Is it all in the genes?
Professor Peter McGuffin CBE FMedSci
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You can wonder why a philosopher got into this topic, but I actually think it is a pretty interesting area. I said that the title of my talk is straightforward. I am going to use a number of examples in the talk, but I am going to focus mainly on the area that I work in at the moment, which is the genetics of depression and an allied disorder called, nowadays, bipolar disorder (it used to be called manic depression), but I will give some other examples as well.

We hear a lot about the 'nature versus nurture' debate, and I think one can date this back to Francis Galton. Francis Galton, in some ways, is a hero of mine. He is a polymath, a very brilliant man, but he did set us up in my trade for a 'nature versus nurture' debate. He was one of the first people to point out that, using twins, you might be able to tease apart the effects of nature and nurture. He did not know much about the biology of twinning, but he did say this in one of his writings, that 'Nature prevails enormously over nurture,' like it was a competition.

Of course, this whole notion of nature and nurture actually goes further back than Galton; it goes back to Shakespeare. I always say you can tell what side of the nature/nurture debate a clinician comes from on the basis of the first thing that he or she says to their patients. The famous psychiatrist Philippe Pinel flourished in France, in Paris, around about the time of the Revolutionary period, and he was the man who was famous for having liberated the lunatics from their chains. According to work by my colleague Sir Michael Rutter, the first thing Pinel used to say to his patients was: 'Have you suffered vexation, grief or reverse of fortune?' So you could tell which side he was on!

About a century and a half later, Eliot Slater, who was the doyen of psychiatric genetics, flourished. He was really perhaps the founding father of psychiatric genetics in the English speaking world. He worked at the place I work at, the Maudsley Hospital and the Institute of Psychiatry. He had a much more terse, British, direct approach. He used to look his patients directly the eye, apparently, at one stage in his career, and ask them: 'Are you a twin?' Of course, it is a caricature. I think both Pinel and Slater acknowledged that there were things that were partly to do with nature and partly to do with nurture, and that is the theme of my talk.

The idea that psychiatric disorders, mental illness, runs in families goes back an awfully long way. It probably goes back into very ancient times, but this is one of the first examples I could find of it that has actually been documented.

One of the hospitals that is associated with the Institute of Psychiatry, the Bethlem Royal, dates back to 1247. There is an interesting association, between Gresham and the Bethlem Hospital, and in fact there is a ward at the Bethlem Hospital named after Gresham. And the original 'Bedlem' (Bethlem) hospital in the City of London was built by Gresham Professor Robert Hooke, one of the founding members of The Royal Society. But that is by the way! In the archives of the Bethlem Museum, you can look at case notes that date back to the early 1800s, and I found an entry in a case note there. On what we nowadays call the front sheet of case notes, the doctor had to write various things about a patient, for example, 'Remarkable symptoms and state of health': it says 'Grand'; but then it says 'Whether hereditary', and there is just a straightforward word here, 'Brother'. Presumably the brother had the same thing that this patient had, or at least the doctor thought that.

If we come up to modern times, there have now been lots of studies which take a much more systematic approach to try and examine whether mental disorders run in families. There is an example about depression. Professor Ann Farmer collected a series of depressed people and looked at their siblings, their brothers and sisters, and she looked at the nearest age siblings preferentially and she called those the D-siblings, and she also collected a series of healthy volunteers, who had never had any psychiatric disorders in their life, and she looked at their siblings and she called them the C-siblings. There are various ways of diagnosing depression, but you can see, whatever method you use you find that depression is much more common in the relatives of depressed people than in the relatives of healthy controls.

Behaviours run in families. The complicated thing is this, though: that the sorts of behaviours that run in families span quite a range. Huntington's disease, for example, is a single gene disorder, so it is what is called, in the jargon of genetics, an autosomal dominant disorder. So if you have Huntington's disease, each of your offspring has a 50% chance of getting that disorder, a single gene disorder.

Then there are slightly more complicated things, like Alzheimer's disease. There are some rare forms of Alzheimer's disease, which, as you know, is one of the commonest forms of dementia, but there are some rare forms, which come on early in life, and they follow an autosomal dominant pattern, just like Huntington's disease. But most cases of Alzheimer's disease come on later in life and they are polygenic, that is to say they are contributed to by many genes of comparatively small effect plus environmental factors.

Depression, as I have mentioned, is something else that runs in families, and so does schizophrenia, but so do things within the normal range: like you can measure personality with various questionnaires, and one tends to resemble one's relatives with respect to personality more than one resembles general members of the population. The same is true of intelligence measured by IQ tests. Another thing that has been studied is religious involvement that runs in families.

Finally, there is a condition that some people in this room have suffered from, I certainly have, attending medical school! When I was working in Cardiff, about 20 years ago, I was approached by a young doctor who said he wanted to do some genetic research, and I said, 'Well, let's study the genetics of attending medical school.' So, armed with a questionnaire, he went out and asked our medical students about their family history, and we found that the risk, at least in Wales, of having a relative who was a doctor or had attended medical school, for medical students, was 80 times the risk in the general population! I am not trying to convince you that you should go out and raise funds or encourage your scientist colleagues to try and clone the gene for medical school - I am just trying to encourage you to accept that the old nature/nurture debate is not phoney. We really need to think about why disorders run in families, and there are two obvious reasons: shared genes and shared environment. Those are the causes of things running in families, or it could be, of course, a combination of the two and, in most cases, it probably is.

The least complicated we can get away with explaining any of this is to have at least three factors going on that cause behaviours. The three factors are: genes, the shared environment, and the non-shared environment. The non-shared environment is the type of environment that makes us different from our family members, and the shared environment is the type of environment that makes us resemble our family members, and of course genes contribute to that resemblance as well.

As Galton pointed out, the ways of teasing apart nature and nurture include twin studies. Galton did not know this, but there are two types of twins basically: there are monozygotic, one-egg twins; and dizygotic, two-egg twins. The idea is that, if they share the environment to roughly the same extent, any greater similarity in monozygotic and dizygotic twins should reflect genetic factors.

Adoption studies are another natural experiment, and it is very simple and straightforward here. The question is: do individuals resemble their biological relatives more than their adopted relatives? If they do, then that also suggests there are genetic factors going on. This type of experiment has been done many times.

People have been fascinated by twins for a long time. There is a picture that used to hang in Tate Britain of the Cholmondeley Ladies. They dressed the same, they had their babies at the same time, and they allegedly behaved in the same sort of the ways. But people in those days did not realise there were two types of twins - monozygotic and dizygotic.

Monozygotic twins have 100% of their genes in common, so they are natural clones, and they have been around for ages, long before Dolly the sheep and all of that, so these are natural clones, but they also have a shared environment that makes them similar; whereas, dizygotic twins have half their genes in common,

and if we assume that they share the environment to roughly the same extent as monozygotic twins, then we can make some inferences about genetic factors. For many characteristics, such as depression, manic depression, childhood fatigue, and so on, by and large, monozygotic twins resemble each other more than dizygotic twins, suggesting that something genetic is going on in these traits or conditions.

You can actually go further. There is an approach called structural equation modelling, which just helps you to break this down a little bit further, so you can derive a series of equations which helps you essentially estimate how much of the variation in the liability to these disorders, how much of the variation in the population, can be ascribed to genes and how much can be ascribed to the environment.

The data from a twin study of depression that I did with colleagues a few years back showed that, for severe depression, the sort of depression that would take you along to see a doctor or a psychiatrist, most the variation is actually genetic, but a great big chunk of the variation is environmental too.

What types of interplay are there between the environment and genes? What are the types of interplay between nature and nurture? What I have just talked about you could call co-action. That is when you get genes and environment adding up together to give you a disorder or a trait. There is also interaction. That is when there is a non-additive effect, so that, because of a genetic predisposition, certain individuals are particularly susceptible to environmental insults. There is also something even more complicated than that, which is co-variation, which is when the genes and the environment are actually correlated with each other. I will give you some examples of these from our own work.

One type of interplay is additive; one is multiplicative; and one is about genes and environment being correlated with each other, being associated with each other more than you would expect by chance.

Co-action is just the phenotype, a thing you observe, a combination of the genes that you inherit and the environment to which you are exposed, and you can divide up that environment into shared and non-shared, with, as I have said, shared making you resemble your relatives, and non-shared making you different from your relatives.

Correlation is when there is genetic influence on the exposure to different environments, whereas interaction is when there is genetic control of sensitivity to different environments. Correlation is when your genes and your environment are somehow associated with each other, and that can be for a simple sort of mechanism. So, when you pass things on to your offspring, you pass on not just your genes but you pass on your environment. Let's say, for example, you had a predisposition to drink heavily, you might pass on genes that predispose you to drink heavily, but you might also bring up your children in an environment where they are exposed to alcohol. That is correlation; whereas, interaction is when there is different sensitivity of individuals to different environments.

An example of gene environment interaction comes from an interesting adoption study. I have said adoption is one of the natural experiments where you can tease apart the effect of nature and nurture. A man called Remi Cadoret, now sadly deceased, in Iowa, in the United States, was able to study individuals who had been raised apart from their natural parents early in life. The sort of behaviour that he was interested in at this particular time was anti-social behaviour. What he was able to do was to divide up adoptees, and he was following them up as adults, into those who had an anti-social parent or did not have an anti-social parent, and those who were raised in an adverse environment versus those raised in a low risk environment. He found that if you have an anti-social parent but you are raised in a rather low risk environment, you do not have much higher risk of anti-social behaviour than individuals who do not have a biological predisposition; but if you are raised in a situation of high adversity and you have the high risk genetic background, you have got a double-whammy and you have got an increased risk of anti-social behaviour. Most other studies that have been done looking at anti-social behaviour in this way do find that there is this interesting interaction between the genes and the environment.

We did a study in Camberwell on life events and depression. What makes people depressed? Bad things happening to them, threatening life events, but we have suggested that one of the things that predisposes people to get depressed is that they have a family history of depression. So you would imagine that if you have both life events and you have a family history of depression, you are more susceptible to get depressed, and that is really what we found. We found that onsets of depression have a more than chance association with adversity, life events, and that depression is familial, but, interestingly, we have also found that life events tend to be familial.

Why might that be the case? What the family studies show is that life events tend to cluster in families. Twin studies show that there is, at least when you take self-report of bad things happening, an overlap

between self-report of depressive symptoms and your chances of reporting bad things happening to you. In other words, there must be some sort of correlation between being the sort of person who gets depressed and being the sort of person who sees the world in an unpleasant way.

However, it is more complicated than that. Some events affect multiple members of a family. Everyone knows from their own experience that there are some events that happen to you, but they also happen to your brothers and sisters and ricochet around the family, so that might be a cause of events being familial.

There is also the fact that some individuals lead rather hazard-prone lives - they take risks and they are not good at planning - and they tend to have more events than people who are more averse to risk and plan their lives, but there is also a finding that there are some individuals who just perceive the world as being far more threatening than others do.

We think there is a combination of all of these things going on. It is not a straightforward interplay between life events and genes and depression; it is a rather complicated picture. So, it is both a combination of gene by environment interaction and gene by environment correlation.

That is all I am going to say about quantitative studies, but people nowadays, when they think of genes, think of not just familiality or twin studies, but they think of actual genes on chromosomes. We have 23 pairs of chromosomes that we inherit, one set from each parent, and strung out on the chromosomes are our genes. We now live in what many people call the post-genomic era, and many people date the post-genomic era from 2001 when, in the same week, in the winter of 2001, Nature andScience both published versions of the human genome - that is to say the entire human genome sequence. I say 'versions of': the version published in Science was funded by a private company called Solera; and the publicly funded version was the one that was published in Nature. Fortunately, they are actually virtually identical. You would expect that to be the case, wouldn't you?! There were some mistakes in this early genome sequence. But, in one of those interesting compromises in science, a dead heat was declared in the race to sequence the human genome, and Nature and Science published the results in the same week.

The nice thing about DNA is that you can get it from almost anyone. You can get DNA not just from blood but from just taking a scrape from the inside of your cheek. The advantage of being able to get DNA is you can do studies not just on small numbers of people but on huge numbers of people. One of the benefits of the human genome study is that we now know an awful lot about the entire human genome sequence, and this information is publicly available. You can go to websites, such as the Ensembl website, which is from the Sanger Centre in Cambridge. You get a nice picture of the 23 pairs of chromosomes, and you can click on a chromosome. Let's pretend you were clicking on Chromosome 12, and you can get a picture of Chromosome 12. There is a list of markers along the chromosome, things called single nucleotide polymorphisms. Each can be considered a little flag which help you find your way around the chromosome. You can get a list of all the known genes that have been sequenced on that chromosome. You can do that for any of the chromosomes, and, it is all publicly available from the website.

What sort of use can you make of that type of information? One of the major benefits of all this information is that you can now find genes. One of the major benefits of the human genome project is that we have a dense map of markers that are signposts for the human genome. You can use these signposts either in studies of families - these are called linkage studies - where you track the way the markers disperse themselves - it is called segregate, in the language of genetics - the way these markers segregate in families. If you have a family where there is a disorder that is segregating, you can use the marker to find which markers actually go with the disorder. Then, if you find that a marker goes with a disorder more than chance, you can make an inference that that marker has something to do with a gene that helps to cause the disorder.

In psychiatric disorders, we are dealing with so-called polygenic trays, by and large. These are disorders where there are multiple genes of comparatively small effect. One of the other types of studies one can do is an association study, and it helps you to pinpoint genes not in families now but in populations. Association studies treat entire populations as if they were families and try and pinpoint genes that way.

Why should you want to bother to find genes and track them down within the genome? Well, if you can discover linkage or association, that gives you a location where a gene might be, and from finding that location, you can identify what the gene itself actually is and what its sequence and structure is, and then you can study what the gene encodes. Genes, by and large, encode proteins, and they also encode some other interesting things, but the gene products, so-called, are really what you're after. So you can take a condition, such as depression, where you do not know anything about the causation, other than it's partly

genetic and partly environmental, and you might be able to track down where the genes are in families and then identify the genes, find out their sequence and structure, and look at the gene products. That tells you a lot about the biology of a condition that otherwise is inaccessible.

What is association then? It is not tracking in families, it is tracking in populations, and you simply take a whole load of people who have got the disorder, cases, and a whole load of people who do not have the disorder, controls, and you just compare the frequency of a particular variation of a gene in these cases and controls. If it is more common in one group than the other, more common in a way that is statistically significant, you make an inference that that tells you something about the aetiology of the condition, the causation of the condition.

You can also do experiments on sibling pairs, brothers and sisters, both affected. I mentioned it earlier in the case of depression, but you can use sibling pairs to track down genes. So if you have siblings both affected by a disease, and they share a particular version of a gene more than you would expect by chance, that enables you to make an inference that that gene might be, in some way, associated with the predisposition to get the disease. You can also look at continuous traits, such as the personality trait neuroticism, and you can take sibling pairs who are extremely unlike on a continuum as well as extremely alike.

I mentioned Chromosome 12. It is of interest to us because we have done various linkage studies, so our study, and various other workers have done linkage studies, and we think, as a result of these studies, that there are genes in this part of Chromosome 12 that predispose towards depression. We are still hunting for them, because it is a huge area in molecular terms, but these are the sort of hints that you get from these so-called linkage studies, where you track genes in families where there are multiple people affected by the condition.

We know something about the way that antidepressants work. There is a group of antidepressants, and the most famous one is Prozac but there are lots of others, which are so-called serotonin reuptake inhibitors. Why are they called that?

Well, there is something called a synapse, which is the place where nerve cells communicate with each other. So, this is one end of a nerve cell, we will call it Neuron A, and this is another nerve cell, Neuron B, and they communicate at this thing called a synapse. How do they do it? Well, Neuron A secretes into the space between the two nerves, the two neurons, a substance, and, in this case, it is serotonin, so it is a chemical messenger, a chemical transmitter. That then sticks on to a receptor on the second neuron, and a message gets passed across. That message would just go on continually getting passed across if you did not have some way of taking the serotonin out of the synaptic cleft, and one of the ways that serotonin gets taken out of the cleft, the gap, is by a protein on the original neuron that secreted it called the serotonin transporter, so the serotonin transporter just sucks up the serotonin back into the nerve cell that originally secreted it, and that stops the message being continuously transmitted.

For a long time there has been a hypothesis around that, in depression, there is a shortage of serotonin, and one of the ways you can increase the serotonin is by inhibiting the work of the protein called the serotonin transporter. That is thought to be how drugs like Prozac work: they inhibit the way the transporter protein actually has its action.

Like all proteins, that serotonin transporter is encoded by a gene. Stuck on the end of the gene is something called a promoter, and a promoter is like a dimmer switch - when it is turned up, it turns the light up, and when it is turned down, it turns the light down. You can inherit two forms of that promoter: a highly active form and a less active form. It turns out that that variation in the serotonin transporter is very common in the population, so all of us in this room will have one or other version of this variant, and we will either have the two long forms, they are called, or the two short forms, or we will have half and half - a long form and a short form. Depending on what type of pattern we inherit from our parents, that determines how active our serotonin transporter gene is.

Why is that of importance? It has been discovered - and this was published just a few years ago in Science by my colleague Avshalom Caspi and his group - it turns out that if you have unpleasant things happening to you - I mentioned these before, life events - and you have the long form of the serotonin transporter gene, you have the double-long form, the long-long, so you have inherited the long from both parents, you are more resistant to life events than if you have short-short form, and if you have the short-long form, you're somewhere in between. So this is now an example of not just a general effect, but of a specific gene effect, where it appears that a specific gene variant makes you susceptible or not susceptible to life events.

I should emphasise, this is not the gene for depression, because there are many genes that contribute to the risk of depression, but this is a gene that contributes towards your susceptibility to react adversely to unpleasant happenings in your life.

You could say maybe this is just a one-off finding. It was very high profile, got into this important journal, Science, and there was lots of publicity about it, and it became very highly cited in subsequent years, but the reason for supposing that this is not a one-off finding is that there is lots of other evidence suggesting that this thing called the serotonin reuptake promoter polymorphism is actually involved in depression, and the gene environment interaction in depression, in lots of different ways.

This variant in this gene does not just occur in people; it occurs in other primates. So, for example, rhesus macaque monkeys have this same variation in this same gene, and it turns out that you can make rhesus macaque monkeys depressed and anxious by separating them from their parents early in life. Whether you should or not make them depressed is another matter. I am not going to defend animal experiments, but these experiments have been done. It turns out that the rhesus macaque monkeys that actually get most depressed when they are separated from their parents early in life are the ones who have the same genotype, the same gene variant that I was mentioning, people susceptible to life events.

When you get exposed to things that make you anxious, it is now known that there are actually physical things happening in your brain, so parts of your brain light up when you get anxious or depressed and, in particular, if you show people fearful stimuli, and you stick their heads in a type of a scanner, called an MR, Magnetic Resonance, scanner, parts of their brain light up more than others. There is a bit called the amygdala, which is buried on the inside of the brain, and it has often now been called the fear centre because the amygdala lights up if you are shown fearful stimuli and you have your head inside a scanner. It turns out though that the people in whom the amygdala lights up most are those people who have that genetic variant that I was mentioning, the less active form of the serotonin transporter.

I have mentioned already the interesting study by Caspi and colleagues showing that the short form of this gene predisposes you to depressive symptoms when you are exposed to adversity. This was subsequently replicated in our own centre by Thalia Eley and her group, in children, and it has been now replicated multiple times elsewhere in the world.

There is something more interesting, which is that response to antidepressants, serotonin reuptake inhibitors, so-called, are also influenced by this particular gene. We just had a study published, with my colleague Rudolf Uher and Kathy Aitchison and others, where we were able to replicate the finding that response to antidepressants is actually influenced by this particular gene.

There are lots of pieces of evidence. You could think of them all as straws in the wind, but they are all certainly blowing in the same direction, suggesting that this serotonin transporter gene is not the gene for depression, but it is one of the genes that contribute to the risk of depression and contribute to the way antidepressants work and, indeed, contribute to the way other primates get distressed and anxious.

So, we now have a number of specific genes that influence how we interact with our environments. I do not have time to go into all of them. I have dwelt at some length on the serotonin transporter, but there is another gene that made headlines: the monoamine oxidase A gene. This is also work done by Avshalom Caspi and his colleagues - Caspi and his colleagues showed that, if you have a certain form of this monoamine oxidase A gene and you are exposed to adversity in childhood, maltreatment in childhood, again, you tend to have a high risk of anti-social behaviour. So this is another type of gene/environment interaction. It is, if you like, a counterpart to the adoption data that I was showing you earlier, but it is now focusing on a specific gene.

There is an interesting gene called COMT, catechol-o-methyl transferase. You do not need to know anything about it, except that it is involved, again, in the metabolism, that is to say the biology, of chemical transmitters in the brain. It is involved in particular in a chemical transmitter called dopamine. We know that if you smoke enough cannabis, you can get high, but we know that some people, when they smoke cannabis, or eat it, not only get high, but they actually develop mental illness. For a long time, it has been known that there is an association between cannabis and schizophrenia. It turns out that you have a particular susceptibility to getting schizophrenia when you take cannabis if you have a variant on this COMT gene.

That is three interesting examples of what some people call candidate genes. We call them candidates because they are genes that we have picked out because we know they are involved in brain metabolism, the way that the brain works. They are involved in the way that chemical transmitters, chemical

messengers, actually act.

But there is another way that one can now discover genes, that we do not know anything about previously from previous studies using information from pharmacology or how drugs work, and this way is called the whole genome association study, or the genome-wide association study. The first one of these was actually published just 18 months ago now inNature, and it was published under the auspices of the Wellcome Trust, who funded a very expensive experiment called the Wellcome Trust Case Control Consortium. It looked at seven common diseases - six physical diseases and one psychiatric disorder, bipolar disorder, and it compared cases with controls and it mounted a search throughout the entire human genome, that is to say the 23 pairs of chromosomes, for genes that might contribute to these conditions. It was a highly successful experiment because it did find new genes involved in coronary artery disease, Crohn's disease, rheumatoid arthritis. It was somewhat less successful in hypertension, but subsequent studies have been successful there. I am going to focus of course on bipolar disorder because that is what I am talking about today.

What is bipolar disorder? I have talked a lot about depression. Depression, also called unipolar disorder, is when you get recurrent episodes of low mood. Bipolar is when you get recurrent episodes of not just low mood but also you get episodes of mania or high mood elation, which is an even more disruptive condition than unipolar depression.

So, what did the Wellcome Trust Case Control Study do with regard to bipolar disorder? Our group at the Institute of Psychiatry was involved in this, together with groups in Cardiff, Aberdeen and Newcastle. It was actually run largely by Nick Craddock in Cardiff. Essentially, we took 200 well-defined cases of bipolar disorder and compared them with 3,000 ethnically matched controls. This study focused entirely on people of white European origin from the United Kingdom, and why white European? Well, doing a case control study is like doing a family linkage study, and just as you want to make sure that somebody in a family linkage study really are biologically from the same family, in a case control study, you want to make sure that people are from the same ancient ancestor origin as each other, so that is why we picked people who are all of white European origin. This study used something called the Affymetrix 500k chip, which sounds very mysterious.

The chip that was used in that study was literally a glass chip. But the remarkable thing about this chip is it has half a million of these markers, signposts, which we call single nucleotide polymorphisms. If you put DNA from any one of us on to one of these chips, you could get a readout of what variants in these signposts, these half a million single nucleotide polymorphisms, we actually have. The idea is that you compare all of your cases with all of your controls, and you see what are the differences between the cases and the controls, and that might help you to pinpoint genes that are adjacent to the little flags that are involved in the disorder.

Interestingly, in the two years since this study has been published, you can now not just stick half a million of the signposts on a chip - you can stick an entire million of them on a remarkably tiny little chip and get a readout which is even more detailed. This technology is progressing all the time.

Since the Wellcome Trust Case Control Study, published 18 months ago, Nick Craddock, who led the bipolar bit of it, and Pamela Sklar, who did a similar study in the United States, got together and put all of their data together, which gave them a massive number of cases of bipolar disorder, and they were able to compare those genetic data with 6,000 controls. They came from the US, the UK and Ireland, again, all of white European origin, and what they were able to do as a result of this was to identify two completely novel genes that no one had ever thought about before, which it turns out appear to be involved in the causation of bipolar disorder.

One of these genes is called CACNA1C. It encodes a calcium channel. A calcium channel is another one of the types of receptors that sits on the surface of cells and helps in communication between nerve cells, but this particular one actually lets calcium into the cell. Ankyrin encodes a protein that makes the skeleton of a cell. Cells have these little skeletons inside them that hold them up, and they anchor the things that sit on the surface of the cell, the receptors, and what Ankyrin does is provide that skeleton. No one knows quite how these genes are involved in the causation of bipolar disorder. They are just a couple of a large number of genes that are involved, but we are now beginning to make some headway into the biology of this condition by studying these types of genes.

Another area I just want to touch on is so-called pharmacogenetics. If you go along to see your doctor about any common condition, it is likely that you will get some sort of medication that the doctor hopes will

help, and you hope will help too, but the general response that you get to therapeutic drugs is not always a good one. So you hope for efficacy, you hope that she or he gives you will be efficacious - it will make your symptoms better and may even make your disease better: it will cure your depression or cure your sore throat or whatever. However, we know that quite often when you go along and get a medication, there are actually little or no efficacy. And it gets worse: sometimes, not only will a drug just not work, but it actually is toxic. At worst, it kills you; at best, it gives you a rash or makes your stomach upset. It is also pretty bad if the drug makes your symptoms go away but it gives you the rash or the tummy upset or whatever.

Now, the other thing we know about getting medications is that not everyone is the same. So there are some people where the drug works wonderfully and some people where the drug has little or no efficacy. There are some people where the drug is toxic, and there are some people who can tolerate the drug quite well. The question is: can we predict who will get the side effects and who will get the benefits? The answer is, at the moment, by and large, no, for most drugs, but I have already hinted that there is one drug in psychiatry, or at least one group of drugs, the serotonin reuptake inhibitors, where we now have a gene that gives us some prediction of efficacy. Would I advise that gene be tested in all people who go along to their GP to be treated for depression? The answer is no, because the effect of that gene is a very small effect on its own. But we have some other studies, which we are just getting the results of, which show that, if we look at a number of different genes at the same time, we can begin to draw up a profile of who will or will not benefit from certain types of antidepressants. We just, within the past week or two, are getting some quite interesting, and even possibly exciting, results, where we are doing one of those genome-wide studies I was telling you about, searching completely throughout the genome for novel genes that we previously have not even thought of that might be involved in antidepressant response, and we think we might have one or two, which we previously have not thought of, which will predict treatment response. So, the question about pharmacogenetics and genetics, why do it, this is the reason why. We do not have any really good tangible results to demonstrate at the moment, but 'watch this space'! I think we are going to go 'individualised medicine'. A lot of people do not like the term, but we are certainly going to get more individualised treatment than we used to, for all sorts of common conditions, psychiatric conditions included.

A lot of my clinical colleagues ask me: where is all this leading? I am a clinical psychiatrist as well as a geneticist, but many of my clinical colleagues used to say, 'It's all very well doing all this type of research, Peter, but it doesn't really have any impact on what we do in day-to-day practice of psychiatric medicine.' But I would like to put it to them that the results are now coming through thick and fast, and they are beginning to have an impact in a variety of ways.

I have mentioned targeted and tailored treatments. Pharmacogenetics is all about tailored treatment. I hope that discovering new genes that tell us about the biology of the conditions that we deal with will lead to new targeted treatments. Now, these are not going to be developed by academics; they are going to be developed by pharmaceutical companies, but one of the reasons that pharmaceutical companies are very interested in genetics is to find new targets for drugs, not just in psychiatry, but in all sorts of common diseases, because there is a paucity of new targets. The genes that I have just mentioned, the calcium iron channel, for example, is an eminently drugable target, so, not surprisingly, pharmaceutical companies are getting interested in those sorts of targets.

Psychiatric diagnosis, up until now, has all been based on symptoms and a few clinical signs, so it is a clinical set of diagnoses, and therefore, it is not all that refined. In fact, the classificatory system that we have in psychiatry was invented over 100 years ago by a man called Emil Kraepelin, and we have not progressed much further, 100 years later. But with the sorts of technologies that I have been speaking about, I think we may get closer to refined diagnoses in psychiatry.

An understanding of the neurobiology is going to be terribly important, and, hand in hand with that, is what I have mentioned: being able to predict risk in a more refined way; and also, being able to look at gene/environment interaction effects and covariation effects, and I have given you some examples of that.

This is a public lecture, and part of the motivation of people like me for giving public lectures is that they alter public perception and ultimately reduce stigma. Some people that I have talked to in the past about psychiatric genetics have said to me, 'Psychiatry is a bad thing, frankly, and genetics is a bad thing, so it's a double bad thing!' I hope that I have convinced you today that it is a double-good thing because the public perception of psychiatrics is awful and there is a lot of stigma associated with these disorders. Why is there stigma associated with these disorders? It is a rhetorical question, but it is one of those rhetorical questions where you can actually give an answer. There is stigma because these are frightening conditions

and most people do not know what on earth they are all about and what causes them. I would like to put it to you that the types of study that I have been reviewing for you should tell us a lot more about the causation, as the doctors say, the aetiology of these conditions, and therefore, hopefully, they will become less mysterious and much more generally accepted, and public perception will improve.

When I started out training in medicine, around 30 years ago, there was a lot of stigma associated with cancer, because we knew almost nothing about it. Now we know lots about cancer, about its biology, and people are not afraid to stand up and say, 'I've got cancer.' Nowadays, people are even beginning to stand up and say, 'Yes, I've got Alzheimer's disease,' or 'A relative of mine has got Alzheimer's disease,' because Alzheimer's disease, described by the psychiatrist Alois Alzheimer 100 years ago, is a condition where we now know quite a lot about the neurobiology, largely from genetic studies that I have not mentioned today.

started out by saying there was a nature/nurture debate, and I was trying to convince you that this was a rather phoney debate. I made the same opening statement in a lecture I gave in Cardiff when I first moved there, before I moved back to the Institute of Psychiatry in London, some years ago, and one of my predecessors in Cardiff, Ken Rawnsely, told me about one of his early teachers. This teacher was a psychiatrist, a doughty Scot, and for his opening gambit he used to say, 'I ken (I understand) life has not been kind to you. Tell me: is there any other insanity in the family?'! So, with that nice blend of nature and nurture, I would like to thank you very much for listening!