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11 Michael Shepherd

Psychopharmacology: specific and non-specific

You were in the US in 1956, just after your reserpine trial was published, just when things were beginning to roll in psychopharmacologically-speaking. How did the field look to you then? Were you at the Conference on the Evaluation of Psychotropic Drugs in 1956?

Well what I can tell you what happened. I was working at the time at John Hopkins. I was on a postgraduate fellowship in the School of Public Health. Because of my other interests I had made contact with a lot of people in the States and one was of them was Louis Lasagna, who was really the driving force behind clinical pharmacology. He was familiar with some of the work that I had been doing and was still doing. He was the editor, at the time, of Journal of Chronic Diseases and he was also a very nice man. Clinical pharmacology is a very curious subject. You are squeezed between the God-like figures of medicine who believe they know all about treatment and the pure pharmacologists who are only interested in receptors and so on. You need to have a certain element of determination and he had it.

He and I got on very well and it was he, I think, who first told me about this conference. There was set up, in Washington, a Steering Committee of quite important people – Seymour Kety was one and Ralph Gerard, Joe Brady, the experimental psychologist, and Lasagna. The Secretary was Jonathan Cole, who at that time was a public health employee of the US public health service. He proved to be very efficient as a manager. I was invited to sit in on the planning discussions. I used to go to Washington every month and these rather high powered people would come together and they actually planned the structure of the conference. By virtue of the fact that I was there, I participated. From time to time they would ask me about somebody or some point of view. So I had a ring-side seat at that conference which was the first major national conference in the area.

It also set the seal of academic respectability on this subject. You see in the States at that time there were a number of mavericks. People like the late Nathan Kline. They were pressing for the mass introduction of psychotropic drugs everywhere. It was about that time that the Brill and Paton paper was published from New York State, in effect initiating the era of de-institutionalisation but attributing it to the mass introduction of drugs, which of course was

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meat and drink to the pharmaceutical industry. I think that these hard headed scientifically inclined people, who came from several disciplines – they weren't by any means only psychiatrists, had become aware of the need to begin to take a hard look. That was the first overall attempt to look at the issues within the United States. I suppose I played a minuscule part by just knowing the people and being able to discuss some of the matters. Of course, in the process I did form contacts with many of them which were very helpful later on.

You'd run the reserpine trial before that ? Was that the first properly run randomised double-blind study in psychiatry or was Mogen Schou's lithium study which reported in 54 or Joel Elkes' study the first.

The truth of the matter is Charmian Elkes' should have had the credit for that study. She actually did the planning. I was involved with 2 studies. One was the reserpine study, that you mention...

How did that come about. The subsequent history of reserpine is, of course, that people become depressed immediately on it and throw themselves out of windows but... the results of your study were entirely the opposite, how did that actually come about and how do you account for the fact that it has vanished without trace.

Those are 2 separate questions. I'll try to answer the first because I was involved. The answer to the second question raises the question of why do some studies last and others don't when there's no essential difference between them. I don't think it has anything to do with the quality of the study, it has to do with the receptivity of the scientific and medical community at a point in time.

As far as the first question goes, what had happened was that I was a senior registrar at The Maudsley Hospital, on the Professorial Unit. The drug industry was just becoming alert to the possibilities of something quite new in psychiatry. They were bombarding, on a very small scale compared with what we now have, people in the teaching hospitals to pedal their wares. They sent material to Aubrey Lewis. I don't think they realised quite who he was. I think we had a patient who in some way had either taken reserpine or was taking reserpine and, talking to him at the time I raised the question how difficult it would be to know, whether if we did give this patient reserpine, there would be any difference. And he said 'well have you seen all this stuff', which had come through the mail, which I hadn't.

When we talked about it it was clear that the whole question of the clinical evaluation of treatment was appallingly low in psychiatry. It was one of those areas that it's difficult now to realise how primitive it was. To give you an idea of how appalling it was, people who took William Sargant seriously. In discussing this with Aubrey Lewis, who was very closely involved with the MRC, we naturally got on to the whole business of the clinical trial – Bradford Hill and so on. During the discussion I remember saying well, intrinsically there is no reason why we shouldn't try and do this and he produced some material from I think the New York Academy of Sciences, which was written by a well known bio-statistician, I think Mainland or some such name, and out of that came the idea of trying to see how far you could, at a very simple level apply

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these principles to a psychiatric issue. I now realise I couldn't possibly have chosen a more difficult group ... the idea of taking anxious depressed outpatients makes one shudder because one now knows how difficult it is to construct criteria and refine them and measure them which are essential.

At the same time I did another controlled trial in chronic schizophrenia with David Watt. Now that was much easier in many respects because you were dealing with a relatively homogenous population of inpatients. And although I wouldn't compare them with tuberculosis or rheumatoid arthritis, in terms of the measurements, the principles were much more easily applied. I think the value of these things in retrospect was simply to show that you could do it. This was doing it with no money. We had no money from the industry, we did it ourselves. That meant the co-operation of the nurses, a lot of hard work in collecting the questionnaires and doing the statistics. I certainly learnt an enormous amount about the problems that arise, which stood me in very good stead later on and I suppose historically they certainly do have some value, simply because they were so early. There's nothing especially original about that in itself but it did draw the attention of people who were more academically inclined to the need for this and it stimulated the pharmaceutical industry. I had a lot to do with the industry at that time and they were very aware of the importance of this sort of thing for the large programmes that they were preparing then for new drugs in the future. So I would have thought that it made a modest contribution to the subject at the time.

In terms of trying to parcel out which came first – were you aware of any other trials being run before that within psychiatry? Linford Rees was doing some controlled trials on desoxycortisone and things like that. Did he influence you at all?

No, not at all no. I didn't regard them as meeting the criteria that I felt had been laid down by the people who were responsible for the model clinical trials which had been applied in somatic medicine. You bring back these distant memories. When I started working with reserpine, I had to familiarise myself of course with what was going on. A lot of it was in the field of hypertension. The psychiatric side was very subsidiary. There had been a meeting at the New York Academy of Science in which Nate Kline, as always, played a prominent part and I went to him and he sent me everything. I think it was Ciba who was producing reserpine and he had access to the unpublished material. There wasn't anything. I was looking for some sort of predecessor on which I could base our own study and there was nothing that was available.

You actually used placebo didn't you, which the original Bradford Hill trial hadn't. So the idea of using a placebo was new.

I think placebos had just come in later on after the early MRC studies.

Harry Gold hadn't been doing an RCT but he had been using placebo. Was there anyone else?

Well I wrote a little thing about the placebo recently. That was a very interesting experience itself. When I read that paper, which was about 3 years ago, the

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Chairman of the session was Louis Lasagna, now the distinguished Dean of Tuft's University and of course one of the original collaborators with Harry Beecher on the work that really put the placebo on the scientific map although it's had to battle to stay there. It was very interesting because I read this paper to a virtually all-American audience and as you may know the Americans are not modest at question time – there are no polite this that and the other. When I finished he, as the Chairman, said ' this paper is now open for questions'. Nothing happened. Half a minute elapsed, a minute elapsed and nobody said anything at all. Lasagna then said in his characteristic way that in the circumstances we would have to move on to the next paper but he couldn't refrain from commenting on this unnatural silence. 'There are 3 possible explanations' he said. 'First you were all asleep and therefore you heard nothing. Secondly it was so bad that since this speaker has come 3,000 miles you didn't want to embarrass him. Third it is genuinely so original and new that you don't quite know what sense to make of it. I'll leave you to decide which it was'. Afterwards we had dinner together. He confirmed, because he's a man who knew all about it, that this whole area of the placebo is totally neglected. Did you know about Beecher?

No

Oh I can tell you about Beecher because that's highly relevant. He was Professor of Anaesthetics at Harvard. He was a footballer. I think he played American football for Harvard. Now that puts you in the first division as far as American life is concerned. He was a powerfully built solid character, very much in the mainstream of medicine. During the War he was in charge of a base hospital when the Americans were fighting the Japanese in one of the Pacific Islands. There was a terrible battle going on and the casualties were coming in and emergency surgery was going on 24 hours a day and they ran out of morphia. Well this, of course, is a disaster because they were in shock and pain and you couldn't operate. The story, as I recall it, was that accidentally one of the nurses gave an injection of still water and the patient came out of shock and lost his pain. And Beecher, who was an extremely observant clinical scientist, was struck forcibly by this observation which was repeated. I think for a time they had to use distilled water because the supplies were not coming in.

This was a sort of Pauline conversion as far as he was concerned because he was very much a bread and butter physical doctor and when he came out of the services he decided to study the placebo. Lasagna was one of the group that worked with him in his laboratory. He had psychologists, physiologists, pharmacologists, clinicians and so on. Because of his reputation they all had good positions. He wrote a paper which was very influential in JAMA, called the Powerful Placebo in the mid-50's. There was then the beginnings of a serious interest in the placebo, not as the bit that gets left behind, but as something you really must take in its own right.

The moment he retired the group broke up. I knew several of them. Some of them worked at Hopkins. I remember talking to them one evening and

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what they said was 'well it was all right as long as Harry was there because he looked after us. But if you want a career in American medicine it's better not to study the placebo, its not really a topic that is popular with anybody'. They all drifted into different areas, in the process neglecting the basic work that had been done. And if you look at Goodman and Gillman, 2500 pages, you find 4 or 5 paragraphs on the placebo. Its chalk that you give because irritatingly about 30% of people do get better on it in clinical trials but they pay no regard to the fact that underlying the whole issue of the placebo is the crucial issue which I tried to bring out in my paper of specificity in medicine, specificity of action. The idea that the disease is due to a specific agent which can be counter-acted by a specific substance which eliminates the toxic features.

On that basis which is really Claude Bernard's basis for experimental medicine, the whole of the natural science approach to medicine is constructed and its quite wrong, not in itself but because it's so limited. It cuts out the non-specific factors which are in fact at least 50% and probably more in the aetiology of disease and of treatment and among them is the placebo and the nocebo, both of which are extremely powerful.

When you come to psychiatry, where the bacterial model which is really what underlies this, is largely inapplicable, you find that the non-specific component of both causation and treatment gets bigger and bigger. This is where all the rubbish about psychotherapy, social treatment and alternative medicine comes in – this is all non-specific blarr, some of which may be empirically valuable but you can't tease it out if you begin with the assumption that your only aim is to look at specificity. It all gets obfuscated. So you have psychiatry virtually shattered by pointless discussions – are you a psychotherapist or are you a physical doctor and all this nonsense that goes on. If you shift the ground of the argument to say we are actually talking about degrees of specificity and non-specificity which have to be given operational meaning and then evaluated, in just the same way that you would penicillin or anything of that sort, then things becomes scientific. We don't have many answers but at least you can approach it.

My personal view has always been that there should be a Chair of Placebology which I think would save the National Health Service huge sums of money, it would improve medical education and it would take all these factors into account and give them their correct weighting. Whereas, as you know, so much in medical schools and medical practice is hopelessly weighted in favour of this quest for specificity.

Do you not think though that the introduction of drug treatments as we've had them have worked heavily against that model. With DSM III and DSM IV we're heading towards a psychiatry that's dominated by a categorical model of disorders and the industry invites us to line up and provide magic bullets to hit particular targets.

We are now moving into a much broader area because it concerns treatment and treatment is what doctors are supposed to be concerned with. As far as psychiatry goes my own feeling is equivocal on this. I gave a talk about Kraepelin recently, who is really the representative of all this in psychiatry. This is where

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psychiatry went down the wrong road completely. There was a misapplication of natural science. Not that there's anything wrong with using natural science, of course, that is one of the most important areas of conceptual thinking. But the assumption that natural science is it ignores all philosophy. It ignores subjectivity. You can't put subjectivity into the natural science model – you dismiss it. Psychology is Wundt and Wundt is animals and twitching and what is psychopharmacology – it's updated Wundt's pharmacopsychology, which is where Kraepelin cut his teeth. And what did they do, they measured work curves, tapping and so on. This would be now regarded as physiological psychology and it's fine. There's absolutely nothing wrong with it. But when you say that this is a model that you use for studying bereavement or anxiety states or something of that sort, there's a gap which is only bridged if you assume that you can extend the natural science model to encorporate everything else.

Kraepelin is responsible for this. I don't mean Kraepelin personally, he was merely the representative. And Kraepelin was a fascist – the whole subsequent development of the genocidal racial hygiene policies in Germany stem from this. His successor was a member of the SS. So one could actually see if you look at the facts, which have been very carefully obfuscated, that psychiatry took the wrong road and is still taking the wrong road. It's got much wider aura this question than just what drugs do you give for what patients. It underlines a whole attitude to the subject and it's been woefully misrepresented, which I think is a pity.

Talking about Kraepelin naturally brings Adolf Meyer to mind. Was he still at John Hopkins when you were there?

No he wasn't. Mrs Meyer was there. He had died. I was doing some work on a completely different subject, a clinical subject and I went to the library at Hopkins where I was confronted with large numbers of dusty volumes. The librarian told me that these were some of Dr Meyer's volumes but they were only a small number and if I got in touch with Mrs Meyer, who lived in Baltimore that I would get more. So I got to know her. I used to go out and spend long periods in his library. I learnt about Adolf Meyer through his library, just as years later, when I brought Willy Mayer-Gross' library here, I spent 2 days in his house in Birmingham looking at his library. You get to know a person when they've got 5000 books and you see them.

Meyer's trouble was that he was stranded between the English and German languages. He could not express himself. If you read his papers, they're extremely difficult to follow but he was a vastly erudite man. When Kraepelin first produced his 5th edition of his textbook, Meyer invited him to Baltimore and wrote a review in glowing terms saying 'this is an advance, this is a man who has actually given some order to the chaos of clinical psychiatry'. But 15 years later Meyer wrote a review of Kraepelin's contribution which is really very interesting. It gives him all credit for what he did and then points out how hopelessly inadequate it was. But because Meyer wasn't a polemicist who would rush around and make a fuss, I think his views were accepted as those

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of a distinguished person but when he retired he was swept away by other forces.

His understanding of the situation actually was best represented by people like Aubrey Lewis who took over this broad psychobiological standpoint and tried to put it into practice. Meyer himself, I think, was so hopelessly handicapped by his inadequate mastery of the English language, that he didn't really make these points clearly enough but he appreciated what was going on.

Let me take you back to one of the other trials in this period which used something of a randomised design and also placebo – Mogen Schou's first study with lithium. You obviously weren't aware of that while it was happening but it appeared in 1954. I'm trying to chase where the idea of the randomised trial came into psychiatry from. As I say there's probably about 4 people we need to look at. There was yourself, Linford Rees, Joel Elkes and Mogens Schou.

I was aware of Schou's study. I was aware of most things going on at the time. Yes, I suppose they were for quite different reasons all moving in the same direction. If you take the general view that after all what determines what goes on is events and the climate of opinion rather than some shattering individual that sees through it all, this sort of thing was probably in the air and it was a question of who and how it would be introduced. If you take just those 4 people, I don't know if there are any more, but if you just take Schou, he went through the motions and then in effect said 'you don't need this, it's evident, I know'. Rees never really focussed on just one thing.

I think I became more and more convinced that this was a fundamental axiom in the way you look at the theory and practice of psychiatry. How you applied it was another matter. I was reinforced in that view when the MRC Clinical Trials Committee was set up because then I spent nearly 20 years in close collaboration with Bradford Hill which was an unforgettable experience. He was a most remarkable man.

Why do you say that?

Well I'll tell you a little story. When the Clinical Trials Sub-Committee was set up – this itself caused a little flutter in Park Crescent – the MRC what were they doing with all this strange stuff? But George Pickering, who was very influential was Regius Professor of Medicine at Oxford and he gave the blessing. He had worked a little bit with Bradford Hill and Doll, of course. So they set up this Committee with Bradford Hill as the Chairman and I was the Secretary. Bradford Hill was not medically qualified but he had been borne and bred into medicine, he thought like a doctor and knew a great deal about the medical profession. I had only met him 2 or 3 times. He was a very charming man.

It was suggested that if we were going to mount a trial that we had to soften up opinion. This is the way the Council thinks. One of the things that was decided was that it would be a useful thing, to have a group of eminent senior psychiatrists, professors and mental hospital superintendents come along to the Council for a morning, have coffee and biscuits and be asked what did they

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think of clinical trials and the possibility of evaluating this. I was merely the Secretary, so Bradford Hill did all the talking. The assembly arrived and there were about 10 of them. You could imagine who – they were the people at the time. They were all asked their opinion and they virtually all said the same thing which is that, of course in theory, clinical trials must be supported, after all its science, but this doesn't replace real clinical knowledge. I mean the bedside manner, the understanding, the experience – in my Unit I always teach that etc etc. Well one after the other said this and Bradford Hill was politeness itself. He just nodded and so on. I suppose they were there for about 2 hours and as the door closed on the last of them he and I were left alone. There was a sort of silence and I remember, we were sitting at opposite sides of the table, and he suddenly looked at me and said 'we're going to have trouble with this bunch' and I realised that he was spot on. He knew exactly who he was dealing with.

He always said he didn't understand sums. He had difficulty in multiplying things and so on. He wasn't a high powered statistician. But he had a feel for what was going on. He and I spent a long time talking about the design of the 1965 multi-centred trial. I was very impressed by the speed by which he picked up the issues. He knew nothing about psychiatry. He had been asked by the Council to come in because you couldn't trust ... psychiatrists... so you had a Professor of Medicine and a Professor of Biostatistics and a young nobody, myself, there for the ride just to keep the show on the road. But he understood, in a way that Pickering never did what the problems were.

He was fascinated by the issue of how you measured subjective phenomena. If a chap says 'I'm depressed' you can't break that down to some physiological correlate and assume that this is the core of the disease. For him this posed a real problem and I was very impressed with the speed with which he grasped the situation, the way in which he helped to design a realistic study and then in the analysis of the data and the discussion of its implications how he brought to bear his vast experience in other fields of medicine to make sense of what we'd done. I've never come across anybody who has been able to do it quite as efficiently as that. Right up to the end of his life, he was as sharp as a needle, and he was courteous and helpful and in every way a pleasure to work with, and you can't say that about everybody.

One of the offshoots of the RCT has been the current craze for evidence based medicine, which stems from the Archie Cochran book I guess – the idea that if only we were to restrict ourselves to procedures which were demonstrably effective then we wouldn't be wasting all the money in the health services that we are wasting and we wouldn't be doing some of the awful things to patients that we are doing.

We would also, of course, never make any advances because all advances depend on guesses which we call hypotheses – most of which are wrong but some of which are right. In terms of the logic of the scientific process the evidence comes after the hypothesis. You must begin with a hypothesis and that is a guess. I knew Cochrane but this again is pushing the thing to, I think, an

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absurb extreme. Of course, it's true that the whole discipline is cluttered up with procedures for which the evidence is meagre at best and there is a case for trying to make quite certain that that is minimised. If that's what meant by it – certainly – but it eventually stiffles everything else.

I was talking to somebody about this just the other day. If you take, what I suppose is the biggest issue in medicine at the moment which is the AIDS pandemic, there's an enormous amount known about AIDS. There's an enormous amount of stuff which calls for tidying up, not least the psychiatric aspects of AIDS, but the biological advances in AIDS don't have any evidence yet. You've got to pursue the matter with guesses and experiments and research and so on. Sticking to the available evidence at the moment simply leaves us in a static situation and I think that's true of most forms of mental disease as well. The value of this evidence based medicine is as a method of thinking. If you could really get into medical schools this notion it would help considerably to improve the intellectual calibre of practicing doctors. I think there's a strong case for every medical student to be very familiar with one well conducted clinical trial, or even participate in one if possible. If that's evidence based medicine I agree, but it's role is limited.

One of the concerns that I would have with it is I think most of the evidence today is generated by the pharmaceutical industry so it becomes means for the industry to take over larger chunks of the health care. But on that score, the MRC study in 1965 was fairly independent. I think by virtue of its independence and the eminence of the people involved, it had a huge impact but did you get the dose of phenelzine wrong.

You have to choose a dose and the dose was chosen on the best evidence that was available at the time. This, of course, is an issue with every clinical trial. If you ask questions at that level I think everybody concerned would say, well of course we should have done another study with another dose. And when we get evidence based medicine widely accepted no doubt that sort of thing will be feasible. But you have to put these things in their social context – you have to realise what an extraordinary event it was to have done that trial at all and in that climate of opinion.

Imagine this for the moment: I told you roughly what happened with the 10 dignitaries, we then had the 40 or 50 people who were going to fill in forms and they were summoned I think, rather than invited, to the MRC headquarters from mental hospitals all over the country and they were herded into one of the rooms. George Pickering came in and made a speech. What he actually said to them was 'I want you to understand that you are priviledged to participate in an MRC study. It's going to be a lot of work for you and you're not going to be paid and we expect a high standard but do remember that this is an honour'. And they took it. I remember sitting and thinking surely somebody is going to have the guts to get up and say 'who do you think you're talking to', which is what would happen now. Because all these people now would be paid by the industry to do trials for money. It didn't exist at the time. You couldn't repeat that trial. Because what has really happened is, as you said, the industry

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is taking over the profession. Money is drying up from every other source. Its being done subtly, it's being done sometimes even benefically but in the long run it's disastrous because it's being done for the shareholders in the industry – it has to be. And therefore a study like that one which was absolutely independent simply couldn't be done now.

It's odd because one thinks of this country as having a socialised medical system and the US system has been market driven but the NIMH really has done some fairly independent studies to its credit.

But I can tell you – we used to have Steering Committees for this multi-centre trial and Jonathan Cole, who I mentioned earlier had recruited an assistant, Gerry Klerman, which is how his career began, and he wrote and came over from Washington to sit in on our discussions on how this was going. Many of the NIMH funded studies were actually modelled on the original MRC study. Then their system of course made it in some cases easier and some cases more difficult to introduce studies on a large scale.

The MRC study reported in 1965 but you must, presumbaly, have been actually planning it from..

From 1960. It was a huge undertaking. We recruited the first patients, I should think, in 62. I am speaking from memory.

What about Klerman?

When I gave this lecture on the placebo that I mentioned, which was in New York, it was at the invitation of, I think, the American Psychosomatic Society. I had made arrangements to go just for 3 days or so to give this talk and see one or two people. I got a telephone call from Klerman a couple of weeks before saying that he'd heard that I was going to be in New York and he would very much like, because I hadn't seen him for some time, to meet as he had one or two suggestions, if I could stay on for a couple days. So I agreed.

When I got there, I went to Cornell to have lunch with him and I was absolutely horrified. I hadn't seen him for 3 years. He was in a wheelchair, he was dying. He looked absolutely appalling. I didn't know anything about his illnesses and so on. But his attitude was unchanged. He had just been to Japan and he was planning a trip to Europe and wherever he went there were ambulances and dialysis machines and goodness knows what. He was a highly intelligent and what the Americans call an abrasive character but he learnt from his mistakes. Ever since I have known him, which was when he was Jonathan Cole's assistant, I think it was perfectly clear that I represented something quite different from him, which in one sense annoyed him but on the other hand made him want to try and grasp it. What he suggested at this meeting was two days later for me to go out to the Westchester division of Cornell and not give a lecture but for he and I just to sit together in front of an audience and argue. I think he really wanted to learn more about some of the issues that troubled him, by rubbing off against somebody whom I think he repected in spite of himself.

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I agreed to this but 24 hours later he was dead. He collapsed and was admitted to hospital. I remember I was flying back on the Sunday evening and his wife, Myrna Weissman, who I also knew well, phoned me and said that his funeral was going to be on the Sunday morning and she asked me to attend if I could. Well I had a plane to catch and I had, in fact, to go directly from the funeral parlour straight to the airport but I felt that was the least I could do. It was very instructive because they had russelled up half a dozen people, quite apart from all his colleagues. The Director of the NIMH, Danny Friedman flew out from Los Angeles. David Hamburg was there. Leon Eisenberg came from Harvard and they all gave these speeches. They don't do that here and it was really quite touching. There was a sort of rugged honesty about him and he admitted when he was wrong which is not all that common.

There's no doubt that he played a very considerable part in the NIMH studies as the director of ADAMHA. He had administrative skills and he was a shrewd operator. He got involved, as you may know, in the last year of his life with this business of the case of psychotherapy in which he really went...

The Osheroff case.

Yes, He didn't pull his punches. On the sad occasion that we met for the last time he was just beginning to tell me some of the background and how disillusioned he was as to how many of his colleagues when it came to the point did not back him up. He wasn't afraid of sticking his neck out and you have to respect people like that. There aren't all that many in his position who would have done that sort of thing. So I had a soft spot for him.

Do you think he was right to stick his neck out on the Osheroff case the way he did?

Yes. I think somebody had to, just to sharpen the issues. A lot of people in his positions would have muttered and said 'well these things go on' but he was uninhibited when it came to that sort of thing and I respected him for it. So he undoubtedly played a considerable part. On the other hand he swallowed that whole business about panic disorders and alprazolam.

Yes but do you think the agenda there really was he wasn't so much interested in perhaps in panic disorder or alprazolam per se as in how much the DSM III formulations could be internationalised.

Well that was one factor. But you see this comes back to another fundamental divergence of opinion. The DSM system, whatever you think about it, and I don't think personally very highly of it, the DSM system which has the impertinence to call itself atheoretical is essentially an attempt to standardise Kraepelinian categories. Klerman called himself, as you know a neo-Kraepelinian, and wrote about the neo-Kraepelinian movement. About a year ago, in the American Journal of Psychiatry you know they have a thing called Images in psychiatry and Nancy Andreasen, whom I also know well and who is now the editor, herself, wrote the piece about Kraepelin. I was in correspondence with her about something altogether different and this thing

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arrived so more or less as a postscript I said I was very sad to see that you've turned this man into an icon. He was a monster who has done a great deal of harm. You're the editor of the journal, you're writing this for 50,000 people – you've wasted a generation or more knocking down Sigmund Freud and now you're just sticking Emil Kraepelin in his place. In the long run you're doing a disservice to the profession.

I got back a long letter saying: why do you say this, don't you realise this is science and after all the whole of the APA DSM system is based on neo-Kraepelinism. Of course this is true – you are dealing with a movement. Now Gerry Klerman was one of the key players. I think that if he and I had been together as you and I are now, and this issue had cropped up and I had said to him what I have just said to you, this would have generated an outburst of annoyance and a few personal comments and so on but he would have thought about it and maybe 6 months later he would have said 'well, you know I do see a little bit about..' . You see he could do that.

But because he suffered from the disease of being American – we've all got our diseases, the Irish have their diseases, the English have their disease – the American disease is that you've got to be in the mode. You've got to be seen up there as being representative. And he was driven to be there, so he had his psycho-analytical phase and his psychopharmacological phase and then his Kraepelinian phase and so on, which broadly corresponded to what was going on in the States at that time. It's very difficult to buck the system because you then get frozen out. You don't fit in to any recognisable group and above all you don't get grants which is what matters. So in a way he illustrates I think a general process but actually I liked him just as person.

There are extremely few people I think in the US of the period who were as broadly based as he was. He had a foot in all the camps really.

Yes. He had immense influence in the last 10 years of his life. He never stopped working and he was learning all the time which again is unusual. Most people stop when they get to about 20. He didn't. He was extremely bright. One of the people who spoke at his funeral, apart from all these dignatories was his longest extant friend who was in school with him. I found his address very interesting. He was well recognised as top of the class in everything and there's no doubt that he was a man of superior intelligence but something of a rough diamond as well. So that was really what I felt about him.

I'm sure you've been asked ad nauseam about the lithium controversy. Do you want to say anything about it ?

I've told you a little bit about the way in which it seemed to me that clinical evaluation was a basic component of my idea of clinical practice. I had known Schou for years because we were members of the CINP and I was the Vice President or something glorious for a time and we used to meet at different places. On these occasions at CINP meetings there were always the big plenary sessions and so on and there was a little group of people who always

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talked at a symposium of their own, talking about the use of lithium and the treatment of mania. They were really no more than a dozen and nobody ever went to these symposia because they were largely dominated by biochemical measurement and mania was not regarded as a major issue. Schou was prominent among them because of his laboratory contributions to the work.

He was a genial man. He could be in the members stand at Lords; he wears a blazer; he speaks perfect English; he has considerable charm, he's got this Danish humour and you know we had always got on very pleasantly but he always disappeared to these symposia on the treatment of mania and I never understood quite what was going on. Then what happened was that I was invited to Gottingen to a little meeting organised by the Chairman of the Department who I knew quite well and this was to the German psychiatric Group or whatever. There weren't many people and when I arrived there was Schou with his wife. We chatted away and we went into this room and I was asked to give a talk on something like the Principles of Clinical Evaluation, some general topic and all I did was to try to indicate really what the structure of clinical trial was, what it could do, what it couldn't do, how little it had been applied to the study of mental disorder etc.

Then Schou got up and he was billed to talk about lithium in affective disorders. I expected to hear about mania and whatnot. But what I got for the first time was this view that lithium was everything, that it prevented the disease, that it treated the disease etc. I remember it very well because I was sitting at the back of the hall and one of the Germans wrote me a little note and he said 'this man is contradicting everything you've just been saying'. As I listened I could see that this was absolutely true. I remember also thinking, 'I hope to heaven that I'm not asked to participate in the discussion'. I tried to make myself as inconspicuous as.. but of course I was asked as a guest. I tried as gently as I possibly could to indicate that this was not good enough on the evidence which had been presented. It might or might not be true, but it wasn't good enough.

This would be 61, 62, 63?

It would be about 62. I tried to be as tactful as I could and said 'no doubt the figures will show etc'. Afterwards Mrs Schou took me aside and said 'you know, you were very severe and you've upset Mogens very much'. I said 'well what have I done' and she said 'you've implied that what he was saying was doubtful and that more evidence was needed' and I said 'well surely that is the case', still not fully realising. Then he came and joined us and I can remember it very clearly. I realised that I was in the presence of a believer – somebody who knew. There were a lot of them about in most fields. I hadn't realised this because I didn't go to the symposia on mania and lithium. He told me that a relative had been ill and that he was taking it and that really there ought to be a national policy in which everybody could get lithium. Because he has this jovial manner I wasn't altogether certain that he was serious but then I realised he was.

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In order to try and mollify him I said 'well obviously you've done this study, if I can help in any way send me the manuscript and I'll make what comments I can'. So he did send me the manuscript. I took a bit of trouble and made a number of suggestions. What then happened was the paper was published encorporating my suggestions but twisting them. It gave the impression that he had taken account of all these factors and after due deliberation had decided on scientific grounds that this was so. This I found unacceptable. At that time I cared about these things perhaps too much. I thought this is an appalling thing to happen which is why Barry Blackwell and I wrote a piece really as a warning. We made the mistake of trying to depersonalise it but of course you can't do that when this is a faith for some people. Quite inadvertently we sparked off a nightmare which went on for years. From my point of view it was completely unnecessary. I had to restrain Blackwell otherwise there would have been further trouble. But it didn't make any difference because Schou simply went on and on about this and then well we had other factors. We had the people who joined in like Coppen ...

And Kline and ...

That's right because they saw killing here and of course the industry. The industry had ignored lithium because it's an element, it's cheap and suddenly they saw money. You combine lithium with any other antidepressant and you sell it as both therapeutic and prophylactic. We got involved as a sort of scapegoat in all this because we'd had the affrontery to raise the questions. Well at least it did force them to do a more scientific study. I didn't think that the evidence from the trial justified the conclusions that certainly some of these people took from it, but it was never an important matter to me, whereas it was a very important matter to Schou because it challenged an article of faith and of course his reputation was built on this. Baestrup, was an honest straightforward clinician and he apologised. Schou has never apologised. Baastrup got involved because he was the co-author of the original paper and he's a very modest retiring chap who I suspect supplied the patients and was probably rather horrified at the lengths to which all this was going. I don't regret having done this in any way but I am sorry that it should have generated the emotion that it did. It completely distorted it's significance but the underlying principle is the right one.

Can I push you on that a bit because one of the big arguments from the opposite camp was that we cannot randomise to prophylactic trials because people will die. There will be suicides. Now the prophylactic trials have since been done including the MRC one. There have been some suicides haven't there?

I don't know. To be quite frank I forget all this. I did publish a piece devoted entirely to the ethics of this issue. I don't believe that's insuperable. I mean this is one of the issues that arises from clinical trials.

Can we switch to primary care depression, which you more than anyone else really first raised the profile of. Do you ever think that all you did to some extent was make a mar-

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ket for the industry – enlarge the size of the antidepressant market. Is there any way to avoid making markets for the industry?

Well you're really asking a question which again has to be put in a broader context. What you say is absolutely true. The background in brief was that I had become interested in what is now called the epidemiology of mental disorder, which was not a word that was used then. In fact, I was reprimanded for using the word epidemiology by a Professor of Bacteriology who said you can't have an epidemiology of a non-infectious disease which shows you how rapidly things have changed. It became clear to me, in brief, that if you study psychiatric institutions you learn nothing because most mental disorder doesn't come to them. I learnt a lot of this when I was in America because there was a small group of people in the States completely outside the ordinary run who were interested in surveys and counting and measuring and I knew them all – they were mostly in the public health field and many of them were not psychiatrists. They were just interested in the burden of morbidity on populations – this is what epidemiology is all about.

I thought that the direction was right but it hadn't a chance of succeeding. You can't do that sort of thing in the States because everything is chaotic. Everybody is moving. They won't answer questions. You haven't got a centralised statistical service and the more I thought about it, the more it seemed to me that the National Health Service provided the perfect sampling frame in general practice because GPs had to fill in the forms in order to get their capitation fees and they covered 98% of the population. So why not apply the standardised survey methods to general practice and this is what I did. When I started I was told by everybody I spoke to that I was wasting my time. What very quickly emerged was that far from wasting my time I had, call it what you like, stumbled on a horrifying fact which was that psychiatrists knew very little about mental disorder because they never saw more than a tiny segment of the thing.

This resulted in all sorts of difficulties, I can tell you. When we started to publish which was in the early 60s, I think I might just as well have published it in Serbo-Croat for all the impact it had. It was extremely relevant to public health people, to bio-statisticians and to people who are interested in policy. What they didn't understand was that my personal interest was entirely in collecting information on the nature and distribution of mental disorder but as I reluctantly pointed out in the monograph that we wrote, it had vast implications. I didn't care about them. That was not my job. What I then did was to thank the Lord that we were so side-tracked because it meant that nobody took it seriously. I had quite enough money from the Department of Health, which in those days you got by going up and having a cup of tea with a senior civil servant and somebody saying 'how much do you want for the next 5 years?'. There were no site visits, nothing. They were interested because it helped their statistics. They didn't think it mattered very much but it wasn't doing any harm.

We were given about 15 years grace in which to really work on our own. We were cold-shouldered by the psychiatrists, who were horrified at the implica-

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tions. We were ignored by the GPs who were dominated by Michael Balint on the one hand and the pharmaceutical industry on the other. We just got on with it and in this time I was able to build up a unit and publish 400 odd papers and so on as though we were in a vacuum. Then in the 1980s the bubble burst when it became clear that the whole of the psychiatric service policies were falling to pieces. That terrible errors had been made about mental hospitals. As is always the case with governments and administrations, they look round and here was a cache of nearly 20 years work which was solidly based impersonal, simply giving the size of the problem, the nature of it and among other things the extent of depression. This resulted in a flood of publicity and the work was then ripped out of its original setting and used and misued galore.

Over the weekend, Rachel Jenkins, who used to work with me and is now the Senior Medical Officer in the Mental Health Division and the Advisor to the Minister, has been going over with me the agenda for a conference, next month, organised by the Department, WHO, the College, and some other body with about 50 speakers from all over the world on Prevention in Primary Care. It's totally unrecognisable in terms of the sort of things that we were doing but it's inevitable because primary care psychiatry is now a large growing body all over the world – even more outside than inside the UK.

Somebody asked me about this the other day and asked me what I felt about it. I feel like the magician, from the Sorcerer's Apprentice, who went out of the shop and comes back and finds chaos. It's everywhere. If you say well you know you're responsible for this, this is not necessarily a compliment but I have to say it's not mea culpa – I'm not responsible for this at all. What we did was to outline the whole area. We developed the methods, we did a number of studies, we had them replicated and we trained a generation of people, not only here but all over the world who have confirmed this.

Who were the key people you trained?

David Goldberg, who is Professor here. Brian Cooper, about 20 Chairs, most of them psychiatrists. Robin Eastwood in Canada and Henry Dinsdale. Paul Williams, who's now with Glaxo. Tony Clare, Neil Kessel, Greg Wilkinson, 3 Chairs of Biostatistics, 2 of psychology. There has been Michaele Tansella in Italy, Gia Marie in Sao Paulo, Andrew Cheng in Taiwan and a number of attached workers who picked all this stuff up and through WHO and other fellowships have spread it all over the world. So the indirect influence has been vast actually. Over the years we must have had I should think 30 – 40 people who went on to senior academic positions of one sort or the other. The entire policy of the mental health section of the Department of Health in this country is now geared towards primary care. Rachel Jenkins is honest enough to say she's been dining out on this for the last 5 years.

There would be other people you would know about. For example, you will never have heard of Debbie Sharp, who is now Professor of General Practice in Bristol who did her doctorate with us. The way we functioned was to get these people to do supervised doctorates either abroad or here and then go off

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and spread the word. I think that this is very difficult to measure actually, but the influence is vast and if you look at textbooks and so on, it has brought an awareness that psychiatry is more than schizophrenia and manic depressive psychosis. Unfortunately, it doesn't give you a clear enough picture of just what is involved and this is particularly true of the non psychotic disorders, which of course is meat and drink for the pharmaceutical industry. They have quickly latched onto this, distorted it out of all recognition but that's what they are there for. So you can say, yes, in one sense I was unwittingly responsible for this but I take no blame for it. It's what was done to our studies that I think you're seeing now. Sooner or later it will settle down and the wheat will be separated from the chaff.

Talking about wheat and chaff is the right note for introducing the next question which is this – Ronald Knox looking at the history of some of the Protestant Churches in a book called Enthusiasm, said that the greatest danger of all is enthusiasm but of course the most important thing of all is also enthusiasm. Now enthusiasm connects to the Oedipus Effect to which you have ascribed an important role in the history of the period, do you want to pick this one up?

I would say that if you want to sum it up that what you need is controlled enthusiasm. Without enthusiasm nothing happens. Unrestrained Auschwitz happens. The inquisition happens. The atomic bomb happens. So you're caught. You have to accept that this is part of the motivation, the actual mechanism of human activity which keeps people moving, but God help them if they don't ask where is it going – on the assumption that you can control it. You see if you take the general practice story as an example, I had absolutely no way of controlling the way that this happened. As it got better and better known, we were approached by more and more people. We were offered more and more money but at a cost, which is that we produced results and now you have another issue which crops up, which is that many of the people who latch on to this sort of thing, which has got public health and policy implications, are paid to produce the right results.

The advantage of the work that we did in primary care was that it didn't matter at all. It was a piece of academic research, a series of studies which were designed to add to knowledge. Now it so happened that they had implications which is, after all true of high speed physics – the atomic bomb came out of it. Not that I'm comparing what we did to that but the same process is there. It's curiosity really which is a form of enthusiasm. You become wrapped up in 'my goodness that's interesting, I never realised there was so much psychiatric morbidity in general practice'. That's interesting because it leads on to other things which have got nothing to do with how many antidepressants do you give or what would be your profit ratio if you doubled the antidepresant dose to anxious people say.

I think what is true about this particular thing is that it is very unusual to have a series of studies which were published and lay fallow for nearly 20 years with nobody realising just what was implied by them if you took them seri-

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ously. This comes back to your earlier question – Why didn't the reserpine paper have an effect? The reason was that people were not thinking like that. It looked very strange, that you're writing a paper about treatment in The Lancet and what's the paper, it's half a dozen tables, statistics and Chi squares and so on. It wasn't what people expected in the clinical field and certainly not in the psychiatric field at that time.

There's also the other bit there, which is in order to make the catecholamine hypothesis the idea of reserpine made you depressed was quite crucial, so contradictory evidence wasn't going to be particularly welcomed. And its a curious irony in that the preceeding piece to your paper is one of these anecdotes about people becoming depressed on reserpine.

That's right. But you are interested in my work only in so far as it opened up the awareness that there was this issue?

Well yes but one of the things that happened when Kuhn introduced imipramine first of all was that it took 2 years before Geigy decided to actually market it. The reason seems to have been that people thought that there were only very depressed people out there, people who could be treated with ECT and the drug wasn't going to be as good as ECT, so where was the market? It took a person like Kline with his flamboyance to some extent to force the companies down this route..

He did and not only that. I once went with him to hear him talk to a congressional committee in Washington in 1955. Henry Brill and Frank Ayd were also there but he was the driving force. He was full of what the Americans call pazazz which is an untranslatable word. He made these congressional characters feel that if they didn't take this on board they were doing the gravest disservice to the American nation since King George III with the British Army. It was a wonderful performance. He undoubtedly played this enormous role. I knew him quite well. There were his counterparts in this country, people like Sargant but Sargant was restrained by the system. I remember thinking at the time that if you had behaved in that flamboyant manner with television appearances, the girlie magazines, the whole business,... at that time you'd have been drummed out of the profession. The GMC would have said this is unprofessional behaviour.

His private practice was like something out of a Holywood movie. It was hardly describable but this is what you paid for. His sales pitch to all these rich suckers who would go to see him was that they were going to get the latest drug which nobody else had access to. But of course what they didn't know was that these were drugs that were still on trial and he was using them as guinea pigs. And he got away with it. He became famous and a rich man and so on in a way that is inconceiveable here. He was a public figure in the national press. I once went with him to a television studio to listen to him give a talk and it was like listening to an advertising agent. But in a funny way, he too, was sincere. This was the American way of doing things. And of course it raises the even bigger issue, if he really believed this, as to how far was this self-deception to chime in with his own wellbeing and the system and how far was it actually related to

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reality, bearing in mind that he was a doctor and he wasn't selling toothpaste. There have been a lot of others who have clambered on the bandwagon since but Kline made the bandwagon. He was rather a different phenomenon.

Heinz Lehmann puts it in terms of liking the way Kline didn't stand for any kind of pretention. That he was a little bit of a joker to some extent.

Well there are many funny things about Kline. First of all he was an unexpectedly intelligent and educated man. He had a degree in philosophy and he had a taste in people. For example, he had the highest regard for Aubrey Lewis, which is extraordinary, when you think you couldn't possibly have two more dissimilar figures... They are hardly of the same species but he was a bit like Klerman. He would respect something that was however different if it felt right. And this is what made him more than just another salesman. There was that side to him but he was a much more interesting and complicated person.

One of the impressions that comes through the literature is that the scientifically minded approach that you had seemed to people like Kline and others as though you and people from The Maudsley were negative as regards drugs. This sort of insistence on scientific ...

Well it is now generally accepted that the core of the scientific method turns on the concept of refutation. If you want to call that negative, then all of science is negative. If you can't refute a contention you are not talking about something scientificially. If I say schizophrenia is due to rhubarb, which it may be for all I know, you have to test it in some way and you can't test a positive. This is now widely accepted... if you call that negative you're playing with words and....

But what comes through in the actual correspondence between Blackwell and Kline for instance on lithium, where Kline says 'I've heard this tone before. It was used when we introduced the drugs in the first place and we didn't have RCTs to introduce them. But of course, Dr Blackwell, in addition to thinking that lithium doesn't work, perhaps thinks that none of the other drugs work either.

But that's a standard rhetorical game – you hear it in the parliaments of the world. Its chop logic. The real issue is that these topics have a scientific core and if you look at the scientific side of them, there is only one way to proceed and that is to attempt to put forward the hypothesis and refute it and if you fail you've got something positive which you can then build on etc. That's true in every branch of science. But these topics have spin off's – like money, reputation, fraud and publicity and 101 other things, which you can take out of the issue and make your own without ever actually getting involved in the scientific issues concerned. That's I think where the conflict takes place and it can't be resolved. Its got nothing to do with whether drug X affects condjtion Y. It's a question of whether Mr A or Dr A or Professor A wants to get something which is non scientific out of an issue which has a scientific basis. That's true in every business. Think of Cyril Burt. This sort of thing goes on and on and it's part of the process. You must recognise that it exists, that is always has exist-

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ed and that it always will exist and if you don't separate from that the fundamental scientific issues, you just get lost and the whole thing gets degraded. That's happened sadly.

Where do you think things will go from here. We may be at the end of an era. Perhaps we will have time to stop and take stock.

It's anybody's guess obviously and mine is no better or worse than anyone elses' but I would have thought that if what you say is true, that this penny in the slot approach has paid good dividends and it's no longer working, I would have thought there would be two barrels to fire. One would be to approach the whole issue from the biological side in a different way. I would be personally inclined to follow the molecular genetic line to see if any of these suggestions should materialise what their pharmacological implications would be. Pharmacogenetics would be a potentially productive line. The other would be to take the opportunity of the pause in the propaganda and so on and start looking at the non-specific factors sensibly. Begining with the placebo and then the environment and inter-personal issues – not in the haphazard way that they have been done.

To do that, would we have to have an independant psychiatric profession. do we have one still?

I'm talking about the issues in theoretical terms. If you're asking who was going to do it? ... well it will only happen if there's a need for it. I could see for example an enlightened pharmaceutical industry saying 'well look we'll call it a day for 20 years and go back to the laboratory, we'll buy up the best people and we'll tell them to get on with it'. Which is what the MRC used to do. The MRC is finished as a serious element in this. But the industry could if they were far sighted enough because they could pay the best people the requisite salaries and not put pressure on them. The other thing is looking at the issues, as they are now, calls for a body of clinically informed scientists, who are able to appreciate what the issues are and put them to the test. I don't think they exist in the psychiatric profession. I don't think the standard is good enough. So either you do something radical to lift the whole thing up or you admit defeat – look at the fate of mental subnormality – it's ceased to be part of psychiatry.

I think the psychiatrists have now got to show what they're made of. I think it's anyone's guess as to how it will materialise, fortunately I am not going to be responsible. We have to raise the right questions – you don't have to give your own answers but the questions are important. We must first define what there is to be done.

Is there any hope that Meyer's kind of thinking will come back. That the wheel will turn yet again.

The real problem if you're asking about this, is that if you are to influence people within the profession, you've got to stand up and be counted. You've got to be seen to do more than talk about it. I can remember, for example, week after week in this building here, at 12 o'clock, on a Monday morning,

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Aubrey Lewis took the clinical conference. The first 2 rows of the conference room were occupied by every consultant in the hospital. The registrars were at the back and the discussion was between the professor of psychiatry and his senior staff. There they all were hand picked so that you would get the Jungian view, the biological view, the eclectic view, this that and the other view and the registrars would be transfixed listening to this and realising that nobody knew anything. These were all people expressing personal views. The actual substance of the material was extremely tenuous. But it was an educative experience and this is psychobiology in action. To be able to do this you've got to be respected enough and to have sufficient authority to get away with it. If you don't, it's a farce.

It just so happens that last week I happened to see the weekly programme here. There's still something called the clinical conference on Monday at 12 o'clock but it isn't taken by the Professor of Psychiatry. It's taken by a mixture of people and the thing that really struck me was the words '12 o'clock clinical conference, presided over by so and so, 12.30 pm lunch by Whoever' and that is what's happened. I'm sure people go there for the sandwiches and once this happens, you're lost. The only way that anything carries any force is by example. After all as anybody who has been to a medical school knows, we all remember our professor of neurology, or a paediatrician and so on, who impressed us by their bearing, by their authority, by their this that and the other, in addition to their clinical knowledge, because medicine is an apprenticeship, You have a model which is in a medical school. That's where you pick it up. Not from reading and certainly not from libraries or anything of that sort. You've got to see the way the boss actually behaves on the ward with the patients, because that's the only argument that's going to carry any force. The psychobiological example is very difficult to define and to carry off – not as a theoretical matter but in practice. When it works it's unforgetable.

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