



Nature and nurture: Mental health and illness

Professor Robert Plomin

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Introduction by Professor Dr Raj Persaud

Welcome, ladies and gentlemen. I am Raj Persaud and I am the Gresham Visiting Professor for the Public Understanding of Psychiatry, and I am really delighted that so many of you have come this evening to listen to what I think is going to be a very interesting talk. Many of you will know that whenever I introduce a speaker, I mention the fact that I work at the Bethlem Royal Hospital, and Professor Robert Plomin, who will be talking this evening, is a Professor at the Institute of Psychiatry, which is the research arm of the teaching hospitals which are at the Bethlem Royal and the Maudsley Hospitals. I often comment on the fact that in London we are privileged to be in a city with such ancient institutions, because the Bethlem was founded way back in the 12th Century, and of course Gresham College was founded in the 17th Century. My ward is called Gresham one Ward and I suspect that Thomas Gresham may have had something to do with the naming of the ward way back in the distant past.

The talk tonight by Professor Plomin is on a very important subject. It is often a very controversial area, the link between genetics and our behaviour, and genetics and mental health. Often politics seems to come into this area, and we often find it very difficult to think about the notion that we are choosing our behaviour in terms of free will. The idea that genes might determine or influence our behaviours is often a very uncomfortable idea. But putting the politics to one side, the advances in genetics and mental health are very important, because at a molecular basis they are about the underpinnings on our behaviour. So we are at a very exciting moment in terms of our understanding of the links between genes and behaviour.

So it gives me great pleasure to introduce to you tonight Professor Robert Plomin. The professors from the Institute of Psychiatry that we select for these lectures at Gresham are very carefully chosen to ensure that they are people who give very interesting and entertaining talks, and Robert Plomin is one of the most entertaining speakers at the Institute of Psychiatry, as I am sure you are about to discover. Ladies and gentlemen, Professor Robert Plomin...

Professor Robert Plomin

Thank you very much Raj. I would like to give you a general overview of nature and nurture, genetics and environment, and mental health and illness. I am going to try and finish in 35 or 40 minutes or so because I think it is a topic that people have lots of questions about and I would really like it if we could have plenty of time for a discussion.

The word 'nature', I am sure everybody knows, refers to genetics. Usually when you think of the word 'nature' you think of very nice things, like scenes in nature, and if you think of 'nurture' that is also a very pleasant word, with ideas of parents caring for their child. But if you put the two words together, a

psychologist or psychiatrist will think of 'controversy'. It is the oldest controversy in the behavioural sciences; the extent to which genetics and environment is important in behaviour.

I think that if we asked, 'Why are people different in height in this room?' most people would accept that height is highly heritable. However, you will be surprised to know that not all people believe that. Indeed, as we will hear later, what you think is heritable or not is not a very good judge of what is heritable or not. As it happens though, height is very highly heritable. About 90% of the differences of the people in this room are due to genetic differences; there are some non-genetic differences, but the vast majority of differences in height are heritable - i.e. due to genetic DNA differences among us.

But what about weight? I have done this sort of survey before, so I know most people say, 'Well, maybe it is got some genetic influence, but it is mostly environmental.' Why? You would say, 'Because, if you stop eating, you lose weight.' But it turns out that the individual differences in weight are almost as heritable as height; they are very substantially genetically influenced. It makes the point that to say something is genetically influenced does not mean you cannot do anything about it. You can lose weight, as we all know. However, I am sure everybody has been dieting at one time or another, and you know you can lose weight if you stop eating, but you also know most diets do not work very well and you end up back on a trajectory. It is an important point because if anyone thinks mental illness is something people choose we can ask the question of whether you choose to be overweight? We do often blame people for being overweight - it is a current topic right now - but if you recognise how much genetic influence there is in it, you recognise it is easy for some people to eat a lot and not to be very heavy, and congruently, some people do not have to eat very much and they can be very heavy - they just have a genetic propensity towards weight.

Today I am going to talk about nature and nurture in mental illness. I do not know to what extent people here think there is genetic influence on mental illness. For a long time, people had environmental hypotheses. If you were fortunate enough to go to the Tate in the last month or so and saw the Hogarth exhibit you would have seen the Rake's Progress which gives an environmental theory of mental illness. The protagonist in the series leads a dissolute life, and as a result of his sins ends up in Raj Persaud's ward at the Bethlem Hospital! If you have heard Raj talk before, you will know that that really was Bethlem Hospital, the founder of the current Maudsley Hospital. The word 'bedlam' comes from Bethlem. In 1948, the Bethlem merged with the Maudsley, and the IOP is now the research arm of the Bethlem.

The Institute of Psychiatry is the biggest research institution in psychiatry, just about in the world. It is certainly the largest in Europe. There are 300 PhD students, and there are ten departments. I am the director of one of these - the Social, Genetic and Developmental Psychiatry Research Centre. Our goal follows on from the first work in psychiatric genetics that was done in the world by Eliot Slater, at the Institute of Psychiatry.

He came to the Institute in 1938 and then in the '50s, he began doing research on genetics, using twin methods and adoption methods that I will tell you about in a little while. He published the first twin research on genetics at a time when people assumed it was environmental, but his work showed that there was a substantial genetic component to mental illness. He also published the first psychiatric genetics textbook.

The goal of the SGDP Centre is to bring together social, that is environmental factors, and genetic factors to study the development of mental health and illness. The idea is that the nature/nurture wars are over and thus we do not need to argue so much about whether, say, nature is important. I hope you will see from this talk that both are important. In studying these complex disorders, we need all the help we can get. So instead of arguing about whether it is nature or nurture, the answer that I hope you will have at the end of this talk is that it is both. Therefore, if we are going to understand psychiatric illnesses we need to study both, and how they interact and correlate in development.

How do we know that nature is important, or nurture? The first thing is: does it run in families? For a long time, people have known that mental illness runs in families, but that does not mean it is due to genetics. It could be either nature or nurture. For decades now, people assumed it runs in families for reasons of nurture; because you share the family environment with your parents. So family studies do not prove whether it is nature or nurture, but the other two methods of behavioural genetics give us more purchase on that question. One is the twin method, comparing identical twins and non-identical twins; and the other is the adoption method. Let me tell you about both of those in relation to schizophrenia first.

The twin method involves comparing the two types of twins that we have. One percent of all births are twins, and a third of them are identical twins, called mono-zygotic, because they are one zygote - so they are a single fertilised egg that then splits in the first few days of life, and if they split later than 7 or 10 days they will be Siamese Twins, where they do not actually end up splitting completely. Identical twins are more clones than clones, because if you were cloned, your clone would be reared in a different mother, in a different generation, whereas identical twins are genetically identical - that is, all their DNA sequences, 3 billion nucleotide bases of DNA, are exactly the same. So they really are clones, and when people ask if cloning be problem, we can say that it would not be, because we have got clones already, in identical twins.

One third of all twins are identical twins, and the other type of twins are called non-identical, or fraternal twins, and they are di-zygotic. They are just two separately fertilised eggs that happen to be fertilised and grow at the same time, and grow up in the same womb. So like any brother and sister, they have 50% similar genetically.

The twin method then consists of comparing identical twins, who are genetically identical, to non-identical twins. If you take a trait like schizophrenia, if there is genetic influence on schizophrenia, you would have to predict that identical twins are more similar than non-identical twins because they are twice as similar genetically.

In the results of about 10 studies now, identical twins are almost 50% concordant for schizophrenia. The base rate in the population is 1%, so one out of 100 people will be diagnosed as schizophrenic at some time in their life. Schizophrenia's onset is usually in the early adult years. So perhaps the danger is less serious for most of us here, but for the population as a whole it is still 1%. But identical twins have a 50-fold greater risk if their twin is schizophrenic. Whereas, if it was a fraternal twin, your risk would be something more like 15%. For first degree relatives, on the whole, it is more like 10%. That is a bit of a complicated story, but second degree relatives are about half of that, 4%. So your risk, genetic risk, goes up directly in relation to your genetic similarity to the person who is schizophrenic. So identical twins are much more concordant - your chances are, say 1%, but if you had an identical twin who was schizophrenic, your chances are 50%. In medical risk terms, this is astronomical risk. If you smoke two packs of cigarettes a day, your chances of dying from lung cancer I think is something like 10%, which gives you a sense of what a risk that is.

That is the first message. Twenty years ago, the message was schizophrenics are 50% concordant for schizophrenia. Now the message is they are only 50% concordant for schizophrenia. The distinction is this: that 20, 30 years ago, people didn't think schizophrenia was at all due to genetic factors. We know it runs in families but people assumed it

was due to nurture, not nature. Most people believed that schizophrenia was caused by the way your mother treated you in the first few years of life. There is no evidence that that is true. The reason I think parents of schizophrenics are strong supporters of genetic research is that they have been made to feel as if it was their fault for a long time. So your child becomes schizophrenic, not at two but at twenty and then you are told it is what you did at two - you cannot go back to when your child is two so it is too late. So there was a tremendous culture going on for parents, and so the National Alliance for Mentally Ill, for

example, support genetic research. Some people say that this is bad because it lets parents off the hook, but my point is they should never have been on the hook in the first place. Genetics could never do as much harm, in my view, as environmentalism has done, because if you are told that you caused this disorder in your child when they were young, because you were too cold or rejecting of your child, for example, I mean that is hugely devastating to parents. So it is important to note that genetics is an important influence in your risk for schizophrenia, but if schizophrenia were entirely a genetic disease, what would you expect the risk for identical twins to be?

That is right - 100%, because they are genetically identical. So now that I think the battle has been won, and at least in psychiatry, everyone accepts the strong genetic component, I have almost found that it is almost the other way now: people treat schizophrenia like a genetic disease. Again, it is because people want to say 'Is it nature or is it nurture? We thought it was nurture, and now you say there's some nature, so now it is nature.' There is genetic influence, but 50% of the time, these clones of one another are discordant, life-long, for schizophrenia, and because they are clones, they are genetically identical for every base pair of DNA. There can be no genetic explanation of that. It has to be non-genetic. This is not just to say, 'oh, let us all be friends and it is nature and nurture'; it is just really what the data says. There's a strong genetic component, and if you do not recognise that then it can cause problems, like if parents do not think genetics is important when they are rearing their kids; but if you, as is true in a lot of psychiatry now, think of it as a genetic disease, you are also really off-base.

There are some classic examples. The Genain quadruplets are identical quadruplets, where their mother was very severely schizophrenic, and they all became schizophrenic.

The other method is the adoption method. This is an experiment of nature, where you have these two types of twins. Adoption studies are a social experiment where some children are adopted away from the biological parents at birth, and so you have parents who share genes but not environment with their children. In the literature we call them non-adoptive parents. Parents normally share genes plus environment with their children, and that is why family studies cannot separate genes and environment, but adoption does separate that - the nature and nurture - because if a parent adopts away a child at birth, then that child is still genetically as much related to the parent, but is not environmentally related. Thus there is also the family in which the adopted child lives, and those parents are environmental parents of the child. So the adoption method separates the genetics and environment by studying adopted away relatives of biological parents and then the adoptive parents of those relatives.

Len Heston, in the '60s, conducted the first adoption study of schizophrenia. He did this for his dissertation work at Midwestern University in America, and he could not get funded to do this study. He wanted to do an adoption study, because twin studies at that time were suggesting genetic influences were important, but he asked whether there was something funny going on with twins. What is good about the adoption method is that it is so totally different. So he was keen to do an adoption study, but he could not get it funded - despite trying three times - because everybody thought they knew schizophrenia was due to environmental mechanisms. It just seemed preposterous to propose that genetics was important. So the way he funded his dissertation research was to drive rental cars back to their source, so everyone from the East drives them to the West Coast etc., and he would drive these cars back. On the way he would visit families around the United States who had adopted a child from an institution in the state of Washington, in the North-West, from these very severely affected schizophrenic mothers. People become schizophrenic as late as thirty or even later, and so they could have had children by then, so it is studying the adopted away children of these biological mothers. What he found is that the risk of the adopted-away children of schizophrenic biological mothers becoming schizophrenic is just as great as the risk for children reared by their schizophrenic parent. At the same time, as a control group, he studied non-schizophrenic parents and their adopted children, just to make sure there wasn't anything going on with adoption, and he found a risk of zero percent. So this is very strong evidence that the reason schizophrenia runs in families is largely genetic.

The same sort of story comes up with mood disorders. The two major categories of mood disorders are depression, major depression, like uni-polar depression, and another type of depression that alternates from depression to mania. I will not go into the details of these but I just want to emphasise that this is not just getting the blues; we are talking about depression that requires hospitalisation.

Family studies of first degree relatives reveal a story like that of before. The population base depends on how you diagnose it, but say you diagnose it in a way that gives you 3% of the population having major depression, there's a three-fold risk if you have a first degree relative who meets that criterion for depression. Similarly, with bi-polar, it is even greater: the risk in the population is lower, and so there's something like an eight-fold risk if you had a first degree relative who is bi-polar.

The twin studies confirm that most of that influence is due to genetics - that is, what runs in families is genetic. For major depression, identical twin concordance is about 40%, as compared to 50% for schizophrenia, and then again, the non-identical twins are much less at risk if one of them is schizophrenic, so the risk there is more like 10%. This 40% versus 10% suggests substantial genetic influence. The fact that the identical twins are not 100% but rather only 40% suggests environmental influence. For bi-polar, identical twin concordances are very high - something greater than 70% - and again, the non-identical twins have much less risk, about half that risk, suggesting strong genetic influence on bi-polar. Most people feel that bi-polar is more highly heritable than uni-polar, major depression, where you do not also have the mania.

If you look at other mental illnesses, you will see that identical twins are more similar than non-identical twins. This includes Alzheimer's disease. At the Institute of Psychiatry, the first studies were done by Professor Sir Michael Rutter at the Institute on autism. He was actually coming from a socialisation perspective, and just even 25 years ago, autism was thought to be an environmental disorder. So he was going to use a twin study to prove that what everyone assumed to be true was true, that identical twins would be no more similar than non-identical twins for autism. So he studied most of the twins, autistic twins in England and found that, to the contrary, there is the biggest difference between identical and non-identical twins, that identical twins are 60-some percent concordant for autism.

There have been four subsequent studies in different countries, all yielding the same data for autism. So on the basis of twin studies in about thirty years autism has gone from being considered as an entirely environmental disorder to one that shows perhaps the most genetic influence. There are now a dozen international collaborations trying to find the genes that are responsible for this heritable influence in autism.

If you look at the other disorders, they make an interesting point. It is sometimes surprising for some people which disorders are more genetic. Often people are shocked that Alzheimer's is more heritable than alcoholism. It is not clear just by thinking about it, but research shows that the developmental disorders, like hyper-activity and learning disabilities, are also very highly heritable, with some of the highest identical twin concordances around.

If I had asked you how highly heritable breast cancer was, you would have said, 'Really highly heritable.' However, it is the least heritable thing around. In studies of thousands of pairs of twins only about 15% of them are concordant and 85% of the time discordant for breast cancer. Fraternal twins are about 10%, which is like the base rate of the population. So there is hardly any genetic influence on why one woman gets breast cancer and the other does not. We here see that it is really important that you assess rather than assume what's important in genetics. The reason you think it is highly heritable is because you hear about these genes for breast cancer, but they are actually very rare genes and are not a major cause of breast cancer. They are still important, and very dramatic for people who have them, because they usually involve early onset, they are very severe and are ovarian as well as breast cancer. But most of the reason why one woman gets breast cancer and the other does not, is non-genetic. That there is 15%

concordance for identical twins, with the base rate in the population at 10% proves this. So if you have a clone who has breast cancer, your risk is really not much greater of having breast cancer. It is really important that we do these sorts of studies rather than assuming what is heritable.

I also know, if I asked you about epilepsy or especially ulcers, you would say, 'Well, they are something that is environmental', right? But actually, these are some of the more heritable characteristics. Even though stress is related to whether or not people get ulcers, just like a lot of disorders, even infectious diseases, the genetics comes in in your susceptibility, your vulnerability to these things, even though there are environmental agents that are the proximal cause of them.

That is the nature/nurture first part of my talk, and I will not bang on about it too much now, because I think most people do accept a kind of balanced view - that for mental illness, as well as a lot of other behavioural traits, both genetics and environment is important.

To prove that, because no one has ever done a survey of it, a couple of years ago we did a very large survey of over 1,000 parents and 1,000 teachers of kids in elementary school, and asked them how heritable they think each of these things are on a one to 5 scale. The findings were that for both parents and teachers, over 90% felt that genes are at least as important as environment. They weren't saying it is all genetic; they were saying it is about 50/50, which is actually pretty close to the data. I wish we had done this survey in academia, because I believe the man on the street has a more balanced perspective on these things than some academics. I am actually doing something to see if I can get that done, because it interests me. So the reason I do not worry about trying to come on too strong about genetic influence is because I think most people accept it.

However, I must say there are some people who are finally thinking about having their child after putting this off for so long and a lot of them behave as if genetics is not important. They act as if all it takes is tender, loving care. But because they are so worried about this fragile baby that is going to break and go wrong for the rest of its life, I do not think they enjoy having their children - they worry a tremendous amount. I am not saying we shouldn't worry about anything, but if you think your child is a blob of clay that you mould to be what you want it to be, and then if that moulding goes wrong, it is your fault, if the moulding goes right, it is your credit - it is a big mistake, because genetics is really very important. A neat quote is that 'Parents are environmentalists until they have more than one child.' I think that is true of psychiatrists too. With your first child, you can explain anything away environmentally. Like personality traits, one of the most highly heritable personality traits is shyness, which might surprise people. You would probably think activity level, aggression, or something like that, but it is shyness. You ask parents why their child is shy, and they will give you one of two answers: 'My child is shy because I took her out too much when she was young,' or 'My child is shy because I didn't take her out very much when she was young.' Environmental explanations can always explain things after the fact.

Then they have a second child. The first law of genetics is like begets like, and the second law is like does not beget like. Believe it or, that is what sex is all about: it is mixing up genes so that first degree relatives are 50% similar genetically. You are 50% similar, but you are 50% different. So if your first child is very shy, the chances are, by genetics, your second child is not going to be as shy. And then people say 'I did not do that' and they begin to recognise that children are different from early in life. It is not to say you cannot do anything about it; it is just that it is important for parenthood, education and a lot of things, that we do take genetics seriously. I am not saying it is all genetics, but you are never going to study the interaction and the interplay between genes and environment, unless you believe both are important.

So we see that most research now is not just asking 'Is genetics important?' because everywhere we have looked, we find genetic influence. In fact, I do not think there's any area of mental illness that has not been reliably shown not to have genetic influence. It is almost like the shoe is on the other foot now, that genetics is important across the board, but it is nature and nurture. So the research is going beyond this

kind of rudimentary question about nature and nurture to ask questions about development - how early do genetic effects appear?, do they change during development? These are multi-varied issues of which I am going to give you an example now, and then the interface between nature and nurture, which is what our Centre is about, and a lot of people are interested in that. If both nature and nurture is important, how do they work together? Do they interact or do they correlate? It is a topic I would love to come back and talk about sometime, but in the interests of time, I am just going to talk about this one example of multi-varied issues.

Here in England twelve years ago I carried out the Twins' Early Development Study, which was a study of the twins born in England and Wales in '94, '95, and '96. There are about 7,500 pairs born a year and we had about 18,000 pairs agree to participate in this study. It focused on areas of development that haven't been looked at developmentally very much, like learning disabilities, and language or behaviour problems in childhood. We have studied throughout the years and now the oldest ones are thirteen.

We get the twins from ONS at birth and the parents are asked to participate after we make sure that there has not been infant mortality - twins are more likely to die in the first few months of life. Then we study the twins at two, three, four, seven, nine, ten, and now twelve years of age. Just to give you an example of this multi-varied type of analysis, I want to talk about autism spectrum disorders. The idea of multi-variant is that we are going to look at the relationship between things. So instead of studying this one disorder and asking whether there is genetic influence, and then studying another one, we are going to study several disorders at a time and ask about the causes of their overlap and co-morbidity.

The example I will use is Autism Spectrum Disorders (ASD). There are three components, but I am going to just focus on two here: the social component, and the non-social component. If you saw Dustin Hoffman in Rainman, or if you have heard Raj Pershad talk, you know that there is a social component, like not looking at someone or an odd style of communication; and then there is a non-social component, which has to do with rigidity, such as memorising bus schedules and getting very upset if one's routine changes at all. These two components have only been studied together in genetics as part of the traditional diagnosis of ASD. The reason we got onto this is some of our TEDS, this twin study's mothers came to us. They had children they thought were classically autistic, but they could not get into social services because they didn't meet the diagnostic criteria. They seemed so completely classically autistic, but with one exception or the other. The typical one is, if the child would look at the clinician, that would almost exclude a diagnosis, because autistic children just will not look at you. Then we asked ourselves where the evidence that these two components of ASD are related was? So we used multi-varied genetic analysis for the first time to see, to what extent genetic effects on the social aspect are the same genetics effect on the non-social. You would expect, if it is one disorder, there is a lot of the same genes involved. To the contrary, we have found in three studies now that the social and non-social components of autism show the lowest genetic correlations you can find in psycho-pathology. There is so much co-morbidity in psycho-pathology, for all types of disorders, so people who have one are very much more at risk for having others. But multi-varied genetic analysis allows us to look at not just the risk for one trait of identical and non-identical twins, but the cross risk. So we can find out, if one identical twin has a social type of ASD, what the chances are the other twin will have the social type. In fact it is very high for identicals, very low for non-identicals.

But what about the cross resemblance, if one has a social type of disorder, what is the risk of the other having a non-social type? If there was a strong risk, if it is all the same genetic disorder, you would expect the same result. If one identical twin has the social type, the other is just as likely to have the non-social type, because they go together genetically. But, to the contrary, we used the multi-varied genetic analysis to show that the genetic correlation is very low. It is a very important finding, because it suggests that there are two different disorders here genetically. Which is why molecular genetics studies that are having a great deal of difficulty pinning down the genes for autism. It is like mixing apples and oranges, and it is going to be very difficult finding the genes if you have got two different genetic things that you are putting together. Therefore, I think that is a very important example of multi-varied genetic analysis, and it is one way in which research now is not just asking about nature and nurture but is going beyond that. Development, multi-varied, nature/nurture interface - this is what all the research is about now, and there is a huge amount of research in this area. It is very exciting because it is cumulative; you really feel like you

are learning something about these disorders.

The hottest area by far of course, and this is what Raj Persaud was referring to as molecular genetics - if there is so much genetic influence, can we find the DNA of the genes that are involved? It has been called the century of the gene. The word 'gene' was not even invented until 1903, and then it was exactly fifty years later that Crick and Watson found the structure of the double helix of DNA. We did not even know what the hereditary mechanism was until then, and just fifty years later the three billion bases of DNA have been sequenced and we know the entire human genome sequence. So the progress of the past fifty years really makes you wonder what is going to be happening fifty years from now. Genetics is an area of science that is unparalleled. It is not just that we have three billion DNA bases. About one in 1,000 base pairs are different between us, at a reasonably high level, so there are about three million major DNA differences between us. You hear about this stuff about us being 99% similar to chimps - it is a very confusing issue. Every gene in our body can be different functionally from every gene in a chimpanzee's body, because the average gene has 3,000 base pairs and we are talking about one out of 1,000 base pairs being different. So when you hear that sort of simplistic slogan, just note to be careful in interpreting it.

What we are interested in finding out is saying to what extent particular DNA differences are related to particular disorders. Even though we are 99.99% similar in all our DNA sequences - that is what one in 1,000 differences is - it is the differences that matter so much. So we are going to be looking at those differences in DNA to ask if they account for these genetic differences we see in the disorders. There are some replicated successes, especially in schizophrenia, to some extent in reading disability, hyperactivity, some inklings of findings in autism, and there is a really important finding in dementia where there is one gene that accounts for maybe 15% of the liability to late onset Alzheimer's. The Alzheimer's genes we know are these rare single gene disorders that do not account for much Alzheimer's, and again, like breast cancer, they account for a very severe form that is early onset. If you were a GP, you would hardly ever see any of those cases because they are so rare. But there is one gene that has been discovered for dementia but it is still only accounting for perhaps 15% of the liability to late on-set Alzheimer's dementia.

Progress over the past ten years has been a lot slower than people would have expected. This is because it is as if we have been looking for a needle in a haystack, but we have only had techniques that would allow us to find very large needles. There is one gene for late on-set Alzheimer's which has been found, but only because it is that big. But most people now recognise that what we are looking for is not these major gene effects. If they were there, we would have found them by now. To the contrary, genetic influence probably involves many genes of very small effect. These are called QTLs, Quantitative Trait Loci, for reasons I will mention in a minute. The main point is that we are looking for tiny needles in the haystack, and you can imagine how difficult it is going to be.

People often think about genetics in the wrong way. For instance, there is a gene for Huntington's disease, and if you get that gene, you will die from it - it is deterministic. Therefore, unless something else kills you first, it is necessary and sufficient for the disorder. Mendel's studied traits in the pea plant that are like that too - single genes completely determine that characteristic. This is the way people often think about genetics, and that is the reason they have problems with it - they think of it as purely deterministic. But now, if we accept what I said just now, people recognise that most disorders are actually dimensions. They are like quantitative traits and there are several genes involved.

If we take the example of autism, it is a combination of genes with leads to the condition. Having more of the genes leads to a higher score and higher chance of having autism. So they are associated, but they are not at all necessary or sufficient. There are some people with high scores without many of the genes; there are lots of people with low scores who have many. So this is really what we are talking about Quantitative Trait Loci, QTLs. The implications of this are huge. First of all, it means that it is going to be very hard to find these genes, because they have small effects. From a molecular genetic point of view that is important. However, to me it suggests a completely different way of thinking about disorders, and

that is that there are no disorders. All there are dimensions, that is, the genes that are associated with, say, reading disability, are the same genes that account for heritable variation throughout the dimension, so that disorders are only quantitative extremes of the same genetic and environmental factors that account for variation throughout the distribution. So there are not genes for reading disability. When we find those genes, they are going to be related to reading ability. If two siblings are good readers, they'll predict that the one with that form of gene will be a better reader than the other. It'll have just as much an effect at the high end as the low end. It really is a completely different way of thinking about disorders. Rather than worrying so much about where we draw diagnostic lines, we realise it is a myth: there are no disorders; there are only continua.

That is not to say that disorders are not important. People who have high scores, say on autism or schizophrenia that is the business end of this dimension, and we have to be concerned about that as a society. But this does not mean we have to think of it as a class, a dichotomy of you either have it or you do not. The other nice thing about this, from a societal point of view, is we all have these genes. If there are hundreds of genes involved in schizophrenia, we have all got them. It is just a question of how many you have, and that is what the genetic risk is about. Parents of children who have problems actually welcome this, because they say it stops the sense of 'We are normal - there is us and then there is them'; to say that it is all us and it is quantitative.

In schizophrenia, there are two genes that people are very excited about. Linkage studies have shown that certain sections of the chromosomes are important. You can then focus in on only them and find out which genes are at play. But after fifteen years of work it really is slow progress, and I think people are recognising that, even these genes, if they are true, have a very small effect. So we are probably not talking about two or three, but might be talking about 200 or 300 genes that account for the risk. Similarly, reading disability was the first disorder where people got positive results, and there is a gene in this area where several studies suggest there ought to be a gene, and people are quite excited about that. None of these have been nailed down yet, even though in the States there are parents going to court saying that their child has 'the reading disability gene', therefore they need \$30,000 a year to get special one-on-one tutoring for their child. You can see that is just crazy from the word go - even if it is associated, it is a very small effect. At an individual child level, it is not going to mean anything at a predictive level.

Journalists are not responsible for the headlines, the headings of stories, but whenever you carefully explain 'We are talking about many genes involved,' the storyline comes out 'The gene for...' So whenever you hear 'The gene for...' you know to jump up and down and say, no, that is not it. It is not going to be this gene that predicts reading disability. It may be we get to the point where we have 50 or 100 and we can make some prediction.

The biggest thing that has changed is the invention of micro-rays that can genotype a million DNA markers on something the size of a postage stamp. It is revolutionised the ability to do this sort of high throughput work, not just looking at one or two genes, but looking at the whole genome. It is sometimes called the gene chip because it is a silicon chip. I think eventually we are going to find these genes, but I have been saying that for a while now. It is just that they are very small effects - you can see how hard it is to find them. I think what we need to do is to step back and say we are looking for lots of these, and not to spend all of our energy chasing after one lead at a time. But eventually, with micro-rays, it is no problem, and I think eventually, we will have DNA routinely collected to. You will not need blood - you can just scrape the inside of your cheek and get enough DNA to do thousands of DNA markers.

When we get the genes, and we have micro-rays that look at the hundreds of genes that come on at different points in development and predict interactions with the environment, and also predict which treatments might work better, I think people will be collecting DNA routinely. This will help us in our diagnoses and treatment programme by having individually tailored sorts of treatments. The ultimate goal, as in all of medicine, is to move towards preventive medicine, and the great thing about DNA is that it is the only game in town, I think, for predicting genetic risk, because DNA does not change during development,

so that you can predict from very early on when children are going to be reading disabled. Just as with obesity and alcoholism, we are not very good at putting Humpty-Dumpty back together again when they fall off the wall. It is so much better in all of medicine to prevent rather than to treat after people have the problem, because so much of their life has fallen apart after they have those problems. In research the great thing about DNA is it is the most common denominator we have that ties together all of the life sciences. There is a lot of interest in finding these genes and working up to understanding how they work. We call it not just the genome now, the transcriptome, RNA, the proteome, how RNA is turned into proteins, and then into the brain. That is the bottom-up agenda, but I am very interested in, and our Centre's focused on, top-down analysis, using these DNA markers as genetic risk indicators to help us understand behavioural development and how genes and environment interact in development. I think it will get us quicker to translational research, where we can actually turn this research into something useful at the level of diagnosis, treatment and prediction. But in the end, because DNA is this common denominator, these bottom-up approaches are going to meet the top-down approaches in the brain.

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