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Phenomenology, Psychopharmacotherapy and child psychiatry

Can we begin with where you were born and why you went into medicine?

I was born and grew up in New York City and come from three generations of mid-town Manhattanites. The only background in any way relevant is that I had a grandfather who produced Second Avenue Yiddish Theatrical for many years. I say this because I think some small fraction of research involves an enjoyment of presentations. But, except for a distant relative who was a dermatologist, the first real impression came on me in my senior year at high school. My closest friend's mother was a physician, Dr Ruth Fox. She was a psychiatrist who developed Antabuse for alcoholics. That was a very radical treatment then. In her case, it came out of very traditional women's values. Her husband, who was McAllister Coleman, who ran for Vice President on a socialist ticket all those years back, was also sadly known for his alcoholism. She quickly realized that most of the psychotherapies weren't any good. She was at Cornell, teaching, and she pioneered the use of Antabuse, which, over about a 10- or 15-year period, probably was the most novel and possibly one of the most useful ideas around. Watching her life and her ability to make a difference and, more important, the fact that she was someone not passively going along with treatments which weren't working, at least certainly not in her case, made an enormous impression on me, particularly one summer when they invited me along on a summer vacation to Mexico. I was to be a companion to the daughter. But the visits to the Alcoholics Anonymous of Mexico City, who were largely ex-patriots from other countries, was absolutely fascinating, seeing people struggle with this disease and not get anywhere through the usual treatments that we know.

Very much Malcolm Lowry country – he went to Mexico and wrote Under the Volcano *about his alcoholism.*

She was also was giving me a very good time. Her husband had died of this disease and this was not a widowed woman sitting at home worrying.

Was it this, then, that led you into medicine?

No, actually, as an undergraduate at Swarthmore College, there was a group of potent teachers at the time, giving brilliant seminars in experimental

psychology; there was little in clinical psychology. This was a Quaker school and very academic, so the experimental psychology department was basically all there was, and it was dominated by Gestaltist psychology. This had absolutely nothing to do with the Gestalt psychotherapy school. But it was relevant to a career in psychiatric research, because what the Gestaltists, what Wolfgang Kohler showed us then was that perception, for example of form, or large 'molar' units of behaviour could be measured scientifically. At the time, learning theory had to do, for example, with how rats learned mazes – Spence, and Hull at Yale. Whereas what was much more interesting to the Gestaltists was how people actually perceived a design, saw figures 'reverse', or how people solved a problem.

I think that the most useful message I got out of that was that one could do reliable research on quite complex behaviour. Solomon Asch, for example, was doing these studies of line length judgements with groups mostly consisting of planted individuals who raised their hands saying that one line was shorter than another when, in fact, they were both the same length. Some of the naive subjects were just embarrassed to disagree, but others 'really saw' the lines as the same length. Anyway, these were unusually complex phenomena to be taking on in the days of Tichner and psychophysical scaling. I wasn't aware of what a rich legacy I was getting. What was clear was that the Gestaltists were 'not quite making it'. My friends' Masters or PhD theses were on the Muller–Lyer illusion or on how people scale weights as opposed to how they scale intensities of colour. It wasn't how I wanted to spend 4 years, but the goal of doing research on very complex behaviours stuck with me. So I was a natural for medical school, for thinking about some of these behaviours. Now, fortunately or unfortunately, the department at Harvard was very dominated by psychoanalysts.

Who was there at the time?

Well, Greta Bibring was, I think, the best-known psychoanalyst at the medical school at the time. She was the 'doyenne' of Boston psychoanalysis, although there were a few others. None of this research reverberated with them; neurologists, like the paediatric neurologist Phil Dodge, were very interested in the sort of thing that I had been led to believe research would be like in psychiatry from my undergraduate experimental psychology training. The neurology teaching included considerable phenomenology and was remarkable. In the 3 months that I spend as an elective in London at Queen's Square, I bonded even the Harvard neurology was a little too much away from the phenomenology to suit me. But, between Drs McCulloch and McDonald Critchley, there was creative work relating to the phenomenology of subtle central nervous system (CNS) abnormalities. I think those 3 months were probably the most decisive 3 months of my life. Not the exact studies – they were a little too bizarre. For example, McDonald Critchley had five patients on a ward with congenital sensory neuropathy – they never felt pain or had any other surface sensation on their bodies. Critchley wanted to know could you feel tragedy, could you appreciate Shakespeare, if you've never stubbed your toe?

It was a wonderful way to start thinking about brain and behaviour. I realized that that was why I had gone to medical school! They also had two pairs of Siamese twins, both from India, and Critchley wondered about synchronization of behaviours: one was asleep, could the other one be awake? He was interested in the question of a sleep hormone. The notion of such naturalistic experiments and how much you can get out of accurate observations on a more ordinary scale made a permanent impression. I never stopped thinking about such studies for the rest of my time at medical school, so much so that, during my internship at Mount Sinai in New York with an excellent neurologist, Dr Weinstein – who had invented the Amytal interview – I had applied to three neurology and three psychiatry residencies.

Well, yes, why did you do psychiatry, given what you've just described?

I was never quite sure, actually. Morris Bender was the dominant figure in neurology at Mount Sinai. I thought he was truly remarkable, not just his knowledge of neuroanatomy, but he was always thinking out mechanisms and phenomenology. He was using double 'simultaneous stimulation' to infer cortical lesions. They were among the first interested in some of the neglect phenomena, sensory gating and so on. I was accepted to the residency at Mount Sinai and another one, but I guess the call of going back to Harvard lured me – there had been some interesting people when I was a medical student at the Mass Mental Health Center and so I started my residency there for a year. It was the mixture of old-time psychoanalysts, who still had a certain mystique in their Beacon Hill homes, arcane seminars with wonderful food and a sense of the inner sanctum.

Who are you thinking about? Elvin Semrad?

Semrad certainly, I knew him from my undergraduate medical school training. Ives Hendricks impressed us all. He used to talk about the most astonishingly personal and bizarre experiences. I think that the theatrical nature of this had strong personal appeal for us. It didn't quite hold out though. First of all, I married a classmate who, inconveniently, was down in Bethesda in a neurophysiology laboratory at the NIH. He had completed an internship but always knew he wanted to do basic neurosciences and biophysics. He'd gone to medical school but did not want to spend time in a residency. I accepted a position to do research at the NIH at the time, which would have made me the first women clinical staff fellow. Now, David Hamburg, who was the person who offered the fellowship position, resigned to move to Stanford and the fellowship disappeared. It also became clear that I needed residency credit in psychiatry. So I went to Saint Elizabeth's, where I was immediately given a building of 300 patients to attend, and left Freudian Boston for a more Kraepelinian training period.

You mean you had to look after 300 patients?

That's right; that was the size of my building. This was 1961. There was somebody who would appear occasionally – I don't remember her name, an

elderly German women. She mostly objected to my changing any medication and many of these patients were on at least half a dozen medications.

That was a shock. Back at Harvard, there was an hour of supervision for every patient hour, whereas I had a few hours a month at St Elizabeths. It was very hot that first summer and the building wasn't air-conditioned. I'd spend about 10% of my time signing death certificates, because in the summer many elderly patients died. Just looking at the ward was a lesson in the history of psychiatry: looking at someone who had gone and curled up in a fireplace for 30 years; looking at catatonics; looking at Ophelia-like creatures floating around. It was absolutely astonishing and I started to read Kraepelin and Bleuler.

Were all these people still there, even though we had had Thorazine for 5 or 6 years at that stage?

Yes. Well, it hadn't quite filtered through in terms of the doses, we also know that years without treatment may influence chronicity. Thorazine wasn't doing that much good in these cases; I'm not sure that we will ever see people in this country again who had had 25 years of flagrant untreated psychosis. On the other hand, of course, there may have been sampling bias. Anyone who had had a very good treatment response would probably not have not been in that hospital building anymore – they might have been in a boarding house or halfway home in DC.

When you saw all these people who weren't responding all that well, did you not want to leave – particularly if you couldn't make a difference to them?

Well, several things made it a good change. There was a feeling of freedom. I had about thirteen supervisors in the year at Harvard and daily seminars. It was liberating to make my own observations and form my own conclusions. So it wasn't all bad. Secondly, this was not a career job. Stanley had decided that what he wanted to do was leave the National Institute of Health (NIH) neurophysiology lab. and go to Sweden where Professor Torsten Teorell was a biophysicist. His own background in physical chemistry made him fascinated by the interface physics and biology. So I knew that, somehow or other, we were going to Sweden. So, when I wasn't looking after my building of patients, I was making application to find a mentor in Sweden. Owing to an accidental meeting with someone at a party in Bethesda, I did, indeed, find somebody and we were able to get 'his' and 'hers' postdoctoral fellowships, after I'd been only 14 months at Saint Elizabeth's.

So you then went to Sweden; to do what?

Officially, we spent our 2½ years in Uppsala, where the person that was my official mentor was a fellow named Ingmar Dureman, who turned out to be an interesting but sad man. He was one of the first people doing systematic studies on amphetamines at a time when there were no controls and very little knowledge of their potency or addiction. I was supposed to be learning infrared pupillography and completed this with a study of motion perception. He was interested in the use of drugs and we added some Gestalt measures of

perception of motion, namely the study of satiation with earlier fixation on rotating patterns of various speed and direction. There was still an experimental psychologist in me from my 4 years at Swarthmore; adding amphetamines to it made it more medical. But Ingmar had personal problems which led to his being out of town and unavailable for months at a time. He died a few years later ~~of an overdose of amphetamine~~.

This sad misfortune led to a wonderful opportunity for me. Professor Sjogren had just retired from the Karolinska; he was a psychiatrist and geneticist who had done some fine work on the genetics of dyslexia. A new department head replaced him, Börje Cronholm. Börje had just started this new job, and wasn't prepared to take postdocs, but I appeared with my own money and, as my husband was staying in Sweden for 2 years, Börje took me in. The other director of the small research programme in psychiatry at the Karolinska in 1962 was Daisy Schalling, a physiological psychologist, who was particularly interested in autonomic arousal in relation to psychopathology.

The first thing Börje and Daisy told me when I arrived was that they had planned to wait 2 years before they accepted fellows. The second thing they told me was that it was very good I came when I did because 'Sweden was so far behind it was ahead', which was prophetic. Now, this is an anti-woman's lib. statement, but getting married and not being able to stay at Harvard and then being dragged off to Sweden under protest were the two things that contributed to my academic career in psychiatry.

The Karolinska turned out to be a superb experience. Swedish psychiatry was more like McDonald Critchley neurology. Börje Cronholm had written his medical thesis on phantom limbs. I think he was one of the relatively unrecognized, enormously creative people in psychiatry. If he hadn't died at 55 of a brain tumour, he would have become much better known. There was another side to him: he wrote a monograph, which fascinated me, on two Swedish artists who had been intermittently psychotic. Börje described differences in their art between psychosis and well periods. This remains a fine paper on the nature of the thought disorder in schizophrenia. This neurophenomenology was like the best of the Queen's Square training – I felt that I was home.

Two projects were chosen for me. *Time* magazine had run a misleading story about a women named Sherry Finkbein who had been prescribed Thalidomide for morning sickness and had had an abortion in Sweden, where the laws were, in fact, rather restrictive. She gave an interview for *Time* magazine saying that Sweden was a wonderful country and anyone that didn't want to have a child should come. At this time, even public discussions of the topic were difficult in the USA. So Börje suggested that I do a study on the abortion-seeking women flooding Sweden. I did, and it was published in the *Archives of General Psychiatry* some years later. It was the first open systematic paper on which US women were seeking abortion, the outcome, diagnosis – or, in almost all cases, the total lack of it. Why was it they were having the abortion, and so on? Most were turned down but were brave enough to report about subsequent abortions in other European cities.

The other project was a Broadbent-type memory study with depressed patients having electroconvulsive therapy (ECT). While the project was academically successful, it never captured my heart. I realized you didn't get better from ECT, because you forgot your problems. But following Professor Cronholm on rounds gave me the flavour of Swedish psychiatry. They had their arcane diagnostic nomenclatures, which somehow involved electroencephalograph (EEG) patterns. Not all of it 'took', but those were wonderful times and guided the next several years of my life.

Upon return to the USA, I again tried to get a job at NIH. But, by this point, such positions were sewn up by MDs avoiding the Vietnam War. The Washington DC medical schools, unlike the present, basically just cared for patients of private practitioners. However, NIH had recognized there was a drastic shortage of people who were interested in child psychiatry and even a more severe lack of child psychiatry research. I'd become somewhat interested in this because of the abortion study. And it turned out that a child psychiatry fellowship in DC was well funded – it paid almost the same as an entry level job in the local medical schools. Since there were no jobs available, I took a child psychiatry fellowship. This included rotation through an excellent paediatric neurology clinic at a children's hospital in Washington.

When you entered child psychiatry at the National Institutute for Mental Health (NIMH), what did things look like? It was obviously not a pill-oriented field. A few people like Leon Eisenberg had begun to do some work in this area, but how did it look to you?

Well, I had a job before I went to the NIH, working in a city clinic. This was part of the liberal movement of the 1960s, when there was a large number of white psychiatrists working in inner cities. That's relevant because the District of Columbia had so few facilities that you had to treat as an outpatient what in my former training sites I would have put in a residential treatment centre or hospitalized. You really were desperate. The city monitored clinic medical staff by tabulating the number of patients you saw each day to decide if you were earning your salary. Drug clinics were the only way you could do this, and then you could see a few patients more intensely. So everyone ran psychopharmacology clinics. While the children were our official patients, I sometimes treated the mothers with antidepressants and the parent–child relationship would blossom. I was also using antipsychotics for our large waiting list group; by the time the child's turn came to go into residential treatment (a year later), almost half of them no longer needed to do go into residential treatment. So, I learned an enormous amount about using drugs. You felt you were in the peace corps, on the battle lines.

Given the climate of the time, did you not have the expectation that you should talk to the children, you should work on the families?

Of course, and we tried our best to do this. But they really wanted results! This was a very deprived population and what they needed was to have 'junior'

better enough so that grandma could look after him all day while mother worked, because she was going to lose her job if she was called any more. I made one of my more useful discoveries at the clinic, or, at least, more useful observations. Families often shared a bathroom down the hall with other families. If there were medicines at home, they were sometimes kept in the most medicinal-looking place in the apartment, the refrigerator. So, on two or three occasions, I saw non-hyperactive normal siblings who had taken some of their brother's amphetamine or Ritalin from the fridge. The mother would bring them to me in a panic – 'Help! He's taken Jimmy's pill'. I saw that on stimulants these calm children got even calmer – from my small study of 3. I documented this, and a few years later one of the first studies I did at the NIH was a single-dose normal child amphetamine study.

Who were the normal children, because the myths are that you used your own children and the children of other staff members? Is that the case?

Yes. There was nothing like the ethical debates going on in research at that time. Even though it was a single dose of amphetamine and of placebo, I took care with sampling because I had to document informed parent consent. Thus, all the children's parents were doctors, lawyers and in one case the president of the Washington ACLU locally. My own sons were the first two subjects. The children had to be considered problem free, to have good grades, to be on student council etc. Given their maturity and high level of performance, it was absolutely remarkable how much they improved on the various tests given during their day at the NIH. That was published in *Science*, and made a strong impression on preclinical and clinical fields.

Well, it did, I guess for a few reasons. One thing that Rachel Gittelman Klein would say, of course, was that this was just one dose and you can't know for sure that normal children chronically on this would have the same response as hyperactive children.

Absolutely, but first there were some replications. John Werry looked at whether children with mild bed-wetting got better on a tricyclic antidepressant or a stimulant in a comparison group. Subjects took 3 weeks of each drug and he measured bed-wetting and, of course, the stimulants didn't help that at all. John had a rationale that it would lighten and decrease sleep. Now, most of these children who were in this study had no psychiatric problems and John found the same performance benefit group with 3 weeks of drug. More recently, a group in Stanford which was doing functional magnetic resonance imaging (MRI) of hyperactive children gave a stimulant to a normal group – their data also replicated my findings.

Up till you did this, there had been the notion that normal children would be hyped up by a stimulant, whereas hyperactive children were calmed down. They were helped to eat and sleep, whereas in the normal child it would interfere with their eating and sleeping. This helped legitimize the notion that hyperactivity is a real condition. Did your work undercut that to some extent?

Well, everybody used the result for their own purpose. The anti-drug people said, 'You see, this isn't a diagnostic test and you're just drugging children' – although we did loads of studies to address that. The pro-drug people said, 'Isn't that interesting. The problem's 'up stream' from where the drug acts'. Many of the basic physiologists, who had no feeling on the ethics of drugs for hyperactivity one way or the other, were concerned because they saw some kind of rate-dependent behavioural effect, rather than a regression to the mean. I sent my data to Robbins and Sahakian at Cambridge. They wanted to see if within the normal group the more active children got more. But since our very quiet children got still quieter and hyperactive children also got quieter, there was no plausible 'regression to the mean' interpretation.

What was just as interesting is that we showed that stimulant drug effects were not paradoxical with respect to age. Being at the NIH, I had more interaction with people like Julie Axelrod and other basic physiologists. They were more curious about age effects. We studied a group of young adults whose first exposure was to amphetamines in our study. They were either Mormons or from other religious orders such as the Old World Amish, groups who fulfilled their obligation by participating in medical research and the money went back to their communities. I'm quite sure it was their first exposure to amphetamines, just as for the normal children. These young adults had very similar responses to the children – with the exception of mood. When they were doing sedentary tasks, they had more 'time on task' behaviour. That's what amphetamines do. That contribution that I made in psychopharmacology I owe to the inner-city experience of seeing the healthy siblings who had mistakenly swallowed amphetamines and who became unusually quiet and attentive for a few hours.

So you're saying it's not a paediatric response even?

It's not paradoxical with respect to anything, diagnosis or age. It fits in with what Mr General Public thinks about amphetamines in terms of racehorses and football players: they don't move less when they take a stimulant.

How did attention deficit hyperactivity disorder (ADHD) look to you at the point you did this work? What were the theories about what this condition was? Did people generally accept it was a real condition or were there concerns, as there are now, about children being over-drugged?

I think, on the question of the impact of drugs, you're asking a more sophisticated question than the field had at that time. These were the key questions about 10 years later. At this point, the main acceptable source of knowledge in child psychiatry was from talking and playing with the child for several years. There was a sense that some children had 'constitutional' problems. I recognized, in terms of efficacy, that the only time a principal ever called me up to say 'What did you do? You're the most amazing doctor I've ever seen,' was when I had written a stimulant prescription for a hyperactive child. It never happened in my therapy patients.

There were two areas at that time bringing science to child psychiatry. One was epidemiology, where there was an established methodology from that field. The other was controlled clinical trial methodology, which was really only established in 1948. So, this approach was still new to medicine in general. Just having a mindset that people I worked with needed to get inter-rater reliabilities and to make observations blind to treatment condition had a strong effect on the field. So the basic approach was at issue. Implied in our polarized discussions was, 'Are you a Good Person who talks in a free way or a Superficial Person who doesn't really like people and who uses rating scales?'.

Do you recall the conversations with people, the arguments, the debates?

Oh, absolutely. Although Yale now has a very active and excellent programme looking at Tourette's syndrome, obsessive–compulsive disorder (OCD) and hyperactivity and so on, the fact that we started to use structured interviews around that time brought letters of protest to the *American Journal of Psychiatry* from the senior Yale Child Study Center Faculty: surely the child will be hurt by this kind of direct questioning, and so on. No study would go on at Yale without such measures now, but they felt compelled to protest then.

What was the problem they were having? Was it that you had to see the child within the family system or we're they just nice people saying 'How could you impugn our motive by saying we've got to do things in a standardized way?'?

The idea was, if you're going to relate to a child, particularly one, say, between the ages of 5 and 10, you would get more profound insights by naturalistic, interactive observations. And that would be a deeper and more meaningful and more therapeutic way to relate to children. Our structured interviewing was seen as intrusive. What if the child wasn't ready to tell you about their fantasies? We used very direct questions, such as, 'Would you rather be a boy or a girl?', or 'Do you use drugs?', or 'Have you thought about killing yourself?'. They thought you must build up a relationship first before you could ask these questions.

Let me hop to DSM-III. I know you were involved in trying to draw up the criteria for DSM-III. How did the DSM-III process go down with the average child psychiatrist or child mental health worker?

Badly. GAP (the Group for the Advancement of Psychiatry) had just worked on their own approach to nomenclature some years earlier, which was based on a complex mixture of direct observations plus interpretation of behaviour. You classified hyperactivity, for example, as to whether it was anxiety driven or not anxiety driven. They felt DSM was superficial, a throwback to the former generation's way of looking at patients. I think there was less of an issue in Europe, say with ICD.

Well, I wonder, even in the UK, until recently, there were many people whose proudest boast is that they haven't ever given a pill in their life.

Or that they've never left the Tavistock. The issues of what ADHD really is, which were very appropriate and very good questions, came along somewhat

later. But I must say, the other studies, which I consider my major contribution to psychiatry to date and to psychopharmacology, came some years later, when I was no longer at this inner-city clinic and no longer in the paediatric department in Georgetown. These were related to OCD.

Shortly before I started work at NIH, I went back to visit Sweden. Börje wanted me to meet the person who had replaced me, their first planned research fellow, Dr Marie Asberg. She became a symbolic sibling and we've stayed close friends to this day. She was, of course, very interested in cerebrospinal fluid serotonin and suicidality. There had been a preliminary study by Martin Roth, based on an even more preliminary study from Spain, that had indicated that clomipramine might help obsessive–compulsive disorders. Also, Börje and Marie were starting a small study on obsessive–compulsive patients which they'd brought to the Karolinska research ward from hospitals all over Sweden. Well, there I was, I had started a new job as the first research child psychiatrist at the NIH, and was rather missing Sweden. I made rounds with Marie and in my rusty Swedish interviewed the adult OCD patients, asking them, among other things, about their age of onset. By coincidence, six out of six patients of this particular group had had their onset in childhood – it should have been 50%.

I took a brief history in Swedish of how they had kept their rituals and thoughts secret, and how their parents and friends hadn't known, and how it had secretly affected their functioning but only became obvious to the world when they became adults. I started a parallel study at the NIMH, partly because of that observation and partly because I thought it would be nice to keep contact with my old friends. The first study was the normal child amphetamine study, but my second NIH protocol, which came along within a year of the other, was a controlled trial of clomipramine in obsessive–compulsive children. Everyone said there weren't any – it was terribly rare and it just couldn't be found. So we started advertising throughout the USA and Canada, to get cases, throwaway brochures and so on, and even contacted military hospitals, because of our federal government network.

The patients were slowly trickling in, very slowly, until one of our patients went on the local radio with me, and this teenage boy simply described his experience. After that, the phone never stopped ringing. This was about 1978/79. After another programme on local television, we never needed to recruit outside of the Baltimore Washington area. We usually had ten or twenty OCD subjects on a waiting list. That was the beginning of a US OCD conflagration. It seemed counter-intuitive that OCD, which had seemed so 'psychological', responded so dramatically and selectively to serotonergic medication. What's more, the response was quick, and it reversed when the drug was discontinued, unlike the usual use of tricyclics where, in depression, you have one major drug-induced remission. To further test the specificity of the anti-OCD drug effect, we switched to a crossover design used for quite a few subsequent studies, comparing desipramine and clomipramine.

When you say at that point in time the condition looked so psychological, what do you mean? What were your theories?

Well, Kraepelin's original work had noted the way the patients with OCD didn't deteriorate and how they functioned well apart from their OCD behaviours. He was always using this as a contrast to schizophrenia, which he believed to be a brain disease. He'd say, 'In contrast, look at the intact capacity of OCD within their limited area of impairment'. OCD was real neurosis. That was how it had struck me, too.

Many of these patients did seem fraught with a metaphorical impairment. One boy in our study couldn't sit in a chair if a girl had sat in it. It all seemed so obviously 'psychological'. But what was astonishing was how well the drug worked and, during clomipramine–desipramine crossover, how patients relapsed on desipramine.

When you used the pills first, there would have been the idea that, if an antidepressant works, it works on a mood component to the problem.

Oh yes, and Isaac's Marks had been quite outspoken on that point. In fact, he'd taken Marie's data with adults and reanalysed them, claiming that the baseline depression score predicted OCD outcome. One reason we switched to the clomipramine–desipramine design was because they were relatively equipotent as antidepressants and, of course, the side-effects were similar, so patients really weren't that sure when they 'crossed over'. The OCD scores would go down on clomipramine and not on desipramine, while the depression and anxiety levels weren't changed. This really selectively effected change in OCD.

But studying children was a lucky choice for our group. I'm not sure I would have become a child psychiatrist if that hadn't been the best way to get a job in Washington in 1965. But it turned out to be most fortuitous, because new clinical associations leapt out from this study. Young children would often have 'pure' motoric compulsions without any notion of why they were doing it. Occasionally, one would come up with a theory. They might have been at a science fiction movie or something, where they thought, for example, that maybe there were good people from Mars making them do that, just like they saw in the movie. In one movie, the boy told us that this was how the Martians told this person he was chosen to be helpful. It was a happy movie and he was a happy kid. The point is that no consistent pattern of bad child-rearing emerged.

Not only were we seeing OCD children with an initial motoric component, but also, although we were not interested in Tourette's Syndrome or tics, we were finding almost 40% of our children had chronic motor tics. This work continued to take off in several directions at once.

Public interest increased steadily. Our family studies showed that the first-degree relatives were more likely to have either OCD or Tourette's Syndrome – the first publication of that finding. Apart from Marie Asberg's controlled trials, our studies were the first systematic trials in OCD. This was a boost for

child psychiatry, as children are generally therapeutic orphans – investigating a treatment with children typically comes later. Here, too, Sweden was so far behind that it was ahead.

New clinical questions opened up. What were the boundaries of OCD? There was a point, people teased us, that anyone who walked into the clinical centre was put into our clomipramine–desipramine study. It wasn't quite that extreme, but we proceeded to study women who pulled their hair out (trichotillomania), sexual offenders, compulsive shoppers, with the latter two responding equally to clomipramine and desipramine. Other kinds of hoarding behaviours seemed to respond to clomipramine.

Our most colourful study came after I had been on a national radio programme, discussing our hand-washing children. Three different people called up who happened to be psychiatric social workers, who talked about how their dogs licked their paws all the time. They turned out to be large, affectionate and emotional dogs, mostly labradors but occasionally great danes: these dogs had a condition called canine acral lick. They asked if this was OCD. The vet, in one case, had told them to replace the companion dog, which had died, with a new companion. The dog was much happier, but the paw licking went on. A second social worker was told by the vet that the dog licked its paws because it was lonely now that the kids had left for college. She moved her office home; her dog was happy with that. But the paw licking continued. Now, canine acral lick is potentially fatal, because the dogs can get osteomyelitis and severe cases have to be put down. We carried out a parallel design of four serotonin uptake inhibitors, placebo and desipramine. We had to make house calls to monitor this study because the clinical centre only allowed seeing eye dogs to enter the building. But the selective serotonin reuptake inhibitors (SSRIs) turned out to be dramatically effective, and canine acral lick remains the best animal model for OCD. It's interesting genetically, both within breed and within families within the labrador retriever breed.

Now, you also wrote the book The Boy who Couldn't Stop Washing, *which is a classic. Why did you write it and when did you begin?*

Well, after 10–15 years of these studies, it was clear that we had interesting stories, which weren't quite what the NIH pays one to publish, and new ideas kept coming. Our OCD studies got me thinking in areas that went beyond my job as chief of the child psychiatry branch, for example about the brain's role in mediating certain relationships between ritual, religion and art. Were certain religious groups more likely to have OCD? Did this behaviour get hard wired in the first place? What was the history of the Catholic Church's treatment of scrupulosity? Also, about the borderline between OCD and things like these erotic psychoses or compulsive personality. Literary figures provided some of the best examples of these issues.

I collected materials related to these questions over 16 years, not quite sure where I would put them. As I mentioned, I came from Manhattan, and one of my childhood friends, Richard Marek, was president of E.P. Dutton at the time.

He asked for a sample chapter with outline. So I sent a sample chapter with outline and heard back in a few days that he thought I didn't need an agent and should come in to sign a contract. At the time, I didn't realize that most people had agents. He promised a good contract, and it was. Since my mother and his mother were friends and we'd played together since the age of 5, that seemed all one needed to know. It turned out that it was, in fact, a wonderful contract. It stipulated that the book would be on the cover of the booklet that the publisher's salesmen took to the book stores; the contract also guaranteed a twenty-one-city author tour.

It was so interesting. Having to discuss my work with the public was so stimulating. Oprah or Donnahue were not as intellectually stimulating as public radio or even Larry King – who turns out to be a brilliant interviewer who actually reads the books he discusses – but I was impressed how stimulating television appearances were for our research at NIH. You don't usually think about television talk shows as a source for your next study, but at least three of our studies were inspired by questions from the enormous audiences these shows brought us. And my wardrobe also changed for the better.

It has to have been an interesting experience, trying to take this to the public in this way, and not just the simple experience of having the feedback.

It had a dramatic effect on us all. It stopped my inverse snobbery at once. I had insisted that none of the calls in response to the author tour presentations should come to me, because, even before writing a popular book, I already had a 4-month waiting list for my small consultation practice. But a national self-help support group, the OC Foundation, had just been formed, and so the 400 plus programmes on TV that I appeared in sent all calls to the OC Foundation. You know, on Donahue, by the time it was replayed three times, an estimated 50 million people saw the programme. Many of the patients in my book and others were eager to go on this programme, with the message that 'This is a neurological disease'. Patient availability made it even more attractive to the programmes that don't just want talking heads. Any one of those programmes did more good in terms of public health education than many PhD careers in public health accomplished before TV.

It's sobering, isn't it, when you put it like that?

About 5 years later, the OC Foundation started a fund-raising drive and gave a dinner dance in my honour at the Hotel Philadelphia. It was an unforgettable evening, with presentations from OCD sufferers whose lives had changed because of my book. Each had written about this and I was given a scrapbook, which was a testimonial to the power of this medium. *The Boy who couldn't Stop Washing* was translated into twenty-two different languages. It doesn't compete with Jacqueline Susan, but if you count these twenty-two countries, I think it had sold close to a million copies.

That's extraordinary, isn't it, for a psychiatric book about a hard-wired condition as opposed to one about the meaning of life?

Absolutely. And my minuscule practice, when I'm in town, still consists of people from all other countries and cities flying in to discuss some aspect of their OCD.

You obviously brought OCD in from the cold, but there's always the hazard with these things that it can go too far, that we begin to pick up milder and milder variants of behaviour and say, well this is OCD as well and you know you ought to have pills. Do you think things went too far?

Well, it was clear from the beginning that this was a danger. In fact, on each of the shows, there was always a celebrity interviewer or a camera man who called me over afterwards to discuss their habits – 'I count steps every day when I go out of my house but I'm really doing fine'. It got to be a routine in the media presentations that I would start off by confessing how I count to seven on my fingers as I walk down the street but this isn't a problem and isn't a diagnosis. Also, I'd explain how one doesn't make a diagnosis without substantial impairment over a long period of time. I think that this message, by and large, did get over to the audience. I mean, everyone still says that they're compulsive, meaning that they balance their cheque-book or something – I don't think that'll disappear from our vocabulary. But, in general, those in OCD research caught on very fast that we needed to make clear what was normal and what wasn't.

When you were talking about the canine acral lick, you said you used all of the 5HT drugs. When did it become clear that there was something specific about this to the 5HT system?

Well, back with clomipramine, which had been around for 30 years before it got on the market in the USA, as I'm sure you'll know. I think our crossover studies showed this. Our double-blind crossover studies documented the specificity of 5HT uptake inhibition for an anti-OCD effect. The very different uptake inhibiting pattern between clomipramine and desipramine was well known. But it was our crossover studies, where subjects relapsed to baseline illness on desipramine, that brought home that at least the first step involved is 5HT. It remains a mystery what the last step is.

Moving on from that, showing that, for OCD, drugs active on the 5HT system do things that the other antidepressants not active on the 5HT system didn't do opened up this idea of a serotonergic spectrum disorder. When did all of that begin to build up momentum?

Well, around 1986/87 it all started happening at once. Outside the NIH, several groups started looking at body dysmorphic disorder from an OCD perspective. There were several studies of spinal fluid correlations during drug trials. The notions of OCD spectrum and of basal ganglia circuits took hold. But no direct abnormality in serotonin systems *per se* has ever been documented for OCD. The best and most robust correlations, which do not address neurotransmitter specificity, have been the brain imaging studies of OCD implicating basal ganglia disorders and frontal striatal loops. In terms of neurotransmitters, the studies of blood, urine and spinal fluid in drug-free patients and even correlates

of drug response have been disappointing. In contrast, there was a great wealth of converging evidence supporting frontal-basal ganglia circuitry abnormalities in OCD.

What's your feeling at this point about what the drugs that help are actually doing? If they're not working by lifting mood and that helps the whole picture, have you any hunch as to what they're doing?

I don't know in the sense of what the proximal action is, but I think that hard wired into this loop, of which, presumably, serotonin is the first step in some cascade or network of neurones between the frontal lobe and probably striatal, globus pallidus and possibly thalamic systems. In this network, serotonin sets off a normalizing cascade. These complex behaviours involve some kind of cognitive/motoric ordering and arranging, which must have survival value. Various ethnological studies come to mind, and there are some ways of looking at this cross-culturally that we are testing.

There has also been a relative failure in the neuroendocrine area. There have been some CSF neuropeptide correlations with drug effect, and initially vasopressin looked like it might have anti-OCD effects, and then that didn't hold up. The imaging research remains the most consistent.

I think there's still an important opportunity for research here. Some of the latest work is being done independently by Dr Susan Swedo, a paediatrician, who is now head of a separate research branch in NIH. Her first project in 1985 was based on observation 100 years ago that 70% of Sydenham's chorea patients have OCD. Sydenham's chorea follows on in about 20% of patients with rheumatic heart disease, a disorder caused by a cardiac-tissue autoimmune response to *Streptococcus*. Presumably, although it's not well proven, Sydenham's chorea produces a selective autoimmune attack on the basal ganglia, which brings out the choreic and other symptoms, including the OCD. Dr Swedo has taken this model and identified a group of children without the rheumatic heart disease or chorea, who just have post-streptococcal tics and/or OCD. What's been very interesting in the rheumatic heart disease field is that there's a B cell marker of vulnerability for autoimmune reaction to *Strep*. Most people exposed to *Strep*. get a sore throat but don't get rheumatic heart disease. So, a group at the Rockefellow have gone around characterizing people who get rheumatic fever and Sydenham's chorea, and the highest rates both for this marker and for Sydenham's chorea are in Brazil and in the Aborigines in Australia's Northern Territories.

A novel question is what is the form of the OCD in such cultural groups? While cross-cultural studies of OCD in general show great similarity, a more interesting question has to do with the nature of the hard-wired behaviours and to what degree these in turn have influenced culture and cultural rituals. You could speculate that some ritualistic behaviour is a by-product of the immunological host, and in this case streptococcal agents. The aboriginal people in Darwin, Australia, have the highest rate of Sydenham's chorea in the world, in the more intact native populations. One might examine symptom patterns – do

they walk the songlines more carefully? – and perhaps the figures who preside over rituals are more likely to be the ones with high scores of this susceptibility marker. That basic research is what intrigues me the most at this time.

That's absolutely fascinating. OCD, though, in a sense, is an extraordinarily fortunate kind of condition to pick in that it's clear now that, while there was a kind of psychological feel to it that there was ...

Even in the old days, though, the good analysts always felt that they couldn't really touch severe cases. Elizabeth Zetzel in Boston and Anna Freud in London disparaged the efficacy of psychoanalysis in OCD.

Sure, and it was reasonable in a sense to use pills. It's a bit like if you have a child who is having convulsions, it's reasonable to give anticonvulsants; you aren't going to sit around and talk. When the pill produces this huge change in a child who has got OCD, it's reasonable to go ahead with the pill. But then you get into the more soft area, where there's more controversy in the USA I guess, than elsewhere, which involves the use of Ritalin for hyperactivity or antidepressants for childhood depressions. Why is there all this controversy, which began to blow up during the 1980s? How do you read all that?

I think that you're absolutely right about the controversy having several components. The antidepressant controversy is based in part on the fact that they are less efficacious in children. Perhaps, as some recent data from Richard Harrington in England suggest, the younger depressed subjects are less genetic. In any event, most antidepressant controlled trials in children show no efficacy. So I think it's problematic in the paediatric depression field, though every clinician treats a severely depressed refractory child with antidepressants.

With stimulants and ADHD, it has been more of a question of what's the long-term benefit? That's complicated, and there are fewer demonstrations of neurobiological correlates to the disorder. In contrast, hyperactivity has high genetic loading, but it turns out it's a loading for the entire dimension of hyperactivity. The twin studies show the same high genetic influence for middle level hyperactivity as there is for cases at the ADHD syndromal level. The public is stuck on the lack of a biological marker. But genetics suggests a dimension, not a disorder. Much poor publicity is due to the poor training of many teachers about how to propose treatment. Many teachers overstep their bounds here. Stimulant treatment has been terribly mishandled, with some schools inappropriately pressuring families to use this approach. There's no question that happens. Our brain imaging studies are, in fact, finding some subtle abnormal MRI findings that may produce some validation of the disorder.

When we have a meeting in Europe, no-one in the media or anyone else pays any heed to psychiatric meetings, but here in the USA at an American Psychiatric Association (APA) meeting you have to go through a stream of people holding up placards saying these awful psychiatrists using drugs for children – this is the biggest stick to beat psychiatry with – it's quite amazing to see.

Right. That's relatively recent. I mean, the earlier issues were against ECT and all drugs in all adults etc. The scientologists have an across-the-board hostility to psychiatric drugs ~~in general~~. They found a more sympathetic ear from the public with the children's issue rather than attacking drugs for, say, psychosis.

Right, they've gone for this as the soft target?

I can't say they've backed off other issues in terms of what they'd say in their literature, but I don't think they're going to take on olanzapine. They certainly have tried with Prozac, but they couldn't handle that. It's strategically a weak time for stimulants as Ritalin and Dexedrine are off patent and there aren't any drug companies who are going to defend them very strenuously. Other drug companies are developing other ADHD treatments, however. Also, as there isn't a laboratory test – as is true for most psychiatric disorders – so clinicians are open to attack on the diagnosis. There is public sympathy on this issue.

There's been a legitimate concern over the steady increase in the rate of stimulant use. In spite of this, little abuse has been documented from prescribed drugs. But our drug control agencies worry about that possibility. Some data suggest that increased diagnosis in girls, and adults, and the recognition that stimulants are more useful through at least high school years for many children account for the increased use.

Can we pick up the area of the childhood psychoses?

Our latest childhood-onset schizophrenia project was inspired by progress in the neurobiology of adult-onset cases, but also by the challenge of studying the rare childhood-onset patients. In the intramural programme at NIH, you can do studies that are harder to do with extramural funding. An example of such a project is the study of rare disorders. When we started studying childhood-onset OCD, we would never have got a grant for it. Can you imagine telling a granting agency that you need personnel and beds but that it might take the next 10 years to find a sample? That was a wonderful condition to start in the intramural project. Later, the whole country started doing OCD research and so we thought about a new direction. Sue Swedo was doing a wonderful job with Sydenham's chorea and working with immunologists on that model, and the other OCD studies could now be done well at university medical centres.

I was very interested, because of childhood schizophrenia and the hyperactivity project, in doing two things not easily done 'outside'. One was to get anatomic brain MRI norms for brain development – back to the notion of minimal brain dysfunction, a term from the 1950s or 1940s. So we were given the MRI machine at the NIH every Tuesday night and we interviewed and scanned children, and re-scanned and re-interviewed all of them every 2 years. We started this in 1990 and now have the world's only longitudinal normal brain development study. There are loads of infant brain and ageing brain MRI studies, but nothing for the ages of 4 to 18. We're now up to our 2000th scan and we have generated normative curves for every part of brain development. We also have monozygotic and dizygotic twins going through the scan and re-

scan studies, so eventually we'll have some idea of the genetic loading of the rates of the curves for various cortical and subcortical brain regions. We are studying a large cohort of hyperactive children, for whom we have been doing drug studies using our day programme at the NIH. We have been looking at 24-hour activity level, and examining the drug effects on such measures.

But also we had the chance to do something that would be very hard to do anywhere else, which was to study childhood schizophrenia. This probably occurs at 1 in 400 of the rate of the disorder in adults. This is true schizophrenia, narrowly classically defined, but having an onset before the age of 12. Out of 1000 screenings of charts and about 300 in-person screenings, we are about to admit our forty-ninth patient. This study started in 1991. So, unlike OCD, which we thought was rare and turned out to be common, we thought childhood-onset schizophrenia was rare and it has turned out to be even more rare. But this study is just as good an opportunity to find out the basis of abnormal development as the OCD project was.

We've been asking clinical, neurobiological and treatment questions and the answers are starting to influence the field. Our first job was to convince our colleagues that this was the same disorder as adult-onset schizophrenia. So we did the predictable series. By definition, it was the same disorder in terms of phenomenology. But, also, we had to show that their clinical course, MRIs and MRS, as well as their neuropsychological profile, autonomic physiology and smooth pursuit eye movements had the same pattern of abnormalities as in the adult cases. The answer was yes and, moreover, they resembled poor-outcome adult patients.

Then we faced the more interesting job of examining risk factors to see whether childhood onset is more genetic, etc. There were two basic questions: do these cases that shouldn't happen have the same risk factors relative to a normal control group and, if yes, then how do these rates of risk compare to the rates seen in an adult chronic schizophrenic group? We're in the middle of this now.

The most immediately gratifying payoffs with this group have been the brain imaging findings and the cytogenetics. Because they had a mean age of about 13 when we met them and were already psychotic, we were able, for the first time, to look at brain development compared to controls for a group of schizophrenics who were between the ages of 13 and 18. What we're finding is that when they are younger they don't have most of the characteristics of adult schizophrenics in terms of the brain MRI, but by the time they're 18 or 20 their imaging pattern is like that of the adults. So most of the brain imaging pattern that is seen in adult schizophrenia actually is probably a later development.

We believe this is due to excessive synaptic pruning. Our normative study shows this to be going on in healthy children and adolescents anyway. The notion is that children are more 'pure systems', with critical developmental periods, in this case in adolescence. This is, we think, a fundamental shift in our view of schizophrenia. We also have a greater rate of cytogenetic abnormalities such as 22q11 deletions. In addition, genetic factors in the families are higher than seen in adults.

In addition, we were able to do a drug trial that showed that clozapine was superior to Haldol. Now, we have started a study comparing clozapine to olanzapine.

Have you any feel for why it's so much better?

The pharmaceutical industry is still looking for that answer. No luck so far. This is unfortunate, given clozapine toxicity. But when we really have a severe intractable case, the only drug that really helps, if anything does, turns out to be clozapine.

Extraordinary, isn't it, how this drug nearly vanished out of the drug pool as well?

Absolutely. We have more and more 'clozapine' stories with our cases. I could write another popular book about this. Some of the schizophrenic children who had not been normal since the age of 5 were virtually cured on clozapine as long as they took the drug. We had a handful of tragic cases who had a brilliant antipsychotic response, but who couldn't stay on the drug because they were susceptible to seizures and/or a drop in white blood cell count. But we got permission from Novartis to re-challenge them 6 years later, claiming that they are no longer the same people now that they're not paediatric. So we've been re-admitting some of these old cases who had to go off clozapine. There are, to date, two cases rescued for the second time from state hospital status, thanks to clozapine. It's a question of whether they can now live in the real world or will return to incarceration.

It's extraordinary if you're able to produce those kind of changes.

It's not the kind of change seen in the majority. Hopefully, a safe clozapine will come along.

Isn't it a mystery, though, because we've had the drug for the last 10 years now and people have been working so hard on just this issue and they haven't really got a good lead at all? It must be doing something radically different. It's not just the balance of S2–D2. It must be something more mysterious.

Yes, this is one of these cases for which you're going to want to have one of these massive throughputs, get a list of every receptor and every gene expressed by clozapine, subtracting olanzapine and risperidone and Seroquel, and so on. A lot of work, but perhaps the new technology plus informatics will do it.

Can I bring you back and overview the field? Again, with this group of people that you've just outlined, it's clear that if you produce these kinds of changes with pills, there really can't be any argument to using the pills. But in the UK, for instance, there is still a resistance to giving psychotropic pills to children. Why? I mean, we wouldn't hesitate to give an anticonvulsant to a child who is having a fit, but why do we not want to give behaviour-changing drugs to children? What's the basis of the reluctance?

There are a number of issues. One is the generally accurate and, I think, important notion that children need to see themselves as developing a sense of

responsibility and seeing life under their own control. And, in fact, a dominant theoretical structure in social psychology remains the locus of the control issue as intrinsic in terms of how an individual handles society, family, himself, etc. So this strong public model encourages everyone to 'do things yourself'. What's harder to get across is the notion that the locus of control idea only helps when you can be in control in the first place. There was a time when, for a black in the South facing racial prejudice, self-autonomy was not an optimal model. The idea that if they could only change their behaviour everyone would treat them differently was clearly wrong. I think that patients with severe psychiatric disorders are closer to that model. They're out of control and, with the aid of medication, they can then put on the brakes and exert control the way that other people do.

Other legitimate concerns are that the shift in our health care system is leading psychiatrists into a more narrow and over-prescribing mode. This is a real problem we face. However, there's also an increased concern about drugs, not just during pregnancy. The NIH now has an office of alternative medicine, in spite of the fact that these trials have been generally negative. So, there's strong sentiment against the use of medication, proven or not, and this also affects treatment with stimulants. In our research, we are finding certain developmental differences in the anterior frontal lobes and in the basal ganglia in hyperactive children; these studies require large numbers of subjects with repeated MRI scans in all cases. Our findings were confounded with stimulant drug treatment and only milder cases were not exposed to the drug. Nowadays, it is easier to find even severely hyperactive children whose parents won't give them stimulants.

A third factor is the media itself. Since Watergate, journalists feel that their mark of success will be via 'exposure' journalism. It's investigatorial reporting, and most science and medicine is not well served by this.

That's an interesting angle. I haven't heard anyone put it quite like that.

I live in Washington. Read the *Washington Post* everyday and you can see that Ben Bradley, who viewed the Watergate coverage as his greatest accomplishment, has trained a whole generation of reporters that this is how to succeed.

What about the point you raised in terms of OCD, about how a lot of our most precious cultural and religious things might have actually derived from a disease origin? That has to look semi-threatening to some people.

Yes, well, I don't think you would put it quite like that in a federal grant application. You would talk about hard-wired behaviours and, as part of a cross-cultural study of OCD and the D8/17 B cell marker, one might include controls with occupations ranging in ritual content. It could be politically sensitive if presented provocatively. The broader issue is that if you're a biological psychiatrist, you are in some sense a sociobiologist. The ACNP has much in common with E.O. Wilson. We are just questioning why some

behaviours are hard-wired, why they have evolved. It is more useful and interesting to think about OCD in this way than to ascribe these behaviours simply to 'short circuits'.

On the plus side, in the UK I see a group of child psychiatrists whose proudest boast, until recently, would have been that they haven't ever used a pill in their life, who are becoming neuropsychiatrists. You can see that during the hour or two that they used to put in with the children and their mothers, where before they would have been trying to look at the meaning of the behaviour, now they are looking at the form of the behaviour in a way that they hadn't done before. I've been completely amazed by the kinds of people who have come over and, as it were, have found in pharmacotherapy a whole new world. Do you think things have changed completely within the child psychiatry field? Do you think it has gone seriously neuropsychiatric, because, as you say, childhood is a wonderful place to see all of these behaviours come out?

It's complicated, so my answer is yes and no. Eric Taylor, from the Maudsley, and I did a cross-national study about the diagnosis and use of drugs in hyperactivity. We trained twenty US psychiatrists in the use of DSM-III-R and the ICD-9 and ICD-20 in London in the two systems and we taped twenty cases each. Both groups then made diagnoses in both systems. There were multiple effects in terms of the types of cases being referred and the use of stimulants. This was about 12 or 13 years ago. But it was clear there was also a difference by system, by physician training and the nature of the child. Since UK clinicians didn't prescribe stimulants, no-one would refer a case where hyperactivity was largely the main problem. They were referred conduct problems, comorbid, perhaps, with ADHD, which in fact did respond to behavioural management. So their clinical experience validated their initial prejudice, whereas when they saw the type of child the US physicians saw, the ones sent for stimulants, they had much less trouble agreeing on the diagnosis of hyperactivity. So systems and prejudices feed on themselves.

Sure. But when you were trying to draw up the criteria for DSM-III you'd have met a group of people who were saying what we do is far too complex to put into these operational criteria. Has all of that changed?

No. I don't think it has. Every new edition of DSM stirs an argument and I agree most editions were premature. The European Community is much more conservative and ICD-10 is here for the duration. I think it will be a long time before DSM-V. A number of people will oppose the change – the general public, which is hostile in the first place, the psychotherapists, the many psychologists who prefer dimensional to categorical approaches, the psychiatric researchers, whose studies are disrupted by new editions rendering their longitudinal studies obsolete before completion.

And, of course, 30% of the cases clinicians see do not fit into any category and there's no solution for that. Curiously, managed care is promoting DSM because it restricts diagnosis and hence reimbursements. Clinicians are being forced to document abnormal behaviours in order to be reimbursed for a

commensurate level of care. One of my current consultancy jobs is for a company that writes the algorithms for many of the managed care companies in the USA.

Do people fear these algorithms will curtail their freedom?

Yes, of course. The algorithms are reasonable though. It remains open whether the managed care group makes its own changes. They may buy them, but they're not obligated to use them.

Within psychopharmacology, child psychopharmacology really has been an add-on to the adult field up till this. In ACNP, have they treated you in a tokenistic way or do you think the adult field has been ready to take on board how much they could learn from the child field yet?

It's variable, but for the most part the organization truly encouraged the development of this field. I've been in ACNP since 1976 and in the beginning I think anyone doing anything got to be on the programme with children. Now I think they expect more and the programme is much more competitive. The majority of clinical trials, even in adolescents for example, wouldn't be of sufficient research interest. The basic models and translational research – that is, bench to bedside issues – have become the dominant model.

I think, right now, there's a lot of interest in developmental neurobiology. In fact, you'll have whole sessions on schizophrenia with basic researchers talking about what candidate systems there are for errors in embryogenesis. Sue Swedo's work with neuroimmuniological models and OCD has struck a chord with groups looking at immunologic models for other disorders. The work on maternal stimulation in rat pups and its effects on central nervous system (CNS) development – such as that by Sol Schanberg – comes from basic studies. ACNP as a whole is currently turning away from patient-oriented issues. Clinical trials are being run by clinical research organisations and these are less likely to be preoccupied with translational issues.

This is potentially a great disaster. If we don't have control of our clinical trials, I think we're in trouble.

Absolutely. The drug companies feel they've done all the thinking and what they really want is a company who'll focus on ~~speech~~ speed and regulatory compliance. These are tough jobs.

Sure. But it needs people who are clinically skilled to make the observations, to recognize the new things that are happening, which may not be recognized by a nurse working with the CRO.

Exactly. But it will take other centres, perhaps the intramural programme at NIH and some extramural centres will preserve this. The kinds of observations that we and others made and are making are terribly important. It takes a prepared mind to note novel aspects in the clinical evaluation, unique associations, anything related to fragile-X behaviours, and so on. I don't think you're

going to get that in a CRO, and these are terribly important observations. With all these cytogenetic studies, we're finding new diseases within this group.

I always thought drug trials were interesting, but even more interesting are the real research opportunities in the other aspects of study that a homogeneous group of patients assembled for the trial offer. Our most useful observations, like tics and brain imaging in OCD or early autistic symptoms in childhood schizophrenics, were by-products of our viewing a series of patients in a relatively intense and systematic fashion. I don't think intellectual excitement is going to be maintained by the way clinical trials are now done. We're certainly doing that kind of thing, but I am not sure that industry would fund what my group is doing.

The future of clinical research is under current scrutiny. ACNP has played an important leadership role in this area in the past. The Society for Biological Psychiatry is doing this at the present time and they have extended themselves to childhood studies. The ACNP has given a great deal of thought to the need for a balance of clinicians and non-clinicians in its membership and on its programme. But it needs a new creative push.

Who have been the other key people over the last 30–40 years who've helped shape the field of paediatric psychiatry?

Well, among the really early people, not so much known for sophisticated research, Magda Campbell was one. She worked with Barbara Fish and really pioneered the idea that you could do studies on psychotic and autistic children. They were working in Bellevue. Lorretta Bender was another. So that would be one group. Keith Connors had an influence on the field. Leon Eisenberg did, very briefly, with an early landmark study, but then his own work moved from psychopharmacology. As a leader, he was very eloquent in championing descriptive work, 'blind' ratings and so on.

A person who influenced the field of psychopharmacology indirectly was Mike Rutter. His epidemiological study gave a kind of rational overview of the field of child psychiatry. The Isle of Wight studies, in 1970, gave a background perspective to all of the early work.

The interesting thing about the Maudsley was their influence didn't feed through to trying to treat children. They didn't ever become the advocates of trying to intervene. Is that how you read it?

Well, I think Mike would say that he had non-pharmacological treatment approaches. He would talk about recognition and early diagnosis in terms of what were diseases that were high risk and situations of high risk. His studies addressed protective factors in families, subcultures and schools. I think he'd say his studies of children of psychiatrically disturbed parents would have identified populations who should have preventive interaction. He did a study which suggested that school milieu that affects the lives of the teachers leads to different rates of school drop-outs etc. in the children. All of these have social treatment implications, which were clear if not dramatic. So it depends what

you mean by treatment. Mike looked ahead towards prevention. The most exciting thing about the OCD *Strep.* project is that trials of *Strep.* vaccination are ongoing, involving 200,000 children. If a lot of childhood-onset OCD is related to *Strep.*, a lot of cases may be prevented.

It would be extraordinary if we could take out a condition like OCD in the way we took out General Paralysis of the Insane (GPI). It would dramatically change how we view the history of psychiatry also – our ideas about what's been going on.

Well, it's still controversial, particularly with respect to whether this Sydenham's model represents 10% or 50% of childhood OCD. ~~But Dr Swedo's bias is for the larger number and,~~ If so, a vaccine ~~will~~ make this an uncommon condition.

We'll be left in psychiatry ultimately with just the personality disorders.

Possibly, as long as there's a drug treatment. Severe conditions needing drug treatments such as bipolar disorder will stay in psychiatry until gene therapy comes along. When you can really do something important, medicine takes the condition for its own. To end on a futuristic note – ultimately, neuropsychiatry may combine with clinical genetics and genomics for an entirely new specialty.

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