Ulster Medical Society

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My Genes Made Me Eat That:
The Inherited Basis of Human Obesity
Dr Sadaf Farooqi
Institute of Metabolic Science in Cambridge

Professor Brew Atkinson:

Ladies and gentlemen, it's my privilege to welcome you all here tonight to another meeting of the Ulster Medical Society, and it's good to see a good turnout on a cold night in January. We're very privileged indeed to have Dr Sadaf Farooqi to be here with us tonight. The institute in Cambridge is very famous for its work in metabolic diseases and obesity, and I just want to tell you a little bit about Sadaf before she starts her talk. She's a Wellcome Trust senior clinical fellow, and she's reader in human metabolism at the Institute of Metabolic Science in Cambridge. She qualified in medicine from the University of Birmingham in England, and subsequently trained as an endocrinologist in both Oxford and Cambridge.

Her research is focused on a cohort of patients with childhood obesity, and she's played a leading role in that over the last ten years. In 1997, she was one of the group who identified leptin deficiency, and I'm sure she'll be telling us some of that story tonight, and that was the first single-gene defect across human obesity. Since that time, with her colleagues in Cambridge, she's identified patients with a variety of genetic mutations in several genes, and she'll also be telling us about the leptin/melanocortin pathway in the regulation of body weight. Now, this is obviously a very very important topic. While I think it's just important to recognise the work that Sadaf has done, with over 100 original papers, including papers in Nature, in Science and in the New England Journal of Medicine; and she's been awarded quite a number of prizes for her work in this, including the RD Lawrence prize, which is a very distinguished prize, from Diabetes UK; from the International Association for the Study of Obesity; from the European Society for Clinical Investigation. But even more than that, this time 24 hours ago, Sadaf was lecturing at a Keystone symposium, and those who don't know too much about Keystone symposia, or those who have read a little bit about it, but she's been educating me about that. It's a very prestigious set of scientific meetings that are organised and go on, so she's come straight from lecturing at altitude, which isn't very nice to go in to suddenly, in Keystone, Colorado, to Washington DC, to London, for a while, because she's organising a very important part of her research for this Saturday, to Belfast, and back to work in Cambridge tomorrow morning, very early in the morning. And she has willingly said that she would come and talk in Belfast, and we're really, really grateful, and I personally am most grateful. I've heard Sadaf speak before, so I know that we're all going to be in for a treat tonight, and I'm really looking forward to it. Welcome to Belfast for the first time, and we hope it'll not be the last time, and welcome to the Ulster Medical Society.

Dr Farooqi:

Thank you very much, Brew, for a very kind and generous introduction, and it's a real pleasure to be with you today. I will take the liberty of standing here, as opposed to behind the podium, because you won't actually see me if I stand behind the podium. I'd like to share with you some of the work that we've been doing over the last ten, eleven years now, trying to understand why people gain weight, and whether genes may be able to tell us a bit more about that.

This is really just to acknowledge my team on the left-hand side, whose work I'll accredit as we go through, and my long-term mentor in Cambridge and collaborator, who many of you will know well, Steve O'Rahilly .

So really, what we're interested in is obesity, and the problem with obesity is that we physicians haven't really taken it very seriously. We've tended to just think, if simply people pulled themselves together, stopped eating quite so much, and did a bit more exercise, there really wouldn't be a problem with obesity, and unfortunately this kind of attitude towards obesity has got in the way of us understanding why people gain weight. What we do know is that gaining weight is a serious medical issue, so if you look at the left-hand panel, we know that the rise in prevalence of obesity is quite staggering, and that currently at least 20% of people in most western countries are clinically obese, and 50% are either overweight or obese, so gaining weight, and the complications that are associated with obesity, are becoming huge public health problems. On the right, you'll see a panel showing that, as people gain weight, some of the major problems include a rise in the prevalence of Type 2 diabetes. Cardiovascular disease is also common, as are certain forms of cancer. So obesity is a serious medical issue, and given its rise in prevalence, it's becoming a major issue of our times.

What we know is that obesity-related Type 2 diabetes is a huge phenomenon. For those of us who look after patients with diabetes, this is really what lies in store for us. By 2025, over 330 million people worldwide will have diabetes, and 95% of that is Type 2 diabetes, and when we try to understand why Type 2 diabetes has become so common, it's quite clear that 60–80% of the rise in the prevalence of Type 2 diabetes can be explained by weight gain. So people around the world are gaining weight, and as they gain weight, they're developing more and more Type 2 diabetes.

So why are people gaining weight? Well, most people say that's quite simple—clearly what's changed in the last 30 or 40 years is our environment. Our genes haven't changed in that time, and yes, we're eating more and we're exercising less, but actually we

need to look at the pattern of obesity in a bit more detail, shown on this slide here. So what I hope you can see is, the body mass index, or BMI, on the x axis, and the previous pattern of distribution of BMI in blue, and the current pattern in red, and what we see is that, over the last 30 years, the mean BMI of the population has shifted to the right, so your average person is now heavier than they were 30 years ago, and that makes some sense, but what we also see is that there's this great positive skew, so there's a greater proportion of people with severe obesity, and these are the patients who are coming to our clinics now with various complications.

So you might say, well what's caused this trend? Is it that everybody's just eating far too much and that's why we're gaining weight? Well actually, it's not really quite that simple, you need to do some maths. If we do some maths, what we find is that if you eat seven calories a day more than you burn, that's enough to lead to an increase of weight of ten kilos, a change in the BMI of three units, and that's enough to explain the change in the population of the UK over the last 30 years. So actually, it's the fact that your average person is just eating a little bit more than they're burning, that's caused the change in the average BMI of the population, and seven calories a day is tiny, it's half a slice of cucumber, which is quite frightening really.

So the myth, that for people to develop severe obesity, they must all be eating far too much and exercising too little, I think belies the fact that in fact, it's a small consistent trend in positive energy balance that we're seeing. So why should we even be thinking about genes? Well actually, there's quite a lot of evidence now that genes play a role in the regulation of weight, they always have done. People have known for a long time that your weight, like your height, runs in families, and if we look at identical twins, they will have a 90% identical weight as adults. So the problem has always been that we thought there'd be lots of genes, it would be like looking for a needle in a haystack. Lots of common genetic variants would contribute to your tendency to gain weight, and with recent technologies, some of those common variants have been found, but they only account for about 5% of the differences in weight in the population. So in fact what is probably relevant is that, for people who have gained weight, or are more likely to develop obesity, they have genetic variants that are making them susceptible to gain weight in a given environment, and that's really what we've been trying to do, is to say, can we find some of the genes that increase your chance of becoming overweight or obese. How do we do that? Well, we decided to focus on the extreme end of the body mass index spectrum, so severe obesity, particularly starting in children from a very young age, and this started off as work for my PhD and it's kind of carried on beyond that. We've identified over 3,500 children now who are severely obese from a very young age, and really tried to say, can we find if genes are causing their obesity? and that study is known as the Genetics of Obesity Study, or GOOS. So how on earth do we know where to look? If we're trying to find a gene that's maybe causing obesity, where would we look? Well actually we've been very lucky, in the last 10–15 years, there's been a huge amount of science, often based on animal models, that's allowed us to discover a system for regulating weight. Now, certainly I didn't learn about this at medical school, it didn't exist. We learnt about homeostatic systems for thirst, for the regulation of blood pressure, for many other things, but actually there is a system for controlling weight, and this system is controlled in the brain, and particularly at the level of the hypothalamus. In fact, the players in that system have really only emerged in the last ten years. So we know that the hypothalamus receives input from your fat, so your fat is not just there to store extra calories, your fat effectively is an endocrine organ. Your fat, or your adipose tissue, is secreting hormones that signal to the brain, telling you how much fat you have, and what your nutrient energy stores are, and one of the key hormones that signals energy surplus to the brain is leptin, and you'll hear more about leptin in a short while.

So you get your signals from fat, but also you get signals that are short-term signals in relation to meals, so you'll know, and I've just had a very nice meal, that there are lots of signals firing off in my brain right now, telling me that I'm full, and those are neural signals from the vagus, for example; hormonal signals, various gut hormones are released after a meal, telling you that you're satiated; and your brain in particular, your hypothalamus in your brain stem, has to integrate all of those signals to regulate how you eat, and in fact our eating behaviour and our weight are tightly controlled over long periods of time.

Now of course, it's not a perfect system, because if it was a perfect system, we could eat too much one day, eat a bit less the other day, and our weight would remain stable, because of course sometimes we can override that system, and that's shown by the piece of chocolate cake on the top here, where obviously if we see a particularly nice piece of cake, and I'm sure my system's going to be overridden very shortly, that we can override our satiety, and we will overeat, so the system has a little bit of play in it as well. So how do we know this system, most of which was uncovered by studying animals, is relevant to human beings?—and the reason we know that, and I hope you can just about see these pictures actually, is really through the study of patients, and I'm a physician and an endocrinologist, and for me, this is what research is about. Research is about thinking about our patients, and trying to understand what is going on, and whether we can do anything through research to understand the cause of their disease and find new treatments. So, as you can clearly see, these are two of my patients who are severely obese from a very

young age. Here they're at the age of three, they weigh 39 kilos, four-and-a-half stone; developmentally normal—all the known causes for childhood obesity, Prader-Willi syndrome, hypothyroidism, have been excluded, and what we found is that these children were lacking the hormone leptin, and normally the more fat you have, the more leptin you make, so you should have high levels of leptin, but these children have undetectable levels of leptin, and the reason they have undetectable levels of leptin is, they have a genetic mutation in the gene that encodes leptin, and as a result they have complete leptin deficiency, and these are amongst the first children that we identified with this disorder, and this was the first evidence that a defect in a single gene could cause human obesity.

So what actually happens to these children? Well, what happens is, they're born of a normal birth weight, as you see on the right, and the main clinical feature is hyperphagia, and I think for some of the youngsters in the audience, again it's a nice reminder that describing this syndrome was really all about good old-fashioned clinical observation. It was about taking the history, it was about talking to the family, and these children had been seen by many physicians, all more senior than I was at the time, who had considered this was simple obesity and had basically written off the family, and told the parents to stop feeding the children quite so much. But if you take the history, what you find is these children were obsessed with food. They have hyperphagia, they had an incredible drive to eat. They would go around looking for food. They'd eat any kind of food, so when I first met the little boy on the right, and I saw them in the family home, this child would be asking for food all the time, he was only two-and-a-half, and his mother would give him Ryvita—do you know Ryvita, the sort of very boring plain crispbread?—and he would take Ryvita, and he would go, oh, yum yum yum, and I was like, my God, there's something very wrong there, that's a pathological disorder of appetite. You don't need to read any textbooks to understand there is something wrong if a child likes Ryvita!—so again, basic clinical observation, is really what this is about. So these children are incredibly hungry, they like any kind of food. It's amazing, I've seen them eat hospital food, you'd never believe it!—and again, very classical, that must be part of the description of the clinical syndrome, I think. So an incredible drive to eat, they like any kind of food, and I'm going to come back to understanding why that happens. They don't have a defect in their metabolism or their metabolic rate. They do preferentially put on fat. Now, if you see the clinical photos here, they have rolls of fat—60% of their weight is fat, and the reason for that we now know, is that you need leptin to burn your fat, so not only do these children eat an awful lot because they're hyperphagic, but when they eat, they cannot burn those calories that come from fat, so they deposit extra fat, and they have a number of other endocrine abnormalities, hypothyroidism, they would fail to go through puberty, and adults have been identified who have leptin deficiency and remain infertile, and they have impaired immunity, and frequent atopic disease, and some of these children have had siblings with the same disorder who have sadly died because of infections coupled with their obesity. So, now the whole point for us is really, if we can understand the gene or the mechanism causing the disease, can we do anything about it?—and we were very lucky that this is effectively an endocrine disorder. It's a lack of the hormone leptin causing this problem, so if you have a hormone deficiency, you try to treat it with the hormone, and we were lucky that recombinant human leptin, or synthetic leptin, was available, and we started the first-ever clinical trial giving leptin to these patients, and really with pretty dramatic results. This is the same patient before and after treatment with leptin, and really quite unbelievable. Severe obesity, and several years later, daily injections of leptin led to complete reversal of the clinical abnormalities, so leptin is effectively life-saving in these children, and causes them to reduce weight. Interestingly, when they lose weight, 98% of the weight they lose is fat, so if any of us were to go on a diet and lose weight, about 75% of the weight we lose is fat. Here, leptin is selectively burning or oxidising the fat. Really, the most dramatic effect of leptin is on the brain, and it's on appetite, so I told you, they really like food, they eat a lot of food, they eat hospital food. After a week of leptin, they turn away food. The first time we heard that, the mother burst into tears, she'd never heard them say no to food before. So within a week of leptin, that drive to eat is switched off, and what is amazing is that drive to eat and seek food is tightly regulated by leptin, so for example, what we need to do is to measure that.

Now again, as a physician, I know what I see, but I need to find a test—there is no test for measuring appetite in this situation, so I had to devise a test, and tests can be quite simple, they don't have to be fancy, and the test was, take a child, give them an awful lot of food, after an overnight fast, and measure how much they eat, so we give them an ad libitum test meal, which is about 5,000 calories—that's quite a lot for a three-year-old, and we see how much they eat, and when I come in with the food, they look very happy to see me, of course, and they eat an awful lot of food. This is their food intake in the black bars, about five times as much as a normal child. Then we treat them with leptin, and you can see there's a dramatic reduction in their food intake, but what is interesting is, over time, like with any other endocrine disorder, they relapse, so their food intake goes up again, they start putting weight on. I then increase the dose, again it brings their food intake down, they start to lose weight, so we can actually regulate their appetite very tightly by adjusting the dose of leptin.

What else does leptin do? Well, leptin allows these children to go into puberty. Without leptin, they

would not go into puberty, but what we see is, at the appropriate developmental stage, so they don't go into early puberty, they will go into puberty, and we can measure that before we see any clinical signs, by measuring the gonadotrophins, LH and FSH, using this test, and again this is good old-fashioned endocrinology, this is ten-minute sampling overnight, allows you to see the pulsatile release of the gonadotrophins. And we also realised that, for the stage at which this patient was going through puberty, she was developing an interest in Leonardo DiCaprio, so we thought this is pretty much clear evidence of puberty going on here, and also we can see that the link between leptin and reproductive function is incredibly tight, so for example, I told you about those phases where the patients start to relapse—they eat more, they gain weight. If we repeat the pulsatility at that stage, it flattens out. If we increase the dose, we control their appetite, we restore the pulsatile release of LH and FSH. There's a very tight link between the nutritional signal and the signal for reproduction.

The bottom two panels shows some data on the immune phenotype, basically in the absence of leptin shown on the left, the patient's T-cells are very weak, they're very poorly proliferating, and after treatment with leptin, they're restored to normal function. So, if we want to understand more about what leptin's doing, we need to look at the brain. The brain is pretty important, as described originally by Homer, not particularly this Homer, but the brain is an important organ for the regulation of appetite. How can we study the human brain? Well, one of the new techniques that we can use to study the brain is functional MRI, so this is like a regular MRI scanner, so you get the anatomy of the brain, but as well as anatomy you also can look at function, shown here by the red blobs, So effectively if you put people in a scanner, and you give them a certain task, you might show them pictures, you can measure which parts of the brain are activated by changes in regional blood flow, so for example, people who are studying dementia will give people a memory task in the scanner, and see where the blood flow increases in relation to tests of memory.

So the question is, can we use this FMRI to understand more about how leptin works in the brain?—so we needed to give some sort of signal that reflects our particular interest, and we wanted to see the brain response to a particular stimulus, and the stimulus, I guess for us, is food versus non-food as a control. We then wanted to say, okay, what happens in the brain of patients who are leptin-deficient, before and seven days after treatment?—and also, is there a difference depending on the type of food you see? If you see really appetising food like a burger, does your brain respond differently to if you see broccoli?—and I must confess to a personal bias in the choice of the food. So the basic design of the study is effectively, the patients are fasted overnight, they then go into the MRI scanner, they have a structural scan, and then after that they have the functional scan, and above their heads is a small screen on which come these pictures, and they come in random order. Some will be food, some will be non-food, sometimes burgers, sometimes broccoli, different things, and we look at the pattern of brain activation. They then come out of the scanner and are fed a meal of known macronutrient composition and calorific value, and then 30 minutes after the meal, they have a further scan in the fed state. Again similar kinds of pictures, different actual images, and all mixed up.

What we really see is, in the leptin-deficient state, when they're really, really hungry and they like all kinds of food, including hospital food, all the parts of the brain that code reward or pleasure are highly activated, the mesolimbic system, so the same system that's involved in addiction, and pleasure from various other things. So the nucleus accumbens, the striatum, all these parts of the brain are highly activated in the absence of leptin, and after a week of leptin, the activation goes down.

Now, what we see is a really interesting change in behaviour. I told you about this, in the absence of leptin, these children really liked Ryvita, really liked hospital food. Again, I needed some sort of test to measure that, so we asked them to rate pictures of food. In the absence of leptin, you can see they really like the cake, but they also really like cauliflower, a highly abnormal response. After a week of leptin, they haven't lost any weight but it's working, now they kind of quite like the cake, it's about five or six out of ten, but they now can discriminate, and they rate cauliflower a zero out of ten. Now, why is this important? Well, this is important because it shows that leptin has affected their ability to discriminate between appetising and bland food. Now, I told you that I showed them pictures of cars and other non-foods, as a control. What is interesting is, in the absence of leptin, they could rate the Ferrari over the Mini, so they could discriminate between non-food, but all types of food were rated ten out of ten, so the ability to like food is regulated by hormones such as leptin. And just to cut a long story short, is the particular part of the brain that's involved in that response, and that's the nucleus accumbens, so the more you like food, the greater the activation in your nucleus accumbens, and the same happens in all of us, so some of us will be particularly partial to chocolate cake, and our accumbens will be firing off like crazy. There are some people who like broccoli, and that will have the same response for those people.

So moving on from leptin, there's a receptor in the brain where leptin acts, and we find a number of patients who have mutations in the leptin receptor, and what we can do is try and understand why that receptor's not working, model the structural effects of these mutations, and also study the patients who have a fairly similar phenotype to leptin-deficient patients, but importantly, as endocrinologists, we wondered whether the patients with leptin receptor mutations

would have really high levels of leptin, but they don't—in fact, there's no real difference there.

So basically what we know about leptin is that once leptin gets to the brain, it effectively triggers a cascade of neuropeptides, which ultimately regulate your appetite, and there are distinct populations of neurones in the brain which either increase or decrease food intake, and the balance between those signals determines how much you eat, and we now know that if you have a genetic mutation in at least seven of those molecules, that will cause severe obesity in children.

So just one of those I particularly want to mention is the melanocortin 4 receptor, so this is a molecule in the brain that's downstream of leptin, and where 5% of the children that we look after have genetic mutations. So it's the commonest monogenic obesity syndrome, and what we've been looking at is, can we try and devise treatments for those children. I won't go through all the data, but this is just one of the examples of the work that we can do in the lab, is that some of these mutations stop the receptor from getting to the surface of the cell, and what we can do is use some things called chaperones, which are molecules which try and rescue that mutated receptor, and increase the cell surface expression, so you just about can see here, I hope, this is the normal receptor levels shown by the black arrow here; this is a defective receptor, you can hopefully see less red dots in this square here, and then when we add the chaperone, we see an increase in red dots, i.e. there are more receptors on the cell surface. So these are the kinds of approaches that we can do to try and find treatments that may be useful for these patients.

The clinical phenotype of MC4 mutations is quite different. So this is the world's first MC4 deficient patient, and I must say when I first saw him, I wasn't really that impressed. You have to be fairly big to impress me, and he didn't look that big. He didn't have the rolls of fat that we see in the leptin-deficient patients, and there's a reason for that, and the reason is that these patients have an increase in fat, but they also have an increase in lean mass, and an increase in bone density, so they just look quite big and solid. Some of these children, around the age of 15, people stopped them in shopping centres and tried to recruit them to play rugby, because they just looked very big and stocky and big-boned in fact, and that is a different phenotype, and that is the clinical picture we see with MC4 mutations. The patients are often tall, they have severe hyperinsulinemia, more than you'd expect for the degree of obesity, and that's probably the major driver for that.

The other thing that we see is, when we study these patients, it always surprises me that actually their blood pressures are pretty good, and when we see adults with severe obesity, say with a BMI of 45, they have blood pressures of 120/70, 110/68, which is remarkably good blood pressure for people with severe obesity, and when we compare these patients with equally obese controls, we do find they have lower systolic and diastolic blood pressures, and a lower prevalence of hypertension. And the reason for that is that they have impaired sympathetic tone, and that's shown on the bottom graph there, and just to explain to you what we think is going on, so we know that weight and blood pressure are tightly linked. As people gain weight, their blood pressure goes up, and if they lose weight, their blood pressure comes down. What we think is going on is that as people gain weight, they have more fat, they make more leptin. As you make more leptin, that signal through the brain, through the MC4 receptor, to your sympathetic nervous system, driving up your blood pressure. In these patients, they are obese, and they have high levels of leptin, but the signal can't get through because they have a defect in the MC4 receptor, and so they don't drive up sympathetic tone, and they're protected from hypertension, and in fact anecdotally, they seem to be protected from cardiovascular disease. We're studying this now, because only one of my patients has had a myocardial infarction, which again is very uncommon in people with this severe degree of obesity, so we're trying to see whether this may actually protect them from some forms of cardiovascular disease.

When we're looking at these genes, we know they affect appetite. They also seem to affect the ability to burn fat, and this has been shown in mice, and we were able to show that these patients have a high Respiratory Quotient, which basically means that they cannot burn fat, and this really relates to something again, clinically the patients' parents have been telling me for ages, and they say, "Doctor, I know my child eats a lot, but for the amount of food he eats, he gains a lot more weight than you'd expect", and we hear that in clinics, and sometimes when we hear that in clinics, we might say, okay, the patient must be lying, they must be eating more food than they're telling me—that's why they're gaining weight, but in fact we can show that these patients have an impaired ability to burn fat, so when we match the food intake, and we study people in a chamber, and we look at how many calories they burn, the people with the MC4 gene cannot burn the calories they ingest from fat. Just to show you some very new data, we're looking at other genes. This is a particular gene involved in brain development, and we're finding particularly the development of the hypothalamus is impaired in patients with mutations in Sim1, and I just wanted to show you some of the new technologies that we can use to study this. So we find a gene, it's involved in brain development. The patients have severe obesity and developmental delay, so some of the patients, my colleagues in genetics will see, with obesity and developmental delay, may have mutations in Sim1. Now, we have to do quite a lot of work to prove this. We have to do some genetic studies, we have to study the families, we have to look at what are the clinical features, but we also want to say, how does a defect in the gene

stop Sim1 from working?—and the problem is, that gets really complicated. I've got a poor Fellow, a very hard-working young Fellow called Schwaefer (?) who's an SHO, who came to me from Oxford, and is now a Fellow with me, and she's been working for ten months trying to understand how these mutations stop Sim1 from working. But it's quite a complicated system, because Sim1 has lots of other molecular partners, but there's a new technology that we can use to try and understand what's actually happening in the patients. The problem is, it's happening in the brain, so we can't actually get brain tissue, but what we can do is use stem cells, and now the technology exists, where I could take a skin biopsy from any one of you, get your fibroblasts, then add a cocktail of factors, and make your fibroblasts into stem cells, and then I could add another cocktail of factors, and effectively make your stem cells into any other cell line, so I could make them into neural cells. We could then mimic your brain cells. I could make them into hepatocytes, I could make them into fat cells. So here what I want to do is take skin biopsies, which is very straightforward, from my patients with Sim1 mutations, and make them into neural cells that resemble the patient's cells, and therefore you have a model system that most more closely mirrors the patient with the disease.

So what are we doing now? Well, I told you about the GOOS study, we started it twelve years ago, and we now have over 3,500 patients with severe obesity, and these patients are really proving quite a challenge, because although we've found quite a few genes, and we're quite excited about that, they only explain 7% of the patients in our cohort, so is there anything more to find?—and I really think there is. And the reason I think there is, is again, look at the patients—they are definitely telling us something. You can see they're severely obese, and they're very young, and in these cases, all the known genes have been excluded, so I think there are more genes to find here, and certainly the child in the middle is from Liberia, war-torn Liberia. Don't quite ask me how we got samples over to Cambridge, but we did, and yet these children are developing such severe obesity in very different environments. So there are going to be other genes that are causing the obesity in these patients. How are we going to find those genes?—well, there are many different approaches. We can use classical genetics, so autozygosity mapping, which basically means where you have consanguineous families where the parents are related, first cousins or second cousins, and you look for parts of the genome that are shared by, for example, the two severely obese kids, but are different in the thin members of the family, and there's another type of genetic variation that we can look at which is called copy number variation. Now, you'll remember diseases such as Prader-Willi syndrome, where you have a deletion on chromosome 15. Those are deletions that we can see with the microscope, but in fact there are many, many deletions that we can't see with the microscope, and in fact we all have them. So any one of us will have at least 50 small changes in copy number. So again, we were taught that you have two copies of every gene, in fact that's not the case. For some genes, you may have one copy, seven copies, five copies, and those differences between us determine the differences in phenotype that we have. So what we want to do is to try and find some of those genes, and to do that we've been using a particular technology. Again in the old days, we used to have to look at one gene at a time, now we can scan across the whole genome, looking for many different genes at the same time, and basically what we've been doing here is looking for small deletions in patients.

Again, I won't go through all the technical aspects of this, but I hope you can just about see this most recent data here. So effectively we're looking for a loss of a bit of a chromosome, so the control data is shown in grey, and I hope you can see that this red line, which is a patient, dips down, and that dip is a deletion, so for these three patients, they have a small deletion here on chromosome 16, and these patients have severe obesity. Two of the patients up here have a much larger deletion, and they have severe obesity and developmental delay, and the reason they have that is that this larger chunk takes out a region of the chromosome that's known to be involved in autism and developmental delay; so the children with the small deletion have just severe obesity; the children with the larger deletion have severe obesity and developmental delay and autism. So the question is, what are the genes in that deletion? Is there a gene in there that's controlling weight, and when it's missing, it's causing obesity?—and actually there is a gene in that region that is quite important in leptin and insulin signalling. And I won't go through all the details, but the reason we know this gene is important, and it's called SH2B1, is that if you take the gene out in a mouse, you get a fat mouse, so that's pretty good evidence that the gene's involved in controlling weight.

Also this gene seems to control insulin signalling, so mice that are lacking this gene in their muscle develop severe insulin resistance. You could say, why is that remotely relevant?—well, it's relevant because when we study the patients in whom this deletion occurs, who have a small amount of chromosome 16 missing, they have exactly the same features as you might expect, given the mice. So these patients are severely obese with their growth charts, they have lots of fat, they eat a lot, and they have disproportionate insulin resistance, so very, very high levels of insulin, more than all of the other obesity syndromes, and that would be explained by lacking this SH2B1 gene.

I just want to show you one other little bit of new unpublished data that's about to be published in about ten days' time, which I think opens up another huge area. This is another deletion, I told you about on chromosome 16, involved with autism. Now, this is

important for two reasons: firstly, this deletion is out there, it's known about. It was first found in patients with autism and developmental delay, in about less than 1%, so it seems to be causing autism and developmental delay. But some of the patients in those papers were obese, so does this deletion somehow also contribute to obesity? So collaborating with the colleagues I've mentioned here, we've studied patients with obesity and developmental delay, who seem to have much, have a higher prevalence of this deletion, than those just with developmental delay. Is this deletion independently contributing to obesity?—and in fact it is. If we just look at people with obesity, 0.4% have this deletion compared to a very tiny number of lean people, so basically this is data that's very new, and the reason I wanted to highlight it is, because what it shows is, deleting the same bit of chromosome 16 can contribute to both autism and obesity, and this is something that certainly I've thought about for a little while. I think there are common brain pathways which can be affected by certain genes, and can cause autism in some people and obesity in others, and what we need to do is try and work out what are the genes that are causing those problems.

I'm just going to finish up here, just by saying that really we started off looking, taking genetics and using genetics to study patients with a severe disease, severe obesity, find new genes, find new pathways. Actually what we're finding is that some of these genes are going to be important for common obesity. You will have heard about genome-wide scans. Genome-wide scans are telling us about common variation that's associated with diseases like diabetes, hypertension, asthma.

However, we're only finding a few common variants, and that's because even in common obesity, regular obesity, it's going to be rare variants that are causing the disease. So we're using lots of different approaches, some of which I've mentioned today, and one of which I've highlighted here in blue is really the latest technology which is 'whole exome sequencing', which basically means, rather than checking one gene at a time, you basically check them all, and some people are talking about this as personalised medicine. Basically, you could find all the different variants in a person, and try and link them to their risk of disease, so it does sound a bit sort of sci-fi, I suppose, but I think this is really where things are going, is that it will give us the ability to find new genes that cause diseases, and certainly when it comes to obesity, we think there are going to be lots more genes to find. So I'm really going to finish there, and thank my collaborators, in particular the patients and their families, and really, I've got time for some questions. Thank you very much.

Professor Atkinson:

Thank you very much for bringing us right up-to-date with things that are just about to emerge in the press. Who's going to start the questions?

Audience member:

Could I just ask, at birth heel-prick test hypothyroidism, were these children positive/negative, at birth?

Dr Farooq:

Normal thyroid function at birth.

Audience member:

And they developed it?

Dr Farooq:

Yes, so they developed quite mild central hypothyroidism.

Professor Patrick Bell:

Do you think, given the complexities of the central interactions that exist, do you think an approach to treatment based on centrally acting drugs, and we've had another one bite the dust, is sort of doomed to failure?—and we really have to go after the genes? Is that part of the message (?? 0:41:04)?

Dr Farooq:

It's a really difficult issue here, so what is clear is that, if we want to find drugs to suit patients particularly with severe obesity, it's really the brain pathways that we need to target, but I think as we've learnt from the drugs that keep biting the dust, is that these need to be cleaner drugs. They need to be designed at specific molecules. The drug, obviously sibutramine, that you're referring to, had widespread effects on serotonin and noradrenaline systems, so I think we need much more specific targets that do the particular jobs. Also I suspect, given how heterogeneous obesity is, like with hypertension, we're probably going to need to have different categories of drugs, so just as we're now familiar with the fact that we might need a beta blocker, a calcium channel blocker, an ACE inhibitor, I suspect we're going to need different types of drugs to treat complex obesity, drugs that target different pathways, some perhaps in the brain, some perhaps targeting the gut hormones.

Professor Atkinson:

Do you want to comment at all on the role of bariatric surgery, and what it does to these different pathways?

Dr Farooq:

So yeah, I mean bariatric surgery is the only currently really effective long-term treatment for severe obesity. In terms of what bariatric surgery does, again everyone has assumed that it's very simple and it's about shrinking the stomach, causing malabsorption, but in fact it's certainly not as simple as that. We don't actually know why bariatric surgery is properly effective. There's a lot of studies going on at the moment to try and address that. What we do know is that the effects occur very quickly, they occur before people

leave hospital. They can come off their anti-diabetic drugs within a couple of days before they've lost weight, and it's probably effect on gut hormones and on the brain, so we don't actually know why it's effective, but it is effective in some people. Whether it's effective in these patients, anecdotally many of them don't respond very well, but we've not studied that formally just yet.

Audience member:

With the children that are normal birth weight, when do they start gaining weight?—it must be very difficult (?? 0:43:12) children, very difficult to (?? 0:43:16) .

Dr Farooq:

Absolutely, so the children, it's interesting, they seem to gain weight and become hyperphagic after weaning, so that's interesting, and the parents clearly report that, and it's very consistent with the mice, which also take off after weaning, and it may be that something occurs around the time of weaning that affects the development of the pathways in the brain, so it's probably before weaning, certain other pathways are important; after weaning, your leptin pathway becomes important, and then if you don't have leptin, then your appetite takes off, and there are studies in animals that show that those pathways don't actually connect until after weaning, so it's as if there seems to be a timing issue there, and yes, it is incredibly difficult, because this drive to eat is so severe, to control that.

Professor Peter Maxwell:

Thank you very much for an excellent lecture. I'm still intrigued that you've got a very large cohort of severely obese children, and the genome-wide association approach hasn't found very much common variants accounting for that so far, but it's fantastic success you've had, the mono-genetic disorders are only about 7%, I think you had, one of the slides?—so do you think that the whole exome approach that you're taking will find the bulk of the missing variation, is it copy number variation, or is it something in the epigenome?

Dr Farooq:

Yeah, that's the million dollar question really! Common variants in common obesity do not contribute very much. We're doing a genome-wide scan right now on the sub-group of our patients who are UK white Caucasian, and are finding that the common variants that are out there are much more prevalent in these children. So these children are enriched for the common variants that cause obesity, but that's not the major driver for their obesity, so we may find some more common variants. I think the rest of the genetic, the inheritability in these patients, is due to rare variants, which will be a combination of more mutations in other genes that we have yet to find, some copy number variants, some epigenetic effects which I think may be true, so I think there's a lot of different types of genetic variation. It's a little bit of guesswork as to how much of each, but I think the whole exome sequencing will certainly give us some of that.

Professor David Hadden:

It's very nice of you to come over, thank you for coming. Do you think some of these conditions that you're describing could, I'm thinking particularly of the brain disorders, in, was it, the nucleus accumbens, it sounds like the cucumber nucleus!—but do you think that it's possible to get an acquired disorder of that?—and the reason I ask that is, I remember in our old metabolic unit there was a flight of stairs, and one time we had a girl aged twelve or so, who was very, very overweight, and she took it upon herself to stand at the top of the stairs as the visitors were coming, with a tear in her eye, and she would beg them to give her a chocolate or whatever it was, and of course they all did, because they were friendly people, but she had had tuberculous meningitis, and we always put that down, I put it down, that in some way she got brain damage, I don't know what … but clearly it was the nucleus accumbens, is that possible?

Dr Farooq:

Yes, I think it is possible. It hasn't been shown, but we do know that, for example, tumours of the hypothalamus will cause that hyperphagia and that drive to eat, and there are some reports of tumours in the amygdala also causing abnormal eating behaviour, so certainly in terms of tumours, there is evidence for disruption of these pathways by tumours, and presumably as with many other things, autoimmune disease, post-infective … yes, you're right, there may well be acquired forms, and even degenerative forms, I guess, of these pathways.

Dr John Logan:

It's very interesting to hear that all you need is the equivalent of half a slice of cucumber a day for 30 years, and you're suddenly ten kilogrammes overweight. Now, the epidemic of obesity simply can't then be due to more food being available, or cheaper food being available. Is it due to us actually going in cars and using transport and not walking, and therefore not using up those seven calories a day?

Dr Farooq:

So I mean, it is astonishing just how little it takes, to explain the shift in the mean BMI of the population. Obviously for people with severe obesity, there's a greater positive energy balance, and it probably is driven by both things, so both are reduced energy expenditure by cars and less activity, and a modest increase in intake, and the increase in intake is very easy to do, because food is cheaper and more readily available, and the food we eat is more energy-dense,

there're more calories in every gram of food that we eat, so through a combination of those things, it's very easy to exceed that kind of figure, but really on a global scale, a change in physical activity, and going from rural work to urbanised living, is one of the major drivers. Of course, usually where that occurs, also there's a change in the quality and the availability of food.

Dr Stanley Hawkins:

I know there's been a lot of interest in satiety and what drives that, and what encourages us to stop eating when we feel that we have had enough to eat, and there's a lot of variability in that, and the mechanisms are complex. Would you like to enlighten us a bit about that, please?

Dr Farooq:

The thinking is really, that satiety is quite a lot to do with various gut hormones that are released, and also neural signals from the gut in relation to a meal; but also that those satiety signals are potentiated by hormones such as leptin. So for example, the patients with leptin deficiency will have a drive to eat, they'll be very hungry and want food, but also it takes, they eat more before they feel full. So those things are very tightly coupled, and the brain stem is obviously very key to the signal for satiety in ending a meal, so they're very tightly coupled. Gut hormones and signals from the vagus are very key to the satiety signal, but also the hypothalamic pathways modulate how that signal is received. So yes, absolutely, I mean there are lots of other things that modules satiety, and one of them is the content of the food, so I won't show some other data, but you'll be familiar with the fact that people often refer to protein as being highly satiating, so the Atkins Diet was supposed to be successful because people eat half a cow, that makes them feel more full, and then they don't eat other things. So certain macronutrients, fibre and volume also clearly influence satiety signals, but it's all really about how they're integrated in the brain.

Dr Logan:

I'll just ask another question, it's an old rhyme, which I don't remember in full, but it's something to the effect that you'd be better to breakfast like a prince, and do something at lunch, like something else, and then dine like a pauper, so implying that the more food you have in the morning, the better it would be for you, and of course we eat the other way around. Is there any evidence that your intake variation through the day makes any difference to well-being or health?

Dr Farooq:

There's no direct evidence for that. What there is evidence for is that people who skip breakfast are more likely to consume a total increase in calories. So if you skip breakfast, because you're then very hungry, you're more likely to seek out, I guess, more rewarding foods, more calorie-dense foods, and this kind of cross-sectional epidemiological evidence that people, children and adults, who don't eat breakfast are more likely to be overweight or obese. So that's epidemiological evidence, it's not necessarily causality, but there certainly is epidemiological evidence to support that, thus the advice that everyone should have breakfast, and clearly what you eat at breakfast does affect how long you remain satiated, and then therefore whether you're likely to eat in the middle of the morning, for example.

Audience member:

I'm just wondering how your children have done in the long term with leptin replacement and if you had problems with the actual treatment over the years?

Dr Farooq:

Thankfully they've done very well actually, so it's been incredibly safe and well tolerated thankfully. What we have had problems with is antibody formation. So again, as with many other endocrine disorders, because these children have never seen native leptin, they have none, when we give them leptin there's an immunogenic response, and about six weeks after giving leptin, they form antibodies. Initially those antibodies are not neutralising, but after a while they become neutralising and they stop the effect of leptin, then we increase the dose, and once again we can regain efficacy, so generally the antibodies haven't prevented us from treating the patients, and they've all done very well.

One of the patients, the very first one we treated, did become intermittently compliant as a teenager, so at the age of 15/16, started missing some doses, and then actually became tolerant to leptin, so however much leptin I gave her, she'd not lose weight. So then again we did, as you would do with many other drugs, I gave her a drug holiday, it was a bit of a risk. I took the leptin off completely. It took a while, but then she relapsed, and she became completely deficient, became severely obese again, and then I reintroduced the leptin, and then actually she just brought her weight right down again. So thankfully they're all being treated and they're all doing very well. The oldest patient is now 21, at university and studying, and weighs 66 kilos, so thankfully it's been well tolerated, and they've all gone through puberty at the appropriate stage.

Professor Atkinson:

So I'm going to take a bit of a chairman's privilege, just to ask you to put on your forecasting hat, and tell us about obesity in the general population in 20 years' time, and what do you think members of the Ulster Medical Society might be doing about it then?—and you can't give a wrong answer!—unless you promise to come back in 20 years, and we get out

some kind of minutes! What ways do you think it will go?

Dr Farooq:

I think in terms of the trends for obesity, so firstly, there was a lot of scaremongering suggesting that, oh my goodness, already 20% of the population are obese, and if we're not careful, 50 or 60%—that's not the case. The epidemiological data is beginning to be, slowly come out in the media, suggest that those people who develop obesity are those who are genetically susceptible to develop obesity, so it's likely that a certain proportion of the population will remain as severely obese. I don't think 60—80% of people will be obese, so that's one thing. What I think will have changed, and I hope that we as physicians can be key to that, is that our attitude to obese patients will change, because I think we need to start taking obesity seriously, and thinking about it as an endocrine metabolic disorder worthy of serious consideration, and have some compassion towards our patients, so I would hope that the physicians of the future will have a different attitude to obesity than perhaps has been the case before. I would hope that if our work is, ours and the work of many others, is successful, we'll have a greater understanding of how we might treat obesity, with appropriate interventions in appropriate patients. We'll probably have some interventions which will help patients lose weight, then once they've lost weight, we know the patients regain the weight when you stop the drug. Well, that's the same for blood pressure—if you treat hypertension and then you take away a drug, the blood pressure goes up. It's a physiological response. I suspect we will try and have treatments that will help people maintain weight loss. So I think we'll hopefully have a more intelligent way of approaching obesity, hopefully be a bit more compassionate towards our patients, but I think we'll still have a problem with obesity.

Professor Atkinson:

Thank you very much.