan Cole a lot of credit too because the psychopharmacology service center he set up, while it existed, did stimulate excellent research. I would credit Max Hamilton for his scales imperfect though they are. I had a colleague, who borrowing from Max Beerbohm who used to be referred to as the incomparable Max, used to refer to Max Hamilton as the comparable Max. Hamilton was a curmudgeonly man but he worked hard and he did contribute some techniques for quantification. Michael Shepherd was important in getting the concept of trials going and Joel Elkes also had an impact there. In this country, Elkes started the ACNP and he deserves credit for that. Maybe part of the problem today is that there are not a lot of giants around who can go out there and grab our Society and shake it and say come on let's do something about our problems.

Is there a change within the industry ? 40 or 50 years ago you would have had people who were possibly medically qualified to span the whole range of drug development and now you've got the MBAs running the show and looking at the bottom line money wise.

Well on the other hand I would say that during my lifetime I have seen the quality of the physicians in both the FDA and the industry improve considerably. They were often dreadful in the old days. Many were people who could not make a go of it anywhere else. That was responsible in part for the fact that even good people in the industry were often shunned by their academic colleagues. There was a time, believe it or not, in this country, in the 40s or 50s, where if you were a member of our pharmacology society and you went into industry you were thrown out of the society. It showed how pejoratively the industrial side of things was seen. I remember one man who went to Eli Lilly saying to me that he was accused by his former boss of selling his soul for a mess of potage.

Things are better in part because life in practice is not as attractive as it used to be. If you are in research you may say today in industry somebody else is going to come up with the money so I don't have to get a research grant from the NIH or the MRC. So it has gotten better but I can't say that we have a plethora of giants. Maybe it is that our society does not have many giants in general. I was at a meeting recently where they were talking about the history of pharmacology and it was pointed out that May & Baker's sulphonamide was given credit for winning World War II because Winston Churchill's pneumonia was successfully treated with it. It's hard to imagine the outcome of World War II being the same had Winston Churchill not been around. When I look at the people running Governments these days it's hard to say the same, although Margaret Thatcher for all her faults and ego problems was a super woman of sorts.

One of the unfortunate things that has happened in my view is the P value madness. It was just an arbitrary decision that resulted in 0.05 being the magical barrier. As far as I can see there is nothing magical about it. It is encouraging that a few journals like the British Medical Journal and some others have begun saying look don't talk about things being statistically significant or not just give us the p values and confidence intervals and let people judge for themselves because in this world we do a lot of things with less certainty than 95% of the time. It seems to me that the more rigorous you are about that the more likely you are to make type 2 errors.

If you look in the psychological literature and the statistical literature you will find a lot of folks who are opposed to the magic 0.05. Editors by and large are religiously devoted to it and most clinical scientists are. The FDA is as well and it just seems silly to me - a bit like intention to treat analysis. You ought to be able to live with something a little more giving than that .

On the other hand, the literature used to be full of underpowered studies that could clearly miss clinically important findings but a good thing that is happening these days is that the pharmaceutical industry is unlikely to start a trial these days without some sort of power analysis. They ask themselves what would we be unhappy missing 80% of the time. That is all to the good if one thinks back to our failure to do that in the past and the fact that most people if they came up with a 0.10 value act as if there is nothing suggesting activity.

Did the analysis of variance idea mislead us to some extent? It gave us false confidence that we can pick up differences that are statistically significant but maybe not clinically.

Yes that's the other bad part. If you have a trivial difference and you study enough patients, you come up with biologically insignificant but statistically significant figures which again is obviously another reason for putting more reliance on confidence intervals, where you say well it might be as little as this or it might be as much as that. That to me as a clinician is more helpful than knowing that some trivial effect achieves this magical level of statistical significance.

The bad thing that is happening these days is I've noticed that the Editor of the Lancet recently talked about how he might turn down a paper if it did not have women in it for example. He is following this tendency to study everyone - women, the young, the old and so forth. When I read it I thought I hope the paper isn't a study of prostate cancer. It would be a pity if the Lancet got to that kind of Gulliverian craziness. I remember one time going with Beecher to a meeting of biological editors. They had decided that if something had been learned through an unethical experiment it should not be published. And I asked the question what if somebody came up with a cure for lung cancer that had been discovered in an unethical way? Would you really feel good about hiding that from the public or would you not prefer to publish it with an accompanying editorial denouncing how they had done it but thanking god that a breakthrough had come?

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