

## **PREDISPOSED TOWARDS PREDISPOSITIONS**

### **IRVING GOTTESMAN**

#### **How did you end up in the field. What's your primary training and where did you do it?**

My primary training is as a child and adult clinical psychologist. I went into training in 1956, just as the chlorpromazine era hit the United States full force. I started in the US Navy as an Ensign in cryptography during the Korean War. I had enough time in the combat zone to get the GI Bill which then financed my graduate education. I originally went to the University of Minnesota, which I had carefully researched, because they had the clinical psychology training program that was most oriented towards biology, genetics and an objective assessment of personality. In fact they were on the map of psychopathology because that was the home of the famous MMPI, Minnesota Multiphasic Personality Inventory. The inventor of it, Starke Hathaway, was a very active professor there in the medical school, Department of Psychiatry, and he became one of my mentors along with Paul Meehl.

#### **A very famous name.**

Paul Meehl ended up on my dissertation committee which I will come to shortly. I also went there because they were the only place that was trying to train child clinical psychologists and I featured myself as doing that initially. The person in charge of that was Robert Wirt. He's known to some psychopharmacologists because he was involved with one of the very first controlled trials of chlorpromazine which they matched against reserpine and placebo for chronic schizophrenics in the Veterans Administration Hospital of Minneapolis, which is where I did my one year internship at the end of my training. In those days you could actually get through if you were organised, in 4 years, and that would include a 1 year full time psychiatric internship. So I had 3 years of course work, during which time I also worked half time in a child guidance clinic under the supervision of a Freudian analyst, Hyman Lippman, M.D, someone who had actually been analysed by Anna Freud in Vienna.

#### **You say you picked your course because of its biological underpinning.. why, this orientation so early, can you remember?**

I was always interested in the possibilities of becoming a physician but I didn't pursue that line because I joined the service after World War II. I had always been fascinated by biology and chemistry and was a collector of dead animals and interested in bird watching, collecting birds eggs and things like that. I even went so far as to acquire hearts and eyes from the family butcher in order to take them into school to my biology teacher so we could have hands-on dissection experience. So that was rather enterprising and fun. I think I would have become some kind of physician, as it is I ended up being very much a neuroscientist anyway. Also I was impressed by Sinclair Lewis' book Arrowsmith and I think that set me in the direction of realising these kind of things could be done for a living.

For a dissertation topic, it seemed to me that I should try to combine the knowledge and skills I had acquired about personality assessment, especially using the MMPI, the home instrument. Then I had learned in a course on the psychology of individual differences about the research that had been done on twins who suffered from schizophrenia. I especially noted the studies of Kallmann, who was an immigrant to the United States from Germany and Slater at The Maudsley, the Institute of Psychiatry. I had the fantasy that it would be nice to do something like that but I realised it was impossible because of the difficulty of obtaining twins who had schizophrenia and getting enough of them.

While I was taking course work, I took a course in genetics from a well known drosophila geneticist named Sheldon Reed. He had already by that time left drosophila and gone into family studies of mental retardation and psychosis. He actually completed a huge family study of mental retardation in the old fashioned way, using one of our state hospitals in Minnesota. The study was very well conducted because Minnesota was one of the very first states to apply IQ tests to children, so they had reservoirs of psychological test data on individuals who could

be family members of the mentally retarded and they used these data to make some advance guesses about the genetic aspects of mental retardation. Now this man was very interested in trying to recruit a psychologist to be interested in the genetics of behaviour. He, himself, had done the genetics of drosophila behaviour and thought that there was so much there that American psychology wasn't paying attention to and he was actually correct. It just appealed to me. I said that I would like to do a twin study with personality. The last time that had been done in the States was in 1937. He thought it was a marvellous idea and he helped me to organise it and in the process I learned more and more about human genetics.

I carried off this study using the adolescent twins of both Minneapolis and St Paul - known as the Twin Cities - and I had very good co-operation. I did not get co-operation from the religious private schools because they were offended by the personal nature of the items on the questionnaire. So I made do with the public school children and established the fact that the MMPI was a better test for assessing personality than the tests used by Newman, Freeman and Holzinger in 1937. Rather than getting ambiguous results as they had, I got very positive results showing that for most of the standard scales, and using them in the normal range because these were not patients they were normal kids, the heritability was in the neighbourhood of 0.5, 0.6, which made personality traits as genetically influenced as intellectual ability. That came as a surprise to the Faculty at the University who thought that it might come out that way, but they didn't think that anybody could actually prove it. I published my dissertation by 1963. It was rejected by the Journal I sent it to the first time. I sent it in as a monograph and it was rejected out of hand as being irrelevant to psychology. They said that the nature versus nurture battle had already been settled and that nurture had won. So there was no point in bringing it up again.

#### **Wow.**

So I talked to my Professors who were well connected. Paul Meehl was one of these. Gardner Lindzey was another. This was before Paul Meehl had got into schizotypy. I finished and left Minnesota in 1960. My work was a novelty and attracted some attention from people like Franz Kallmann, who at that time was a kind of a hero. I didn't know enough about him to know that there was a dark side as well to his personality and his research.

#### **Do you want to comment on that further, because that's been made something of by the anti-genes lobby.**

I was dealing with second hand information about Kallmann at the time - the way the textbooks, wrote it up, the way the journals wrote it up. It was only later that I got to meet him personally after he had written about my results asking for permission to cite some of the tables. I also then met his younger research associates Nikki Erlenmeyer-Kimling, who is a well known behavioural geneticist, still doing schizophrenia research and I'm a consultant on her projects, and his other research associate Arthur Falek, who is a human biologist, interested in basic processes, cytogenetics and drug abuse. They changed my view about Kallmann. Kallmann himself changed my view, which had been acquired second hand. I got to appreciate that he was perhaps over-selling the field of psychiatric genetics and in the process he was making more enemies than friends. He was very confrontational and would not abide by psychoanalytic interpretations of psychopathology, even though one of his good friends, Sandor Rado, was one of Freud's direct disciples. My views of Kallmann have continued to evolve in a positive direction. I keep learning more about him in connection with recent publications about Nazi Germany and the 50th anniversary of the Nuremberg War Crimes Trials.

Going back to Meehl, it turned out that he had 2 analyses, one by a Freudian who happened to be my mentor in the child guidance clinic during the 2 years I was there. Then later he decided he would have another analysis and this time he picked a Radovian analysis. It was Rado who had picked up on the idea of schizotypy from Kallmann. Kallmann, of course, got it from the rest of European Psychiatry, especially the people around Munich, who were interested in ways

of characterising the not quite normal relatives, sometimes pretty far away from normal but not psychotic relatives, of schizophrenics. So they used this term and Meehl got a lot of mileage out of it. It became a growth industry in the States. Later it was picked up by the Danish American adoption studies of schizophrenia, Kety and Rosenthal, and they made more of it and it ended up having an effect on DSM III<sup>1</sup>.

**Now we are around '63, which must be close to the time when you came to The Maudsley.** I should say that when I left Minnesota in 1960, my first job was at Harvard University, a difficult post to get, but they were interested in somebody different. They thought anybody interested in or a defender of genetics was different and they thought I couldn't do too much damage because they had a set policy that you could only be there for 3 years and then you moved on. There was almost no promotion from within.

I was in the Department of Social Relations, which was very famous because it was a first attempt to combine the disciplines of sociology, anthropology and social/clinical psychology. They managed to pull that off for a postwar generation, in competition with "proper" psychology under Skinner and S.S. Stevens in the Department of Psychology over the road. The people involved were Harry Murray - he was the inventor of the TAT, thematic apperception test. Gordon Allport who single-handedly invented personality theory in the United States. His 1937 book was influential - on me as well. Clive Kluckhohn was the cultural anthropologist. Another person well known in his own field was the sociologist, Talcott Parsons. So there was quite a heady environment. My immediate boss was David McClelland. He is known for his work on the need for achievement and his use of projective tests like the TAT to measure these things. So I was an odd duck advocating the use of this objective personality test, the MMPI, with its roots in Kraepelinian psychiatry.

They had an initial effort to socialise the new boys. My first teaching job was to co-teach a course on personality with Harry Murray and then during the second half of that first year I co-taught the next version of the course with Gordon Allport. So here I was in the beginning of my career and I was sitting next to rather than at the feet of these 2 famous men after having been exposed to Paul Meehl and Starke Hathaway at Minnesota. I was lucky to get such a solid start.

As a result of my dissertation I was invited, at the expense of the American Society for Human Genetics via a travel grant, to go the Second International Congress on Human Genetics in 1961 in Rome. Because of my close association with Sheldon Reed, who was really my closest mentor in regards to the genetics in human behaviour - we were both learning at the same time - I was introduced there to, among other people, Kallmann and Eliot Slater. I knew about Eliot's work and I went to hear his talk. I went up to him afterwards and said it would be nice if some time in the future I could come over and be a post-doctoral fellow and I was sure that there was something that I could find that would be interesting to both of us. He said well if you ever get a chance come along. At that time I didn't know that his brother was a psychologist and later on I realised that was part of the reason he was so friendly to me.

During my last year at Harvard, I applied to the U.S. Public Health Service to have a full time fellowship abroad and it just so happened that at that time there was a big push to try to get people trained in one discipline to obtain training in another and one of the fields they were encouraging was genetics. They were also encouraging ethology and physiology and things like that. So I applied and, based largely on my dissertation, as I had been publishing a few things from it, I got the fellowship. I worked it out with Slater that I would come to his MRC Unit in Psychiatric Genetics and do one of two or three things. One of the things on my wish list was

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<sup>1</sup>See Claridge G, Healy D (1996). The Psychopharmacologists Vol 1

to do a study just like his, the genetics of schizophrenia, using the twins that he had accumulated from the register that he had set up in 1948.

After the War he realised that his own twin study was not ideal because of the sample ascertainment which was just from resident chronic cases in the old traditional hospitals, around London. So he set up a register at The Maudsley and The Bethlem Royal, and in the emergency units of nearby hospitals in Camberwell. He set up a face-sheet in all those places, so that all the intake workers had to ask whether or not you were one of a pair of twins and he managed to get a different kind of register from anything in the literature - consecutive admissions to both in- and out-patient services. This would allow you, for example, to get a case of schizophrenia that had never had inpatient treatment. When I came over and started work, one of the twins on the register had never had an inpatient contact but because of the nature of schizophrenia, it is virtually impossible to stay as an outpatient for your whole life, and by the end of our study every one of the patients had put in time as an inpatient. I was very lucky that Eliot agreed that I could do this. It was such a precious resource. It gave me tremendous advantage in my career to be able to do something this important 3 years out of my degree.

He set me up to work with Jerry Shields. I knew Jerry Shields from the literature because of his world-renowned study on identical twins reared apart. What I didn't know was that Shields was confined to a wheelchair because he was one of the last adults to get polio in the UK and that his formal training was as a social worker. The vaccine when it first arrived was given to children here and then to adults and it didn't get to him on time. We were a very complementary team.

**Can I ask you more about the personal impact people like Eliot Slater and Jerry Shields made on you...**

Eliot was my senior by a number of years. He was a very good mentor. He was pretty much a hands off kind of person. He wasn't interested in micromanaging. He was interested in the grand scheme. I told him what I wanted to do. He said Mr Shields will help you accomplish this. I know you will like him. I explained my scheme to Jerry Shields and we implemented it. What I proposed was to give the MMPI, based on my sympathies with Paul Meehl, to try to assess whether schizotypy was on a continuous dimension. We right away rejected the so-called medical model and shifted towards a model for dealing with chronic diseases like heart disease and diabetes. I was a strange kind of psychologist to be talking like this but this was the way I had been trained by Sheldon Reed to appreciate complex traits from plant and animal genetics work.

I also said that I was going to tape record my semi-structured interviews, which were designed again to get a dimensional appreciation of mental illness. They said, well Englishmen aren't going to let you come into their house and turn on that machine and tape record the interviews. They also probably won't be too happy to fill in the questionnaire asking them about their sex lives and their religion among other things that will take a good 45 mins to an hour. I said well let me try it and I'll see. I went out and I was very lucky initially and that gave me confidence to go ahead even when I obtained resistance. The path had been smoothed by the research assistants in the old genetic hut. This was the MRC Psychiatric Genetics Unit and that was my point of attachment. Eliot provided me with a room there. It was a small wartime hut but it contained Eliot most days of the week, Jerry Shields and Valerie Cowie.

**Can I ask you about Valerie Cowie because if you read the interview by Alec Coppen, he says that she was probably the brightest woman he had ever met. Is this right?**

She was extremely bright. She was kind of a favourite child of Eliot. He brought her along quite quickly in her career. She had the good sense to take his advice and obtain a PhD in Genetics after she had trained as a psychiatrist. She took a PhD in genetics with Lionel

Penrose. Now Penrose and Slater were never friends, they were antagonistic about each other. Penrose had a very poor opinion of psychiatric genetics, or of psychiatry in general, even though I believe he served as a psychiatrist both in Canada and in the UK. At any rate Valerie got along famously with Penrose and she got along famously with Eliot.

I was there from 63 to 64 and came back the following year for 3 months and then I came back every year for 25 years for 2-3 weeks just to work with Shields and sometimes directly with Slater on the data analysis and the writing of the papers and the book, which told it all. The book was published in 1972. In 71, I had published with Shields the edited and collected papers of Slater. We thought we better do that while he was still around to appreciate it. So we stood down work on our own book and pulled together the best of his papers in all the areas that he had worked in.

**It is clear from what you have told me about him and from what he writes in the book that he was reluctant to get involved in this experiment of committing his thoughts to posterity in this form. What sort of a man was he and how do you estimate his contribution?**

He is one of the major figures in 20th century psychopathology. He had the abilities, both technical and personological, to pick important topics and to approach them in a classical British empirical manner and to add to this, a genetic orientation. His own genetic orientation he acquired almost by chance. In the early 1930s, when he arrived at The Maudsley, his mentor, the one who eased him in, was Aubrey Lewis. Aubrey Lewis was well connected on an international basis. Among the many possibilities that Eliot expressed interest in, Aubrey recommended that he pursue genetics, as a post-doctoral fellow. He had to organise so that he could obtain a Rockefeller Fellowship just as Aubrey himself had obtained a Rockefeller Fellowship to do anthropology, when he still lived in Australia.

Eliot went over to Munich at a very obnoxious time in German history. Hitler had just taken over in 1933. Academia was trying to go on as usual but there were splits as he described them to me, which I talked him into writing for the book. Splits between the sensible academic Germans, who were disinterested in politics, and those who worked along with the Nazi overlords and the inclination to abuse both genetics and psychiatry for political purposes. He wrote some very emotional papers after he returned from Germany. While he was there he also met Lydia Pasternak, the sister of Boris, and married her and that's the mother of his children. He also was very keen on art and poetry. He wrote poetry which he published privately. He became a very good Sunday painter. I am flattered that in his will he gave only 2 people paintings, one was Martin Roth and the other was myself. We did become close personal friends, even though there was a big difference in our ages. I think he looked on me as another one of his sons.

He was quite willing to challenge received wisdom and took a great deal of pleasure in it. It got him into difficulties with Lewis, got him into difficulties with the Washington University school of thought, where I later spent part of my career. They got into a big fight on the topic of hysteria. Eliot thought of it as an iatrogenic disorder and in his own work involved with follow up of patients from Queens Square, he was able to show that the vast majority of these people who had a diagnosis, usually of conversion hysteria, later on had something wrong with their brain and he could show it. They had a different view at Wash U. At any rate he spent a lot of energy without having an empire. It is very unlike research enterprises today, where people need a lot of money and they need a lot of associates. He was able to organise himself and Jerry Shields and maybe one other field worker and accomplish incredible amounts of work, of very high quality and then see it through to publication. During the time that I was here he was also the first editor of the British Journal of Psychiatry - under its new name.

**How important was that to the field - he obviously had the discretion to accept articles on the genetics of psychiatry, at a time when you might have found it hard to get them published elsewhere and having him there must have encouraged people to think about doing this kind of work.**

Yes, you're absolutely right. And he had this ability to give advice without being threatening. His letters of acceptance were usually lessons administered in a way that you had no reluctance to accept all of the advice and make it a much better paper - especially knowing that it was going to be accepted. Many papers that had been rejected by American Journals especially, came his way. He shaped those up and they were published in the BJP. Our first paper on the results of schizophrenia in this new sample of twins, was published in 1966 in the BJP in the very same issue that he published results of the first adoption study of schizophrenia by Leonard Heston.

It's interesting to bring in Leonard Heston to the story because Heston was a young registrar when he first communicated with me - we were born a couple of weeks apart in 1930. He heard that I had spent a year here and he wondered whether or not there was any point in him disrupting his life, the way I had disrupted mine to come over to work with Eliot and Jerry Shields. I told him - absolutely yes. So he, on my advice, came over to work with and have his work shaped by both Eliot and Jerry and ended up with his adoption study on the offspring of schizophrenic mothers being published. So 1966 was a momentous year for us with the publication of these 2 brand new approaches. Ours was new because as I've already mentioned I used the MMPI to get continuous indicators of psychopathology and I used tape recorded interviews, but another thing we did was to not allow ourselves to be the diagnosticians, given the criticism that both Slater and Kallmann and the earlier investigators had received. They had diagnosed both members of the twin pair, so there was no way for them to be blind, as to whether they were diagnosing identical or fraternal twins. So if they had a genetic bias, an unhealthy one rather than a healthy one, they could make the results look more genetical than they were. We avoided that by involving a blindfolded panel of 6 judges to whom we gave extensive case history material, MMPI profiles and verbatim interview material from my semi-structured interview. At the time I was using my own purpose-built semi-structured interview, John Wing working next door to us in the social psychiatry hut was working on the PSE. That period 1963-1965 was a very important time for me to be here.

**You then went back - to Minnesota?.**

I went back to the States. I was recruited while I was here by the University of North Carolina to the psychiatry department by George Ham, who most people have never heard of. He had become very impressed with the part that genetics might play in psychiatry and he looked around for possibilities but there weren't many people who had the proper training or background. He heard about me and tried to recruit me. I had no other opportunities and so I was happy to take up the post in the Psychiatry Department, after I had guaranteed that I could also be appointed in Genetics. Also I didn't want to lose my contact with psychology and the Psychology Department there was very happy to have me as a member. I worked in North Carolina Medical School for just over 2 years, as it turned out. George Ham left his post as the Chair and the person who replaced him was not interested in supporting this area.

About that time, I got a call back to Minnesota saying that they were hoping to get a National Institute of Health grant that would allow for the training of people like the person I had become, trained in both psychopathology and in human genetics. They thought if I worked there, they could pull it off and I would be the co-director of this program with Sheldon Reed. It would be housed initially in the psychology department because people like Paul Meehl were all enthusiastic about it. So I went back to Minnesota in 1966 and stayed there until 1980 when I got the call to go to Wash U, where that Psychiatry Department wanted to build up genetics as a major rather than as a minor part of their offerings. In Minnesota I was a full member of the Departments of Psychiatry, Genetics and Cell Biology and Psychology. I was coming to enjoy

being somebody who wasn't typecast but who could operate freely in this larger area that requires an integration of areas. I did a lot of work during my time in Minnesota. For the 14 years there I was mentoring personally 2 PhDs per annum in the areas of behavioral genetics or clinical psychology and they in turn have produced students and it's snowballed in that fashion.

So I have had an influence via my original students who stayed in the area and then very gifted post - doctoral students such as Peter McGuffin and his wife, Ann Farmer, who came to St Louis partly because I was there and they knew of my connection to Slater and Shields.

**When did the concept of Behavioral Genetics begin to crystalise out and who coined the phrase?**

Up until 1960, the area that became known as behavioral genetics usually went by such labels as the Nature vs Nurture controversy. In fact, it grew out of the area of the psychology of individual differences, which has a very German tradition. It goes back to World War I. The Germans were very interested in measuring individual differences in intelligence and personality. It had a military application, as part of their effort to select the best people to do the most difficult jobs, or to decide which enlisted men should become officers. That quickly spread to other countries like the UK and the United States. So there was a big testing tradition behind behavioral genetics. In 1960, the first book was published that actually had the title Behavioral Genetics, and that was the coining of the phrase that stuck. That was by John Fuller, who was a zoologist and an expert in dog behaviour and William Thompson, a Canadian psychologist who brain drained to the States - he was an expert in mouse behavior genetics. The 2 of them compiled the literature going back to the time of Galton, put it together in this book and it became the bible for the field. It had chapters on psychopathology. The Slater and Cowie book was the first that dealt specifically with psychopathology but that didn't come out until 1971.

**When you were in Minnesota at this point, Travis Thompson was also there.**

Travis Thompson was a colleague of mine. We both graduated the same year. We didn't know each other too much in graduate school but afterwards when we were trained, especially when I returned to Minnesota we were good friends. He was my house neighbour. Our families were good friends. Travis wasn't interested particularly in genetics but he realised that pharmacology was a new area that psychologists should be involved in and he became very influential in a short time, training both the MDs and PhDs in behavioral pharmacology. He had been a go-ahead straightforward Skinnerian, trained by Kenneth McCorquodale, who was Meehl's closest friend. So all these things seem to keep weaving in and out and linking.

**Skinner himself had been there during the 1930s with Bill Estes wasn't he, and Howard Hunt was there at one point, and then he went to Chicago.**

Right, they were all there and they all fitted in to the Minnesota scheme, which was pejoratively called dustbowl empiricism. They eschewed theory because theory was considered to be kind of fatuous. They were never a talking club. They didn't want psychology to be near philosophy, which was part of its roots. They wanted it to be nearer to biology, mathematics and the harder sciences which acquired the most money for research from the federal government and from foundations. They weren't going to support the philosophy of X and Y or chitchat but they were going to support empirical research, the result of which could be put to use to improve the lot of mankind. Most of the funds came from the National Institute of Mental Health, which started up right after World War II.

**Was there any reason why Travis was so successful in being able to pull people into the field. What kind of personality was he?**

I would say it was his sincerity, his strength of purpose and his dedication to empiricism. Behavioral psychopharmacology was completely new to American psychology but also a natural evolution as the field of psychology after World War II divided up into specialities. This became one of the specialities that was highly regarded by the Federal Government and the

granting authorities. It immediately attracted the attention of the pharmaceutical industry so that Travis quickly acquired an empire. He was always in the Medical School at Minnesota for his major base of operations. I was a full Professor eventually in the Medical School but my base was in the Psychology Department. Meehl split himself between psychology and psychiatry. Hathaway was full time psychiatry.

Minnesota was an unusual place in that there was no internecine warfare or tension at that time - it's changed a lot since then, but at that time, there was a kind of continuous love affair between psychology and psychiatry. There was no prejudice shown on either side. The Department of Psychiatry had a huge contingent of clinical psychologists, many of them trained by Hathaway and the psychiatrists at that time. Don Hastings was the Head of Psychiatry after the War and he was a very close personal friend of Hathaway. He trusted him completely and allowed Hathaway to, in effect, be the executive administrator of the Psychiatry Department even though he had no formal medical qualifications. He was extremely knowledgeable about psychiatry and psychosomatic medicine and he was also an equipment buff. He was interested in psycho-physiology. He had written the first book of physiological psychology, published in the same series as Skinner's *The Behavior of Organisms*.

### **How did you get involved in the Danish twin studies?**

During the time I was a Public Health Fellow at The Maudsley, I took a study tour at Eliot's suggestion. Through him I was able to go to Sweden and meet Erik Essen-Möller. I liked him and he liked me obviously. I got him to agree to be a blind-folded diagnostician for every one of our twins. This was the beginning of our multi-judge blind-folded panel that got away from the criticisms of the earlier twin studies. He was in his retirement and welcomed the opportunity to have a go at this. Then after that I went to Denmark to visit with another of Eliot's friends, Erik Strömberg who was at Riskov, north of Aarhus. There he introduced me to a young psychiatrist who was doing a twin study of schizophrenia, Margot Fisher. We became quick friends because of our over-lapping interests even though Shields and I were way ahead of her in terms of getting the job done on our sample. I also then went to Copenhagen to visit a friend of mine, Brendan Maher, who like myself was at Harvard in the early 60s and through Maher I met Sarnoff Mednick and Fini Schulsinger. I then spent more time chatting with and communicating with Mednick. From then things sort of went into hibernation.

Then in 1967 there was this famous meeting in Puerto Rico, the Dorado Beach Conference, organised by Seymour Kety and David Rosenthal and financed by the Foundations' Fund for Research in Psychiatry, which had as its goal bringing together in a confrontational manner all of the world experts on schizophrenia whether they be on the far psycho-analytic side or on the far genetical biological side. Because of my normal twin work plus my schizophrenia work, both Kety and Rosenthal knew what I was up to. So they invited not only Slater, of course and Shields but also me and Leonard Heston. By that time Heston had also had a post-doctoral year at The Maudsley in Slater's Unit and he and I had become very close friends. As it turned out he was the best man at my wedding and his wife was Godmother to my younger son. So that's where I got together again with Mednick and Schulsinger and the Danes that had been involved in the adoption studies. I had no idea at that time that I would take my next sabbatical, on a Guggenheim Fellowship to Denmark, which I did in 1972/73.

### **What was the Puerto Rico conference like? You say that they set this confrontational meeting up, how confrontational did it turn out to be ?**

Well nobody came to blows. I think everybody was moved forward toward somebody else's position. They didn't relinquish their own position but they moderated within the direction of, lets say a multi-factorial approach. Some moved more than others. Some made pseudo-moves during the week and then quickly reverted to their original positions, such as Professor Lidz and he certainly was confrontational. The people who believed in schizophrenogenic mothers were there defending their positions and they listened politely. There seemed to be

kind of a sleeper effect because later on some of those people approached us on the genetic end of the spectrum and asked for and took advice about new research they got involved with. One conspicuous example was Pekka Tienari, the Finnish psychiatrist. He had been working on his own twin study for schizophrenia which he interpreted initially to completely support the environmental psycho-dynamic position. He was very much under the influence of Alanen, who was very much under the influence of Lidz. There are a lot of these pedigrees that you can see in the history of this field. Lyman Wynne was there along with Margaret Singer talking about constructs which in Britain would be called EE, expressed emotion. They were talking about such things as communication deviance and affective style. Right now Pekka Tienari and Lyman Wynne are doing a new adoption study of Schizophrenia and I am one of their genetics consultants along with Ken Kendler and they are using the MMPI. So that goes all the way back to 1967..

### **So it was a good thing that meeting?**

Well it was a landmark meeting and the book out of it is a landmark book which is not fully appreciated by the field. The proceedings of the meeting actually included, a fair amount of the table talk, which was recorded. A lot of the slightly cleaned up confrontation was published by David Rosenthal in the book as discussion.

### **How do you credit the contribution of Kety or Rosenthal in getting all of that off the ground plus their role in the adoption work at the time.**

The motivation behind the meeting was to disseminate their major findings, which they knew would shake up the world although they hadn't appreciated that Leonard Heston was doing something similar on a small one man scale and with a sample size of 47 in his experimental and 50 in his control group of children with normal mothers adopted away. But they invited Heston to present his updated results and then they, with great pride, deservedly, presented their 3 strategies. These were presented for the first time at this meeting. It was saved for the end of the week after everybody else had done their thing. Then comes the big surprise, major findings. They were and they are.

I think everybody was very impressed. We all knew that we were present at a major event in the history of psychopathology. To have present at the meeting Manfred Bleuter - he was then near retirement. I guess he was about 68 or so. Eliot Slater also about the same age. Lidz, Lyman Wynne were there as was another pioneer of behavioral genetics Nikki Erlenmeyer-Kimling. Sociologists like Clausen and Rosler were there, who were very interested in rural/urban differences and the impact of sociological things on the incidence of Schizophrenia.

All of these things were put on the plate at one time, so you could see that they each had a role to play and you couldn't reject any completely. But you could now be in a position of assigning informed weights to these factors and clearly genetics came out way ahead and for the first time genetic studies were not vulnerable to the kind of criticisms of the past. Einar Kringlen was there from Norway with his newish twin study of schizophrenia. It was just an accident that 5 of us, started and completed new twin studies of schizophrenia at about the same time - Tienari in Finland, Kringlen in Norway, Fisher in Denmark and you had me and Shields working with Slater in the UK, all of them coming to fruition around 1966 give or take a year. So you had all these laid out and no-one could say then that Kallmann's findings were spurious, the result of a hereditarian attitude or that Slater's results were genetically influenced because he obviously had an axe to grind and so forth.

Then you had the twin studies backed up with these new adoption studies. The strategy that Heston had initiated at the same time as Rosenthal and Kety, involved looking at the adopted away children of schizophrenic mothers. Rosenthal did it by looking at the children of adopted-away mothers or fathers who had schizophrenia. Then Kety's strategy was a study with adopted-away children who grew up to be schizophrenic - he then went back and using the assets of the Danish mental health system tracked down the biological parents and relatives

and the adoptive parents and relatives of these adoptees. There was one further strategy which necessarily had a small sample size and this was called the cross-fostering strategy. The lead on that was Paul Wender, the child psychiatrist, who was not particularly interested in genetics but was drawn in because he was a young man working at the NIMH at the time and was very valued by both Kety and Rosenthal. There they looked at children who were born to normal parents, adopted away into the homes of parents who later developed schizophrenia. All of these findings pushed towards a genetical explanation, as the major but not the exclusive explanation for the data. I think everybody was impressed, no matter what their stance. Those people who didn't put much weight on genetic factors could not possibly avoid them after this meeting.

**There are one or two kind of ambiguities there that you may wish to comment on. One was at the time, the Americans would have been very soft in their diagnosis of Schizophrenia but on the other hand, some of the Danes may have been over-diagnosing manic depressive disorder because of the influence of Lithium How did that fit in?**

There were so many different diagnostic orientations - this is a whole treatise by itself. Bob Kendell's book is a case in point. The diagnoses that Shields and I used were a mix of all these schools of thought because among the blind-folded judges we had Essen-Möller. We had Americans like Loren Mosher. We had a number of British psychiatrists but each of them were of different persuasions. We had Jim Birley, for instance, who was a Schneiderian with a category S+ point of view, making diagnoses. We had Paul Meehl, who was very generous in his diagnosing of schizotypal personality. All these people together allowed us to play an empirical game of picking out the abnormal from the normals. We didn't throw out anybody's information - we used all the information and in our own case we reached the conclusion that a middle of the road diagnosis was the most meaningful one - something that wasn't too generous in diagnosing odd personalities as being schizophrenia-related but would be generous on the other end and not require just a category S+ person to be a Schizophrenic.

Kringlen was using diagnoses that were influenced by Langfeld and Strömngren because at that time Strömngren was the only one who had a Textbook of Psychiatry and that served all of the Scandinavian countries. Later on there were others including Kringlen's own textbook and Welner and Schulsinger's textbook. The Danish adoption-related diagnoses were mainly influenced by the Americans, so when they had a panel of judges perhaps only one of three would be Danish and that individual was usually more Westernised so to speak and some distance from the Strömngren school of diagnosis. It was only later, after the work presented at Puerto Rico, that you could see this influence of what we might now call over-diagnosing of a manic depressive illness because of the enthusiasm in the use of lithium in the Schou and Strömngren school of thought. They were very close friends and aided and abetted each others advocacy of biological psychiatry and a special brand of social psychiatry that's very much influenced by biological psychiatry and pharmacology.

**Later you ended up participating in the Danish twin work yourself. How did that come about?**

The advantage of going to Denmark was so obvious to me that I was willing to disrupt my life and go abroad again for a full year. This time I could do it from a secure base rather than being between jobs. I was lucky to win a Guggenheim Fellowship, which freed me up to do what I wanted to do. I arranged with Mednick to be a guest worker in his Institute where the adoption studies of criminality and schizophrenia were being conducted as well as his prospective, longitudinal high-risk studies of the offspring of schizophrenics.

**Can you tell me some more about Mednick?**

Sarnof Mednick is a famous entrepreneur who has this ability to gather funds for novel research strategies. He recognised the crucial importance of the Danish system in providing you access

to carefully diagnosed unbiased samples of individuals and their relatives. He has the advantage of working in a country that has a national psychiatric register that is now computerised, where there is a national twin register that dates back to 1870, as well as a national police register and a national adoption register which was formalised using the American funds that he helped bring to Denmark via Kety and Rosenthal. Kety and Rosenthal needed their contacts with Mednick and Schulsinger to pull off all this work that has brought them fame in the field.

When I went there in 1972 it was with the idea that I would be working with Margit Fisher in Aarhus on a different project, a new project where we were interested in the offspring born to 2 psychiatric inpatients. Given the Danish resources we could pull off this extremely rare and difficult strategy. It had been tried in Germany in the 1920s and 30s to advantage but those results were lost and they have never been translated to English. It was clearly a very powerful strategy that would inform both taxonomy and genetics. She started collecting data and then I came over and joined her. I brought over American money, from the Scottish Rite Foundation on which Board Seymour Kety sat and helped promote our research. We began that project in earnest and that work is still on going with Aksel Bertelsen because a little bit later unfortunately Fisher committed suicide.

When she did that, it left another of her projects unfinished. This was the project that she published in its initial form in 1971. She was looking at the psychiatric status of children born to the twins as a function of whether or not both twins were schizophrenic or only one in the pair was schizophrenic. This gave you the terrific power to show what became of children of normal individuals who happened to be the MZ or DZ co-twins of a schizophrenic. After her death I then was partnered up with Strömngren's help with Aksel Bertelsen. With him I have been continuing the work on the offspring of dual matings, as we called that project and we finalised the study of the offspring of concordant and discordant identical and fraternal twins to see who has schizophrenia and what does that mean. We didn't publish that paper until 1989. It appeared in the Archives of General Psychiatry and brought us a lot of attention, as it should have. It also led to Fisher posthumously and Bertelsen and myself getting the Kurt Schneider Prize - the first time it was given to non-Germans.

There were other connections with the Danish high risk studies. The high risk studies were separate projects of Mednick and Schulsinger and Fini Schulsinger's spouse Hanna and that is famous in its own right and a major contribution to this field.

**Were they the first to conceive of the idea of a high risk strategy or did that idea come from elsewhere and they just happened to be the ones who were first to implement it.**

The idea came from elsewhere, actually from Minnesota. In a paper published in about 1958, it was suggested as a strategy by a psychologist John Pearson who was a Minnesota trained person influenced by Meehl and his co-worker Irene Kley. Having been influenced by Kallmann's research on schizophrenia, they proposed that the way to get results in a hurry and not have these results be confounded by the effects of hospitalisation and so forth, was to look at the children of schizophrenics, while they were normal and then follow them until the "fated" 10% or so would develop schizophrenia. They couldn't do the work themselves. Mednick noticed this and realised he could implement this in Denmark given all these national resources. So he got a good head start on everybody else. Other people jumped on that band wagon and tried to do it but they were doing it in countries that did not lend itself so well as did the Danish system. So Mednick's findings were the most mature followed by the Erlenmeyer-Kimling findings which are now appearing in the literature in final form.

The strength of these studies converge in showing that children of schizophrenics raised by them develop schizophrenia at the same old high rate - between 10% and 15% or so. But in addition because of the emphasis on schizophrenia spectrum disorder, schizotypal personality,

schizoid personality and so forth, the number of disordered children have grown proportionately so now we realised that many more than this core group are disadvantaged. The strategy of the high risk design allows you to detect abnormalities or deviance from normality on the way toward development of schizophrenia and allows you to do this economically because you only have to study a 100 children in order to get say 15 schizophrenics, whereas ordinarily in order to get 15 schizophrenics you would have to study 2000 individuals from birth till aged 55 to 60. The results of both of these strategies are very encouraging and these findings will be tied to the next generation of genetic studies where molecular genetics will be linked to these traits that feed into the development of schizophrenia proper but which by themselves can be seen as departures from normality that need not necessarily have a pathological overtones.

**Was Mednick just being opportunistic about all this or do he did have a personal vision of some sort. Did he come into this kind of work with any prior beliefs about the outcomes**

He had established a reputation for himself as a well trained experimental clinical psychologist, interested in learning theory as it might pertain to schizophrenia. He also was becoming very interested in psychophysiology, especially the psycho-physiology of the autonomic nervous system, as it might be an indicator of the schizophrenic state itself either in an episode or in remission. And he was curious about what the children of schizophrenics looked like on these dimensions that were relevant to Pavlovian conditioning as well as American style learning theory. So that's how he entered. He was not interested in genetics per se, but he quickly acquired an interest in it.

**And Fini Schulsinger,**

Fini Schulsinger was the Chief Psychiatrist at the then Community (Kommune) Psychiatric Hospital in the centre of Copenhagen. They were personal friends. Fini was the one who greased the skids into the Danish National Health system for Sarnoff. Then the 2 of them together were able to put together a very impressive grant request to the National Institute of Health and quickly obtained the funds to mount the field studies which led, among other things, to the training of an entire cohort of Danish psychologists and psychiatrists in these new techniques of psychophysiology, learning theory and epidemiology of mental illness.

**Danish and possibly Scandinavian psychiatry has always been very biologically oriented. Do you think this work has had a part to play in that, because it must be very hard to be a Danish mental health researcher and not be influenced by all this.**

Right. The people who are of a strong psychodynamic, psychoanalytical persuasion are a real minority and not a big influence. It's because of the general values of the people working in the Danish mental health system that so much of this work has been able to be done so efficiently without resistance..

**What are the values. Because it's odd in a sense that they were so close to Germany and yet all of this has been perfectly acceptable and virtually no problem at all in Denmark.**

The Danes were among the very first countries to pass laws that authorised Health Services to sterilise individuals if they had a severe mental retardation or a severe mental illness but it was never done in a coercive atmosphere which was what distinguished the Nazi approach, from the time Hitler took over in 1933. The Danes had passed these laws, as had the Swedes earlier, but with a panel of ombudspersons to guarantee civil rights for individuals, not to let the wrong people get into the act. Danish psychiatry was very much influenced by biology and by a German tradition of phenomenological psychiatry. As I said almost all the knowledge came out of one textbook written by Strömngren. Strömngren was very influenced by German traditions and like Slater had gone to Germany and had the same reactions - it was a good place to learn about psychiatric genetics, but it was also appalling to see the abuse of civil rights and the going along with the Nazi government of these scientists in order to maintain their empires - which is the main charge laid against Rudin. Other people chose to leave, especially if they

were Jews and they came to the UK or the United States to carry on the way Kallmann did. Some people became a-political and got away with it. They included Bruno Schulz the real mentor of both Slater and Strömngren. Schulz was somebody who just kept his nose to the grindstone, didn't get involved in politics and was extremely talented mathematically. Slater, I think only met Rudin once or twice and then just in passing. Same with Strömngren.

**It's still odd that given what happened in Germany after the War, the whole eclipse of this area of research that one of the strongest places where it then re-emerged was in a place so close to Germany. The Danes perhaps have a funny relationship with the Germans.**

There is no love lost but there is an admiration of their science and of their culture. But the Danish tradition in psychiatry always had a very large, almost dominant role for genetic factors and this can be attributed to Strömngren and the people that he has influenced in the modern generation, like Rafaelsen, Juel-Nielsen, Bertelsen and Fisher, and slightly before her Joseph Welner who was the clinician in the Danish adoption studies. He was the one who actually did the interviews. He was a direct disciple of Strömngren although they went their own ways and he became much more interested in psychotherapy. He was a good friend of mine while I was there and afterwards. He was an extremely gifted clinician. He also became a judge on our Maudsley twins with Essen-Möller.

**You came to Wash U at a time when they were maturing I guess. The first group of people had actually left or were leaving, people like the late George Winokur had gone to Iowa although the links were still there I guess.**

George had left and Don Goodwin had left. The links are still there and form a kind of visible college not invisible college. Some of the individuals who came out of Wash U training went on to become Chairs of Departments, Paula Clayton is the Chair at Minnesota, Don Goodwin went to the Chair in Kansas, George went to Chair Iowa.

**And they see themselves I guess as being seminal within the US context.**

Yes they see themselves as having been responsible for the development of DSM III with its criteria based diagnoses because it depended in part on the scheme that had evolved at Wash U, known as the Feighner criteria. It was paradoxical that it should be known by that name because Feighner was a registrar at the time and he was just assigned the writing up of the paper, so he was the first of a long string of authors that included Sam Guze and Eli Robins.

**So it ought to really be the Robins criteria you think.**

It should be the Robins-Guze criteria, if you want to give it a name. Feighner is inappropriate; he was trenchant and a good worker but he has gone off now to a non-academic career doing drug trials. The other people involved like Guze, Winokur and Robins were all outstanding clinical researchers. Not theoreticians. The theoreticians came later like Ted Reich and Bob Cloninger. The general attitude in Wash U before and after I arrived, in 1979, was that in fact they had more gas-chromatograph pieces of apparatus than they had clinical psychiatrists. They had no special spot reserved for training of their residents in psychotherapy and especially not in psychoanalysis. They always had one psychoanalyst around who would come in and try to bell the cats and some people acquired those skills but they were a real minority. It essentially was a stronghold of biological psychiatrists who then in a natural way branched into psychiatric genetics.

Guze and Robins had the foresight to take people out of service at a great cost to the cashflow of the Department and allow them to go away for up to 2 years for post-doctoral training at the expense of the Department of Psychiatry, to be properly trained as geneticists. So Ted Reich came to the UK and worked in Falconer's Unit in Edinburgh to learn quantitative genetics as it applied to medical genetics and as he would then apply it to psychiatric genetics. Bob Cloninger was allowed the luxury for any doctor or psychiatrist to go to Hawaii for more than a year to

work with Newton Morton, who was the man who devised contemporary linkage strategies on which he had published as early as 1955. Newton Morton was a direct contact with the holy men of population genetics - R.A. Fisher, Sewell Wright, James Crow and T Dobzhansky. Newton Morton has since become interested in psychiatric genetics. I worked with him via D C Rao, who is another one of these catches for Wash U. He is a bio-statistician and a geneticist, who the Psychiatry Department in Wash U went way out of their way to recruit and to make it possible financially. They have done that repeatedly, most recently with Alison Goate.

They did it with me when I was in Minnesota. I had met them socially and professionally at meetings and committees and they made it worth my while to come and have the title of Professor of Psychiatric Genetics - nobody else had that title. I fitted right in to the team approach and I facilitated getting very large grants at a time when the Government was not sure whether they were better off to fund individual researchers or to fund what we call Clinical Research Centres. They took the middle of the road position when they decided to fund both the CRCs and individual researchers but the money that was delivered to CRC's was a very large drain on funding individual researchers. There was a sort of recognition of the fact that you could not do all research on a solo basis. You had to have Manhattan-project-like teams and Wash U was eminently successful in getting not one CRC but multiple CRCs because of the people that they had brought together. A large proportion of the people were basic scientists rather than MDs but Robins and then after him Guze used their own authority and because it was a private University not subject to public oversights, they could say "how about this" and they would get it. They would go out on a limb but they managed to be very successful. They were prepared to go in a hole in order to do that and hope to make it up later on. It does make Wash U nearer to being a mini-NIMH where under one roof you could have MDs and PhDs of all sorts working together on projects. The nearest would be UCLA and New York State Psychiatric Institute.

**Where did the Wash U ideal come from. Was it down to Eli Robins and if so where did he get it from?**

It can be attributed to Eli Robins and to Sam Guze following him. Their orientation to psychiatry is really from internal medicine and via the aristocracy of American Medical Schools, namely Harvard and Johns Hopkins. Both of them were internists at heart who then became psychiatrists and other things. But Eli Robins was specially influenced by O Lowry who was a discoverer of adenylate cyclase and that's where he acquired his enthusiasm for laboratory approaches to psychopathology. He saw psychopathology as just one more branch of medicine whereas the rest of the American psychiatry, influenced by Freudian and other psychodynamic schools of thought, stayed separate from the other parts of the medical school. Sometimes going so far as to be in separate buildings a few miles away from the main medical school.

**Wash U for a long time were outside the main stream - they were doing something that was seen to be quite idiosyncratic but yet it ended up being the winning side. The Feighner criteria were the basis for the DSM III criteria etc. How much though did it take the contributions of someone like Klerman, who was part of the East Coast kind of establishment, very well connected politically to bring the Wash U project to fruition.**

The distribution of large funds for research that I mentioned before was tilting towards CRCs and collaborative projects, which would often involve 4 or 5 different medical centres. Wash U took the lead in the first collaborative study of depression which meant pharmacology. Klerman was involved in a number of ways with this project. I was involved accidentally. When it first came in for funding I was on the Committee that was over-seeing all grants that were worth a million dollars or more. At that time a million dollars was thought to be a lot of money, nowadays it's not. On the Committee at the same were Seymour Kety, Neal Miller, Ed Sachar and Barbara Fish. I am not sure of the sequence here, but because Klerman was the director of NIMH, he got to call a lot of shots and influence a lot of things. The way they talk about it is that we need to have the right stocks in our portfolio. Stock being a research program that will

make science better, but also will make Congress happier and the medical establishment happier that there are such enterprises going on. So they could decide, for example, to have a project on the use of dialysis for the treatment of schizophrenia but they wouldn't do it unless there were a lot of smart people behind the idea. The depression project has had a very long life, it still involves Wash U and is still producing results. It was divided up into a basic and a clinical part. The basic part had to do with basic pharmacology and the clinical part involved people like Myrna Weissman who became Klerman's spouse.

**Were you at the Williamsburg Virginia Conference in 69 which seems to have been the key forum because out of that came an awful lot of the agenda ultimately led to DSM III.**

That was before my connections to any of those people. I was involved in DSM III as a consultant on the schizophrenia section and that could be attributed to my having been at The Maudsley and having been connected to Slater and European psychiatry generally. Because they were not keen to have very many psychologists on those Committees. It was completely dominated by establishment psychiatry. I was on the task-force for Schizophrenia.

**I guess Schizophrenia wasn't really the controversial area in DSM III. Depression was really where the livelihoods were going to be won and lost. But can I switch and ask you about the hostility to genetic research. There is a very trenchantly argued book which came out 10/12 years ago called Not in Your Genes by Steven Rose, Leon Kamin and Richard Lewontin in which they use the ad hominen argument extensively picking out whatever faults there were in the early research that was done by Eliot Slater and Franz Kallmann to tar the whole enterprise. The word determinism tends to recur. Then more recently there have been the conferences on the Genetics of Aggression and Violence which have been picketed, pilloried and otherwise abused. How do you see it?**

Well it's a continuation of general hostility toward anything that can be seen as doing away with free will. Anything that is seen as a personal threat to your own self expression. If you think, or come to believe, that the drive for self expression can be compromised by some kind of wiring diagram in your brain, in your neurotransmitter system, then that is perceived by some individuals, a small group, as threatening and something that should not be encouraged. It is very clear if you read the preface to the book, Not in Your Genes, that it is a political and ideological argument that is about to be vented. The authors all admit to their ideological Marxistic associations in the preface. Most people don't read the preface of books. They jump right in and think these are scientists, speaking as scientists. They are scientists but they are speaking as ideologues in that particular book and in many of their other writings, all of which I find generally offensive to those of us who have no such evil intent but who are interested in the welfare of our species.

I know Lewontin and Kamin personally through various encounters, sometimes pleasant, sometimes unpleasant. I am lucky in that I am seldom the focus of their hostility and criticism. I think it's because I'm careful in my work not to go beyond my data but also because they know me personally so they can't imagine me as being an evil person, affiliated with the Nazis or the racists and so forth. This constant use of the theme of determinism is political. As I was saying in my talk here at the Royal College, all of us are probabilists none of us are determinists. We go way out of our way to find and to use any evidence that suggests that experience and environment in the physical sense is contributing to the variation in the individual's liability to developing any of these major mental disorders or even personality disorders such as anti-social personality. When you get in the same room with them, which I have done, they back off when you show them data. Although when they have the freedom to preach from their pulpit, as they do in the book which is as we all recognise an un-referreed document, they can insult anybody they want, in any way they want short of the libel laws of the country. Libel laws almost never come into play to protect scientists from their politicised critics.

They have some good points and it's worth bringing out that most of us in this business have not until lately gone out of our way to worry about bio-ethical issues or think ahead to the implications for health insurance and the prejudice that accrues to anyone who is either a mental patient or a relative of a mental patient, if someone else has data to show that those disorders have an important genetic component. In fact when we now go about our business of genotyping relatives, we acquire information which would be very valuable to an insurance company but I would think you would be culpable of some kind of negligence if you allowed an insurance company to get information about genotyping that was an accurate indication of somebody's liability for developing schizophrenia or bipolar disorder. Lewontin and Kamin and their colleagues, especially in the Cambridge Massachusetts area, have made a crusade out of this kind of genetic discrimination, as they call it. That's a good name for it and once those of us who are doing the work are aware of it, then we are very happy to join them in their cause but they don't give us the opportunity to because they are so busy attacking us on the assumption that we are evil and that we are producing evil with our data.

A lot of the hostility stems from the old nature/nurture wars with regard to the issue of intelligence. This is associated almost straightaway with racism and race prejudice which was a big thing in the United States. It's probably liable to be a big thing in the UK as individuals with various ethnic backgrounds increase their frequency in the UK population. There are always rightist forces that are interested in maintaining the status quo and they will use anything that comes their way in their own defence. Unfortunately a lot of the data produced by individuals like myself can be misused in the service of these racist purposes. Then we have the burden of going out of our way to deny them the use of our data for their own purposes and point out how they have distorted our findings. This is also a point made in passing by Lewontin, Kamin and Rose and their colleagues but they very quickly get emotional in talking and writing about these things and I find that is very dangerous. When I find myself becoming emotional I realise that I'd better stop and sort things out and try to mount a reasonable defence against the prosecution knowing that I am likely to win when we go with the data rather than with assumptions of evil on our part.

**In the US this is particularly tricky at the moment. I understand there was a major NIMH conference that was supposed to be held some years back that got put off because of concern about the reaction. It was aimed at looking at genetic inputs to social problems.**

Yes, this was directly related to proposals to study the biology and the genetics of violence. Violence being a code word for all kinds of legal offences but especially in our country murder and drug dealing which is correlated 1.0 with murder. I had been involved with this particular controversy from the beginning. It began through the curiosity of a political philosopher, David Wasserman at the University of Maryland. He was intrigued by all of the lack of resolution of issues and by the controversy surrounding the then Director of the NIMH, Fred Goodwin, a well-known psychiatric pharmacologist and author of the major treatise on manic depressive disorder with Kay Jamison, when he spoke in an off-hand manner about the utility of analogising pharmacological and animal research on primates with regards to aggression. He spoke as if this was a model for life in the inner city, inner city being a code word in our country for African Americans. He was set upon by the media and by black members of our Congress. So that anything that he touched was poison. Now he was interested in supporting this meeting, I believe, he saw it as something useful. That of course meant that it could not go forward.

In the meantime a very ideological, psychiatrically trained physician, named Peter Breggin, volunteered to go on one of the cable television channels aimed at blacks - Black Entertainment Television - to explain to the black audience that this meeting was going forward and that the motivation for the meeting included such things as the detection of future law breakers in the black school children population which would lead to them being incarcerated preventatively. It would lead to the development of pharmacology that it would be used as a chemical straight-

jacket as he likes to talk about in his various books even before this time. This brought it to the attention of Doctor Sullivan, an African-American, who was the Head of the Department of Health and Human Services which was the over-riding authority for NIH and NIMH at that time. Mr Sullivan convened a panel to look into this matter to see if it was dangerous inflammatory forbidden knowledge that was being generated. The panel was quite clearly prejudiced against letting this go forward and they came to the conclusion that it should not go forward. This meant a withdrawal of funds, which had already been appropriated by a peer review committee at the NIMH. I had already been told to buy my plane ticket for the meeting and then I received a phone call telling me to forget about it, that it had been cancelled.

It went into a deep freeze. The more Wasserman and the authorities at his University thought about it, they realised that this was a gross encroachment on academic freedom and freedom of speech, which is a very big deal in our country - it's guaranteed by the Bill of Rights. They mounted a counter-attack, which by then was being presented to a different set of administrators. Fred Goodwin in effect had been fired from his job. Mr Sullivan had gone back into the private sector and there were new people to be talked to. They agreed that if the program, as originally formulated, would be opened up so as to invite as many people there who were against the idea of genetic involvement in aggression as there were for it, they could see going ahead with it.

### **Almost in a sense to replicate the meeting that Seymour Kety had put on in Puerto Rico.**

Yes very much like that. Although here we were involving political scientists and certain people in public sectors, involved in the criminal justice system and in the welfare system - all these things are, from my point of view, outside the realm of science. In order to be safe and not allow for unauthorised people to disrupt the meeting, they decided to not have it in the University of Maryland proper but instead to have it in the Eastern part of the State of Maryland at an out of the way spot, so we could have a free and easy debate with papers being presented. I was invited to give the keynote address for the entire 2 1/2 day session which meant that I was the only one authorised to speak for 1 hour. All the rest were given 20 minutes. I did my keynote address and I was severely criticised by members of the invited audience for going too far, for using concepts like heritability, without warning everybody that this was a toxic kind of statistic and so forth - even though I knew I had gone way out of my way to get a balanced presentation. I got through my talk and felt that I had been wounded by these unsympathetic listeners but figured all was fair in war and proper science and the meeting continued.

A lot of the people at the meeting were involved with the group in Boston and with individuals connected to them who wanted to associate anything we did in this area with eugenics. Their definition of eugenics was always Nazi-eugenics. There is a good side to eugenics, believe it or not, which nowadays we call genetic counselling. And that's done without a lot of hassle. But some time during the course of this meeting, someone had organised a disruption. The meeting was disrupted by a group of shouting, men and women, some of them youngish college age, waving flags. Some of them carried the red banner of Marxism and declared themselves to be members of the Communist party. I didn't know we still had one in America, but I guess we do. Others claimed themselves to be the victims of the pharmaceutical industry and psychiatry - that they were the ones who were wearing the chemical straight-jackets and they would have no more of this infringement of their civil rights. They objected to other things in loud voices using their own battery powered microphone system. They completely dominated the meeting and brought it to a halt.

All of this was done in front of the television cameras. CNN that had been authorised to cover the entire meeting from front to end, which meant 25 hours of video coverage from 2 different camera angles. They had promised Dr Wasserman that they would produce a documentary of

the meeting and they more or less promised that they would end up with 2 hours of good video tape to be broadcast on CNN. Because of their presence they were authorised to be the video feed for the other national television systems - ABC, CBS and NBC. These people, who interrupted the meeting, knew that they might make national television that evening but none of us appreciated that that would be the only thing that would be on national television. That's the way it turned out. None of the science, either by the pro or the con school of thoughts made it, other than as very small soundbites. The majority of the coverage about 5 out of 6 minutes was about the disruption, the shouting, the ranting and the raving, with brief interviews from scientists who were in the camp of Lewontin and Kamin. They said to the press, who would speak to them, and the TV cameras about how this would lead to a revival of Nazi-eugenics, a seeking out of the people that have genetic potential for violence and aggression, and either their preventive incarceration or something related to sterilisation. They poisoned the whole atmosphere. It was a very disagreeable 2 1/2 days. Nothing was accomplished. It was not like Puerto Rico. Nobody moved from their position towards some centre position. They ended up hating each other more than before.

### **Can you put a date on this?**

October 1995. I still hear about this because people in the media hear about it who weren't around at the time and they want to re-awaken the interest. I have been asked to appear on television debating with people like Peter Breggin. I refused to do it. I don't want to inflame the situation. I don't want to give him any credibility by allowing him to appear with a scientist.

### **That brings me back to the work with Mednick. You have also done some work, not just on the genetics of schizophrenia but on the heritability of criminal behavior.**

Correct. This was one of the by-products of my Guggenheim year in Denmark. Through Mednick, I met this marvelous sociologist and lawyer, Karl Otto Christiansen, one of my heroes now. He had started the Danish twin study of criminality using all these wonderful resources. He was completely naive about anything genetic. His interest in doing the project was to show how unimportant genetic factors were compared to their alleged importance based on the old German literature from before World War II. Much of this literature was produced by people financed by the Nazi system. There was very much of a Nazi tinge or taint to some of this early work. The Nazis were very interested in minimising the effects of criminality and they had a premature biological and genetical view of this, to say the least. In the process they did some twin studies which suggested that criminality was a genetically influenced trait. But because they were naive in those days, they wanted to associate that with some simple Mendelian form of disease such as holds for Huntington's disease. There was no way for it to be that kind of disorder or condition. They also forgot the fact that the phenotype defined by the criminal justice system of the day was not anything like the phenotype that we would have among the mental disorders, where the criteria are spelled out by ICD 10 or DSM IV. The law changes from time to time. At one time it was a severe offence to be a black person sitting in the front of a bus in the United States but that went by the board with civil rights legislation.

Anyway through Mednick, I was introduced to Christiansen and quickly became his partner when he wanted to get a genetic angle into it. He was a very open person and he realised that there might be something there, even though he had always been pushing for a sociological explanation for crime. He also realised that you had to really do somersaults to criticise the twin data up to that time, plus his own initial results were the strongest evidence in the literature that genetic factors could be importantly involved in felony offending in a country where there is no racial prejudice and no ability to blame a lot of it on poverty because of the system of socialism that had evolved with its social support networks and so forth.

By being involved with Karl Otto Christiansen I was able to write some important papers one of which was a theoretical paper which I wrote with Ted Reich and Bob Cloninger in Wash U, using the techniques that Ted Reich and I had acquired from Douglas Falconer. Douglas

Falconer is a famous British geneticist, still alive in Edinburgh, whose life has been spent developing statistics that go with analysing agricultural features and then he generalised that information to congenital malformations. He did this just at the time when Shields and I were analysing our data on schizophrenia in 1965. When I read the article the month it came out in the *Annals of Human Genetics*, I said to Jerry "lets go and talk to the man, he's only in Edinburgh". That was Jerry Shields home town, born and raised. But he said "oh no, he's an important man, he doesn't want to talk to us about schizophrenia". I said "let's give it a go". So we communicated with him and he was very eager to see how we had applied his theory and model to the genetics of schizophrenia. He was very warm and welcoming. He thought that we had made some improvements in his model actually, which we did accidentally, not by design but he incorporated those suggestions in his next version. So we were in on the ground floor, using this new system for converting qualitative data, plus or minus, into quantitative information to allow us to talk about the liability to developing a disease like schizophrenia or bipolar disorder in a quantitative manner. That further encouraged me to think quantitatively about this rather than in terms of single major genes. Because of this, I became with Shields a leader in the movement to think about these major mental disorders as the result of gene systems rather than the previous tradition of monogenic theories which had also been used by Eliot Slater to account for the origin of schizophrenia.

So Christiansen knew about my work on schizophrenia. He had already quoted it. He didn't expect to meet me and I never expected to meet him. I had heard about his work but I was not interested in criminality at the time, although I have always been interested in anti-social personality and aggressive behaviour on a continuum, since my work on normal adolescent twins way back in the 1950s. So it came full circle. Here I was involved again in anti-social behaviour and enjoying it and realising this is a very dangerous explosive thing to get involved with. Everybody thinks they know about it and you have such polarised opinions about the role of society and discrimination and poverty, homelessness and so forth but nobody had really tried to sort out what was cause and what was effect. Here we were in a position to be able to do it in a solid manner with a twin study, at the same time that Mednick and Barry Hutchings, an expatriate Welsh psychologist, were carrying out an adoption study of crime in Denmark.

We used the same field workers to look through the national criminal register and to identify all of these individuals through the Danish national address register. I learned at the time, because I had better connections to the genetic side of things than Christiansen who didn't have any connections, that he had missed out on a lot of subjects who were in the Danish twin register. He was not aware they existed until I brought in this information from colleagues in the genetic world - Harvald and Hauge. The work went forward but unfortunately Christiansen died while he was a visiting Professor at the University of Minnesota, working with me to finalise the data. It is one of the tragedies of my research career that this study has not yet been finished. I am hoping some day to return to it but it became politicised within Denmark. Some of the other people involved were not so open-minded as Christiansen and after his death they used that as an excuse to close down the project. We still managed to report the final results in chapters that I had written with Cloninger in a book edited by Mednick and in the context of chapters that I have written with Peter McGuffin for Michael Rutter's *Handbook* and with other American colleagues for other books. The data show that there is a clear genetic contribution to the liability to committing a felony offence, but especially to recidivist felony offences. This is the same as the results in the Danish adoption study of criminality, which uses a different strategy but one that complements the twin strategy

**Is it over-simplistic then to say that there will be genes for anti-social personality disorder and they will be possibly discoverable soon?**

I don't think it's a gross over-simplification. Its the way you would put it if you were applying for funds to the MRC or the NIH and you'd be found credible based on these data and studies that are already in the literature. The secret to it, as I see it, is to reduce the phenotype to endo-

phenotypic components which are more manageable and which are less subject to the unreliability of psychiatric diagnosis. You can do this by taking the symptoms that feed into a diagnosis, whether it be ICD or DSM and let the symptoms be the variable of interest rather than the phenotype at the higher level. With these traits then you are in a better position, not only to analogise to research we have conducted with mice and dogs, but also to get a piece of the total genetic picture with individual genes. My hope is that it will come about perhaps more rapidly with anti-social personality than with schizophrenia or bipolar disorder because the genes involved in neurotransmitters such as serotonin and dopamine are already identified and some of these have functional polymorphisms with an already known effect on parameters of CNS functioning and metabolism.

**Where does Lee Robins anti-social personality disorder construct come into this? There is an interesting story behind that, I understand she discovered all these records in a locked room or something.**

Lee Robins has her PhD in sociology and ASP the topic of her dissertation, which was later published as a book - Deviant Children Grown Up. She made use of the cases brought to child guidance clinics in St Louis and then followed up many years later. She was not interested in genetics or biology. She was a traditional sociologist. But because of her work and her expertise on what we now would call conduct disorders and ADHD, or sociopathy, as it was called at the time she was doing her work, and partly because she was the spouse of Eli Robins, she became involved in the DSM III Committees. She used her dissertation results as the source for the symptoms that would become the criteria. As a result she has a huge influence on the American way of making a diagnosis of ASP, in that even now a gateway to receive a diagnosis requires that you meet the criteria for conduct disorder before the age of 15. Now it's clear that when you are making a diagnosis of conduct disorder in somebody who is aged 25 or 30, you are depending on retrospective information, subject to all kinds of distortion. Nobody ever asks the question for any of the structured interviews whether they are telling the truth to the interviewer. In fact it is only the MMPI that detects an untruth using some covert devices. So her role is significant but it may be a role which has to be modified in DSM V and ICD 11 in order to take account of some things that are of current interest, involving say psychophysiology or some non-criminally related components such as cold-bloodedness. I bypass the problem in my own work by focusing on the symptoms themselves instead of on the formal diagnosis.

**There is further a St Louis input there. Bob Cloninger's work heads more toward the symptom area and dimensional spectrums of symptomatology. How do you see that?**

I was present during the entire pregnancy, delivery and childhood of Cloninger's ideas and was able to influence him to pay attention to the psychological roots of his evolving ideas. What Cloninger has done is to improve upon and embellish the ideas of Hans Eysenck and Raymond Cattell with some input from the MMPI via this other instrument that is competitive now with the Cloninger test called the Multi-dimensional Personality Questionnaire (Tellegen). Cloninger is the only psychiatrist who has paid attention to the whole realm of personality disorders. He rightfully saw it as the vacuum within the field and he has been able to capture a lot of the best that was already in personality psychology and bring it in to psychopathology, via his model. In the latest version of it he maintains that there are 7 factors to be derived via factor analysis, whereas Eysenck only worked with 3.

**One feels that perhaps this is the way it has to go but with the profusion of axes one gets a slight Ptolemaic feel - extra universes are being added in to cope with the discrepancies.**

I am sure that the next step will be for someone to come along and administer all these inventories to the same sample, conduct a great big factor analysis and see what they have and then do a secondary factor analysis to see what they really ought to have. But it may be that this is just keeping us busy while waiting for the pharmacologists and the molecular

geneticists to tell us what we really ought to be including - which are the functional polymorphisms. In other words Cloninger is using the top-down approach which is completely legitimate but with the techniques that we now have available we can work from the bottom-up and do it more efficiently. We are bound to meet in the middle. We already are via the findings on DRD4 and some of these measures of novelty seeking and sensation seeking. Those initial findings may turn out to be flukes that cannot be cross-validated but something will come with these approaches.

### **It feels as though we are on the cusp of change?**

I think we are. As we get so many scientists who need to publish or perish and so many gene markers and such easy access to automation of these tedious procedures, we are going to have rapid advances in the next few years. The prediction is that the human genome project will give us all the genes in humans by the year 2005, it actually may be earlier, 2004, if we have more automation coming on-line. All this is being driven by the pharmaceutical industry because of the huge profit that lies there awaiting to be captured by the people who get to these functional polymorphisms first because then that will lead to reverse genetics which should lead to improved pharmacological treatment of these disorders.

### **Will it ? In the case of disorders like peptic ulcers and tuberculosis, there's a genetic component to the heritability but this is a susceptibility component..**

Correct. From the neighbourhood of 5% compared to the rest, a small heritable component compared to the real cause.

**Sure but even so, susceptibility is one way into the trap which is a disease. The way out of the trap, however, may not be back the same path through which you have come in. It could be but I can conceive of certain forms of rapid cycling manic depressive disorder where there might be a thyroid axis component and perhaps the best way out of that is to put right what has gone wrong in the endocrine axis. And often in terms of disease the ultimate way out is surgical which isn't the way anyone got into the problem but it can work pretty well. So while from an aetiological and theoretical point of view, there is a very compelling argument that the genetic route is the way forward, if one looks at medicine and how it works, it tends to be much more pragmatic. We don't really care at the end of the day about aetiology, we go with what works. There's clinical validity but also clinical utility .**

But this is an advance on the simple form of empiricism because it's driven by the specificity of the genes involved in the gene to phenotype pathway. There's a big difference, as I see it, between the use of aspirin for reducing fever versus the use of an antibiotic for getting rid of the bacterial infection of a certain source. It is that difference.

### **But the antibiotic again will work across bacterial infections**

Correct, but for some there is less of a wide spectrum and more of a narrow spectrum approach and it is the narrow spectrum that I am hoping will come out of this wedding of molecular genetics with clinical psychiatry. There are no guarantees but it seems reasonable that it will be a short cut to looking for something else like aspirin would be for schizophrenia.

### **What access do companies have to genetic material to use in drug development programs?**

There is another aspect of my work, which is not directly related to genetics, it is just my general interest in various forms of psychopathology. As a result of my having been on an Oversight Committee for the Institute of Medicine, which is part of the National Academy of Sciences, which is commissioned by our Congress to be a consultant to the Congress, I was involved in the committee that looked into the effects of the Vietnam War on the Vietnam Vet. Part of this was a concern about the alleged effect of Agent Orange which was an ingredient in

the chemical defoliants sprayed in Vietnam to improve the visibility of the ground for combat reasons.

Before I got involved with that committee, I had been consulted by the Veterans Administration to help them solve the problem of how do you decide whether or not these numerous claims from veterans were legitimate compensable disorders or diseases. I suggested to them that they use the classical twin method with some modifications. Because of the number of men involved in the war, we would have access to twins where one had been exposed to combat and defoliant agents and the other one would have been say stationed in West Germany. They thought that it was a marvellous idea. They had never heard about twins being used like this. They went ahead and formulated a twin register for the Vietnam War. Meantime, parallel to this there was a study of a larger sample of men who are not twins to see whether or not there is anything different about them neuropsychiatrically or in other somatic domains. We looked at such things as sperm count, for example. Dermatologists looked for chloracne, which was the only pay-off in this area and then we had oncologists looking for unusual incidences of cancers earlier than they should have appeared in this population.

None of these things worked out. But because of all the data collected, using psychological testing, including at my suggestion the MMPI, we had a huge battery of neuropsychological and psychological tests on thousands of men and even on some women, who were nurses there exposed to extremely stressful conditions. I am now in the process of analysing these data with my graduate students in clinical or other branches of psychology to make a secondary usage because the data were very under-analysed once they reached the political decision to pay out all claims and not worry about whether Agent Orange did something to the individual. Now we are seeing a repeat of all this in the Gulf War syndrome with similar questions being raised and I have already made the suggestion that we now find all twins who served in the Gulf War and the control twins who were in at the same time, to control for age and so forth, who were stationed some place else. Without sounding like a broken record I see all kinds of continued use being made of this method.

Now in NIMH it was decided during the era of Lew Judd who succeeded Fred Goodwin, who was also both biologically and non-biologically oriented - a man for all seasons - to invest heavily in collaborative research that would give us a head start over any other country in finding the genes for schizophrenia, bipolar disorder and Alzheimer's disease. At the same time another institute was interested in doing this for alcoholism. So there were 4 major initiatives, as they called them, launched. For the schizophrenia dataset, now that the original investigators have had a go at them, it is realised by the current management of NIH, Dr Varmus, that these data are too precious to just be kept under cover and to be used in the relatively amateurish fashion that we do in academia. So he has decided, and it has been agreed, that these data will be made available to any qualified scientist or scientific organisation and that included very specifically the pharmaceutical industry, not only that of the United States but in Europe as well. As soon as this was decided, they needed to have people who would vet the applications, Richard Wyatt and myself were designated as the people to review the applications for schizophrenia and the very first applications that came in were from the pharmaceutical industries.

### **So they really think that this is the way forward.**

They really think it's the way forward and they are getting all these millions of dollars worth of information at no cost to them other than a trivial amount.

### **How did you say it was collected in the first place?**

It was collected by a co-operative agreement among 9 Universities, including Washington University, of course, and NIMH itself with a group led by Elliott Gershon. These 10 sites collected the families, mainly affected sib-pairs. They collected the blood for DNA and they

divided it into cell lines and stored it at a facility, the Coriell Institute in Camden, New Jersey. They then, under contract from our Government, make available the DNA for \$50 a shot per individual. With that comes all the diagnostic information collected and structured interviews and so forth.

**There's another variation of the genetic input to pharmacology, pharmacogenetics or the genetics of individual responses to particular drugs. Is that another way forward. In addition to trying to find the best drug for the condition, we can find the best drug for you with this condition, as opposed to me. What might suit you, might not suit me.** Correct. This is a very important strategy and it's an area that is slowly gaining attention and qualified people but it was explored many years ago by Kalow, who has a book out.

**It was also looked at by Linford Rees and Michael Pare who showed that there were a group of people who were depressed who would respond to any antidepressants but there were some people who were depressed who only responded to MAOI's and some people who only responded to tricyclics and that liability tended to run in families.** There are a lot of those ideas and they came from the British system. I remember that one of our twin pairs was a subject of a case study where one twin was treated systematically with chlorpromazine and the other identical twin, who was also a schizophrenic, was treated systematically with reserpine. They found that chlorpromazine worked and reserpine didn't and they crossed over the other twin and she, indeed, responded. So, this tells you that this is a very important strategy for finding a family's medication. But that leads immediately to questions about possible racism because one of the things that you are bound to find here, as has already been found with some agents, is that they are very bad for some races and very good for others. This then brings to awareness that races are indeed genetically different, although many people would argue there is no such thing as race. In a certain sense they are correct. Race is something that's defined socially and race doesn't mean anything nowadays when there are so many mixtures of individuals. But still you find that some drugs are lethal for some individuals with certain racial backgrounds and for others they appear to be therapeutic.

**How long do you think it is going to be before we begin to get into the area of having blood tests to predict which antidepressant you should take for instance?**

I think it's almost immediate. Because of the risk of liability involved.

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