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'*Insulin Resistance and the Clinician*'
Professor Patrick Bell
Royal Victoria Hospital

Professor Brew Atkinson:

Good evening ladies and gentlemen, and a happy new year to you from myself and from the council of the Ulster Medical Society. It's great to see such a good turnout tonight, but it's really no surprise to see such a good turnout tonight, because we have a very distinguished speaker from our own medical community, and I embarrassed Patrick somewhat, I think, on Monday at the physicians' meeting in the Royal, when I read out the little blurb about him, and I'm just going to do that again as a way of introduction, but just to say that he's such a good friend, he's been such a good colleague to me over the years that we've worked together, that it's lovely for me as your president to have been able to ask Patrick to come and speak to the Society tonight, and I know that this is going to be one of the highlights of the year.

Professor Patrick Bell is one of the most distinguished physicians in Northern Ireland, training here and at the Mayo Clinic in diabetes and endocrinology. He's had a long term research interest in carbohydrate metabolism, and is internationally recognised, and I really mean that, for his work on insulin resistance, and he's going to discuss the relevance of that insulin resistance to the clinician tonight, and we're all really looking forward to that, so I'll ask Patrick to come and give our first talk of the new year—Patrick.

Professor Patrick Bell:

Well, thanks very much indeed, Mr President, Brew, for that introduction. You're a fairly intimidating audience. I see some very senior figures in the profession who've taught me a lot over the years, some contemporaries and peers with whom it's been a great pleasure to work, but it's probably actually the young members in the audience whom I'm particularly pleased who have come along, because they're the ones that are continuing to teach me a lot about medicine as I continue to practise it.

Now, what I want to do this evening is talk a little bit about insulin resistance and the clinician, and try to persuade you that a knowledge of insulin resistance is relevant to all of you, whatever area of medicine that you're practising in.

Now, I've divided the talk into these headings. I'm going to say a little bit about the development of the concept of insulin resistance and its definition, say something about assessment and classification, and then a few words about Type 1 and Type 2 diabetes, disorders in which insulin resistance is very important, and then finally something about the so-called insulin resistance or metabolic syndrome.

Now, in this part of the world, we're quite good at resisting things. This is a wonderful photograph of Edward Carson, addressing a home rule rally; I guess it's about 1912 or 1913. The bit that I really like about this photograph is, I wonder what these other chaps are actually thinking? If you look at their expressions, I'm not entirely convinced that they're really very impressed by the slick Dublin lawyer. I think they could be somewhat dissident in their particular views at that time, and it was just about ten years or so after that photograph was taken, that this photograph was taken. It shows the surgeon, Banting, on the left, the medical student, Best, on the right, and one of the dogs on top of the medical school building in Toronto, where they first identified and isolated insulin and gave it to human subjects. In the next 30 years or so, the actions of insulin were fairly well worked out. We know that it acts on muscle to promote glucose uptake and glycogen synthesis. It acts on the liver to promote glycogen storage, and it inhibits new glucose formation, and it also acts on fat to increase fat storage, and it prevents fat breakdown or lipolysis.

The sort of definition of insulin resistance that I had, when I started in the metabolic unit in old ward 25, almost exactly 30 years ago, was a definition relating to Type 1 diabetes, that it was a disorder in which there was a requirement of 200 or more units of insulin to control hyperglycaemia, and to prevent ketosis. But if I'd been a little bit better read, I would have known that there were others who had already taken a much more subtle look at insulin resistance, and this is a slide from the work by Himsworth, which was carried out in the 1930s, and Himsworth administered glucose and insulin infusions to patients with diabetes, and he found, he divided the responses that they had into two typical sorts. There was a Type 1 response, where the glucose increased. These were basically diabetic patients who were insulin-resistant, and they had what we would call, slightly confusingly in relation to this, Type 2 diabetes, and there were others in whom the glucose concentration remained steady. They were relatively insulin-sensitive, and they are what we would call today Type 1 patients. And of course, anybody who was brought up in Belfast medicine, through the '60s into the 1970s, would remember the work of John Vallance-Owen, who lectured us and told us that the cause of Type 2 diabetes, or non-insulin-dependent diabetes, as it was then called, was the presence in a serum of something called synalbumin which acted as an insulin antagonist.

Now, others weren't really able to replicate VO's work, but it did serve at least to keep the concept of insulin resistance in the public eye, but what really put insulin resistance onto the map was the 1988 Lilly lecture, that Gerald Reaven delivered to the American Diabetes Association, and he put forward the idea of a syndrome, which he called syndrome X, we tend to call it the insulin resistance syndrome or metabolic syndrome, which was characterised by insulin resistance, but in which there were a number of other associated features which are listed here: glucose

intolerance or diabetes, hyperinsulinaemia, increased VLDL triglyceride, reduced HDL cholesterol, and hypertension. And of course, Reaven and others argued that the fact that some of these abnormalities, diabetes, abnormal lipids and hypertension, were themselves associated with a tendency to increased vascular disease, he argued that there was something special about this association, that insulin resistance might be an underlying abnormality causing these other features, and in essence causing the vascular disease that's so prevalent in western societies today.

It was possible to articulate this view on an insulin resistance syndrome over 20 years ago, at a time when we didn't have a very clear idea of how insulin worked at a cellular level, and it was possible to show a slide like this, with the lecturer saying, after years of intensive research, we finally have a clear picture of insulin action, and at the bottom on the right this chap saying, a long way since the black box concept. But if you open a textbook of diabetes today, you will get this type of slide, and it's one of only a couple of complicated slides that I'll inflict on you this evening, and for the purposes of the points I'm making tonight, we only need to be aware of the general outline of what insulin's doing, but basically it's a peptide hormone which binds onto a cell surface receptor, it activates that receptor, there's a process of phosphorylation, there's interaction with an insulin receptor substrate, and from it, two main streams of activity, one over here on the right, the MAP kinase pathway, which underpins the mitogenic and growth-promoting effects of insulin, and over here a PI 3-kinase pathway, which underpins many of the metabolic effects of insulin and the effect on GLUT4 transporters with regard to glucose transport are illustrated here, for example.

But really, the definition that you need to have to get through the rest of the evening, as far as insulin resistance is concerned, is this one—it's rather simple, it's a state in which normal concentrations of insulin produce less than normal biological responses. When we use this term, we're usually thinking particularly of carbohydrate metabolism, but it could equally apply to fat metabolism and to protein metabolism, and it's worth remembering that resistance to each of those pathways doesn't always go together.

Okay, so a few words next about assessment and classification. This is a Zucker fatty rat in the foreground. It's obese, and it's insulin-resistant. As with rats, so, on average with human beings. These are data from the European Group on Insulin Resistance, there are Belfast patients included here, but the point is that the lean subjects, this curve here in blue, tend to be more insulin-sensitive, less insulin-resistant, than the obese subjects, that's the yellow curve, but the point is that it's only on average. If you take an individual patient who happens to be obese, it's not possible to say with any certainty that they're necessarily particularly insulin-resistant—they are more insulin-resistant on average. And even if you apply a certain extra complexity by taking say abdominal obesity, measuring waist/hip ratio, which is a feature that's associated with insulin resistance, even that doesn't give you clear discrimination. So you might wonder, are there other ways that we can assess patients clinically in order to detect insulin resistance? Well, there are one or two, but they tend to be associated with severe forms of insulin resistance, many of them rare inherited syndromes, so they don't, we don't encounter these very frequently in routine clinical practice. Probably one of the commoner features is this, acanthosis nigricans. This is the black, velvety pigmentation which affects the skin creases here in the neck and under the arm, probably a manifestation of the growth-promoting effects of insulin. Ovarian, hyper-androgenism—this is where high insulin concentrations, which are secondary to tissue insulin resistance, stimulate the ovary, which is still sensitive, to produce androgens, can cause menstrual upset and so on. But these, as I've said, tend to be associated with more severe forms of insulin resistance, and are not particularly useful in routine practice.

So we end up having to rely on various biochemical measurements to confirm insulin resistance, and perhaps at its simplest, we could measure a fasting serum insulin, and a plasma glucose, and broadly speaking the higher the insulin-to-glucose ratio, the more insulin resistant that patient would be. But of course that is dependent on the patient having a normally functioning pancreas to secrete insulin, and it would not therefore be relevant in a patient with for example Type 1 diabetes or Type 2 diabetes of any degree of severity.

One can try to get round this by doing glucose and insulin tolerance tests, looking at the response of glucose to insulin or insulin to glucose. The problem here is that you tend to have two things moving at the same time. You can try to compensate for that by various mathematical models. We've not tended to do that in Belfast, and we've tended to stick with the glucose clamp technique, which is a very time-consuming and labour-intensive method, as one or two in the audience can attest, but it is the accepted gold standard. And this just shows the set up that we have for glucose clamping in the Royal Victoria Hospital in Belfast. We've, Kieran Innes, over here, our long-serving and long-suffering technician who's been with us now for over 20 years, he's keeping an eye on a pump here which is delivering insulin being infused at a constant rate into the patient. One of our research fellows, Ian Wallace here, is taking a blood sample. He's going to do this every five minutes, take the blood sample over to the bedside glucose analyser, determine plasma glucose, and based on change in plasma glucose, he will adjust a glucose infusion in order to maintain a constant level of glycaemia in the patient.

It's maybe easier to see in a graphical way, these are the insulin concentrations that are arrived at after

a constant infusion of insulin. These are the amounts of glucose that need to be infused, increasing and then reaching a steady state, in order to maintain a constant glucose concentration. And at its simplest, the glucose clamp technique involves measuring how much glucose needs to be infused in order to maintain a constant concentration of glucose. In this particular experiment that Hamish Courtney did, he found that the anti-hypertensive agent, doxazosin, didn't cause any change in insulin sensitivity compared to placebo. Now, one can put on top of that various complexities, isotope dilution techniques to measure liver glucose production and so on, but that in essence is the glucose clamp technique.

Now, this little hut appeared, it's a slide that we've shown a few times before, at the boundary of the car park in the Royal, and for a brief period, we thought that perhaps management were paying some attention to what it was that we were doing. You can classify insulin resistance in various ways. Perhaps this is a slightly pedantic way, by mechanism—for example, you can have the very rare situation where an insulin molecule is produced which is abnormal, and which the body's insulin receptors don't see, and that obviously would cause resistance to hormone action, but that's very rare. Failure of transport of insulin to target tissue—this was topical and fashionable a few years ago, but has fallen out of favour, the idea that maybe blood supply wasn't opening up normally to allow insulin delivery to certain tissues, and most of the action and interest these days centres around binding of insulin to its receptor, activation of the receptor, and various things that happen downstream in the cell.

Now, this is an unofficial and irregular and unorthodox classification of insulin resistance which I have in my mind, because it gets to what I want really to say. On the top left, there are some rare conditions where insulin resistance, often very severe insulin resistance, is a feature, but none of us see these in routine clinical practice other than very rarely. Bottom left, I've put some conditions which are more common, which we would see—there's liver disease, renal disease, certain endocrine diseases like acromegaly; insulin resistance is a feature, but it perhaps doesn't figure in our clinical consideration, except that I really need to move liver disease across to the right now, because with all the interest about non-alcoholic fatty disease, and its association with liver disease, it should probably come in this group that I've put in bigger print, where these are common conditions, and where I think insulin resistance is relevant to clinical practice—obesity, diabetes, hypertension, polycystic ovarian syndrome, which we won't have time to talk about, and the metabolic syndrome.

I want to move on and talk a little bit about Type 1 diabetes. Now this, as I've said, is the quintessential insulin-sensitive form of diabetes, but insulin resistance is important in several respects. I've listed some of these here, and first would say a word or two about ketoacidosis. Now, ketoacidosis is precipitated by insulin deficiency, but once it is established, it is a condition of insulin resistance. These are data that confirm this from a few years ago, a measurement of liver glucose production in ketoacidosis, difficult experiments, acutely ill patients. They've a big increase in liver glucose production compared to some non-diabetic control subjects, and there was a failure of that glucose production to be suppressed by insulin, whereas in the non-diabetic controls, insulin quite promptly suppressed glucose production.

This is only the second really complicated slide, and there's only a couple of points that I want to draw your attention to, and it's by way of explaining the insulin resistance that is a feature of ketoacidosis. One mechanism is the presence of high concentrations of various hormones, such as glucagon, cortisol, growth hormone, and catecholamines. The other is through the presence of high concentrations of free fatty acids, increased lipolysis in fat tissue, increased release of free fatty acids, which themselves probably cause insulin resistance, and also because there is increased fat metabolism, their carbohydrate glucose is not transported into cells, fat is metabolised preferentially, there is an excessive formation of ketone bodies which produce ketosis and acidosis, and that ketosis and acidosis also causes insulin resistance.

Now, this was the knowledge that Ivan Wiggam, when he was working with us over ten years ago, brought to a study of ketoacidosis, and what Ivan did was, he took some acutely ill patients with ketoacidosis. They received a conventional treatment initially, 20 units of insulin, followed by five units every hour, fluid rehydration; brought blood glucose down to ten millimoles, and in the conventional arm of the study, they then went onto a dextrose insulin infusion with a little bit of insulin, maybe about one or two units per hour, until the patients were ready to eat again and get subcutaneous insulin. But reasoning that it takes rather longer to clear the ketosis and acidosis in ketoacidosis than it does to bring glucose down to normal, and that insulin resistance was likely to persist after blood glucose was brought down to normal, Ivan randomised half his patients to an extended regimen, where they received five units of insulin per hour, with the end point of achieving normal ketone body levels, and resolving the acidosis, using the insulin to overcome the residual insulin resistance. And this just shows us, this slide, that in the extended insulin regimen, he did achieve much faster resolution of ketosis, and this is a fall in plasma 3-hydroxybutyrate, the main prevalent ketone body in ketoacidosis; there was a tendency for faster resolution of acidosis, and although we didn't have a hard endpoint like shorter length of stay, or in a small study, we wouldn't have had a mortality difference, we do believe that this approach, taking account of insulin resistance, managing it with higher doses of insulin to clear ketones, does allow a smoother transition into regular eating and subcutaneous insulin. I have it on

good authority that the Wiggam modification of low-dose insulin is probably going to make its way into the new national guidelines which are being put together at the moment, so well done Ivan.

A couple of other situations of insulin resistance in Type 1 diabetes; pregnancy—we know that during the second and third trimester of pregnancy, a big increase in insulin dose needs to be made. People need to be aware of this, to some extent it needs to be anticipated. Adolescence is also a condition where there is insulin resistance, and it's probably one feature which contributes to the instability that is so common in our young Type 1 patients, although in truth, it's probably various failures of self-management that lead to the frequent admissions that we often seen.

Exercise, in a well-insulinised patient, obviously exercise will pull down blood glucose, but exercise also induces a state of increased insulin sensitivity in the short term, and the classic situation which arises is where the patient with Type 1 diabetes exercises through the evening, comes home, checks blood glucose, finds that it's normal or maybe slightly increased; goes to bed and has a hypoglycaemic episode through the night because of the increased muscle insulin sensitivity, and that's an important thing that patients and their carers should be aware of, so that preventive action can be taken.

The final one in this little section is the issue of hypoglycaemia, and the insulin resistance that is induced by hypoglycaemia. Various counter-regulatory hormones probably contribute, growth hormone, glucagon, catecholamines again and cortisol. This has been studied in quite some detail, this is one particular study that looked at this, a complex protocol, but if you take this placebo situation, here's a measure of insulin sensitivity before patients were hypoglycaemic. Here's the measure after they were made hypoglycaemic; in other words, they were made insulin-resistant. If you give them propranolol during the same experiment, you can eliminate the insulin resistance, implying that it is a beta-adrenergic stimulation that's one of the things that's causing this insulin resistance that follows hypoglycaemia.

If you give somatostatin to cut out cortisol, growth hormone and glucagon, you get a partial reduction in this post-hypoglycaemic insulin resistance. But again this is important, because the insulin resistance induced by hypoglycaemia contributes to glucose variability in Type 1 diabetes, because that insulin resistance is going to tend to generate hyperglycaemia following hypoglycaemia, and you can get into a cycle of variability that can be difficult to break out of.

Okay, a few words about Type 2 diabetes. Now as I said at the beginning, this is the quintessential insulin resistant form of diabetes, and insulin resistance is very relevant in a number of respects, in respect of the aetiology of the condition, its prevention and also its treatment.

This is a diagram which illustrates the aetiology and pathogenesis of Type 2 diabetes. We know that there are various genetic factors. We know that there are various environmental factors involved in the aetiology. We know that if a patient has Type 2 diabetes, they are insulin-resistant and they do have a deficiency of insulin secretion, and I don't want tonight to get involved in this argument about whether insulin resistance, or a failure of insulin secretion, is more important in the genesis of Type 2 diabetes—probably both play a part. What I think is maybe more relevant is to suggest to you that, if we can reduce insulin resistance, I think we can help to prevent Type 2 diabetes.

This is the Finnish diabetes study group findings, and there are a couple of other studies which are very similar. It shows us that if we take some patients with impaired glucose tolerance—not diabetes, impaired glucose tolerance, a higher than normal chance of developing diabetes—and if we randomise them to two groups, one a control group, and another to an intervention which involved quite aggressive dietary advice and exercise programme and so on, you can see that those in the intervention group were much more likely to survive without diabetes than the control group.

Now, insulin resistance wasn't measured directly in this study, but it's reasonable, I think, to assume, we know that diet modification and weight loss and exercise can both reduce insulin resistance, and it does seem likely that this is the mechanism of action that is at play in this prevention of Type 2 diabetes.

Now, whether we can introduce this to east Belfast, I think this is, I'm not sure. Some people would wonder, would it be easier just to give them the drugs? The Finnish prevention study did have a metformin arm. Metformin also prevented Type 2 diabetes, but it was rather less effective than the lifestyle intervention. Another drug that's been used is rosiglitazone. This is from the DREAM study. This was one of these large pharmaceutically-sponsored studies, taking patients with impaired glucose tolerance or impaired fasting glucose, a high risk of Type 2 diabetes, randomising them to placebo or rosiglitazone, and as you can see, those who are on rosiglitazone, that's the thiazolidinedione and insulin sensitiser, were much less likely to develop diabetes over the four years of this study.

Drug use to prevent Type 2 diabetes hasn't really caught on. I think partly there's an expense argument, although metformin's a cheap drug; partly it's because the lifestyle intervention in these studies has been shown to be at least as effective, if not more effective. I suspect there's a little unofficial use of these agents in this regard here and in North America, but that would not be accepted practice.

What about treatment in Type 2 diabetes? Is insulin resistance something that we should take into account when we consider treating Type 2 diabetes?—I think it is a relevant consideration. This is a

famous slide that most of you will know, from the United Kingdom prospective diabetes study. It included patients from the Royal Victoria and Belfast City hospitals, and it's a familiar pattern of improvement in blood glucose control initially, but as the years went by, a tendency for control to drift off, irrespective of the drug or preparation that was used, whether insulin, whether a sulphonylurea or whether metformin, there was a tendency for control to deteriorate over the years. And it's easy to set out, based on this type of knowledge, a slide like this outlining some of the principles of pharmacological management in Type 2 diabetes. As I've said, it's a progressive disorder with a tendency for blood glucose to increase, therefore escalation in dose and number of therapies is required, which should logically relate to the mechanism of drug action, so that we should use agents which are complementary and not two agents that work in exactly the same way, and of course we shouldn't forget drugs to control other cardiovascular risk factors.

This is a slide that illustrates what we often do. We often start with diet and exercise. We bring down haemoglobin A1C, which is our measure of overall diabetes control, but we don't quite reach target, let's say it's a haemoglobin A1C of 7%, and things over the years drift, or over the months perhaps, drift off a little. A drug is added, things improve and then drift up. The drug dose is increased, things improve and then drift off; another drug is added, and so on, and then insulin, and so on and so forth, and in essence what we do is, we sort of oscillate about a point of failure. And of course what the experts would have us do, and what we know we should do, but it's hard to do, is we should go rather more aggressively earlier on, get to target and stay there.

In order to do this, the list of drugs, and I realise it's always very hard to see the bottom of the slides in this lecture theatre, but the new ones are towards the bottom, the top ones are the ones you'll be familiar with, but towards the bottom, you get to things like thiazolidinediones, which came in about 10 or 12 years ago, DPP-4 inhibitors, GLP-1 agonists, so we've a long list of things at our disposal in the management of Type 2 diabetes. Two of them act, that's metformin and the thiazolidinediones, or glitazones, act as insulin-sensitisers.

Now, one point about insulin resistance and drug treatment in Type 2 diabetes is this—that irrespective, more or less, of the agent that you use—if you achieve a sustained improvement in plasma glucose control, you will achieve an improvement in insulin sensitivity. It's something to do with reducing hyperglycaemia, and reducing the toxic effect of glucose on the tissues that are sensitive to insulin. And this is just an illustration of a study I did years ago with [?] Firth and Bob Rizza. It's an insulin dose response curve looking at the glucose utilisation against insulin concentration. Blue shows the normal range, the red, which I suspect is pretty hard to see, shows the response in Type 2 diabetic patients in moderately poor control. They were insulin resistant, the curve was shifted to the right. They entered into a crossover study with insulin or a sulphonylurea, and it's probably appropriate that the yellow and the green almost look the same, because they are the same, they're overlapping, both improved insulin resistance to the same extent. These are agents which are not supposed to have a direct effect on insulin sensitivity, they don't work that way, but by virtue of an improvement in blood glucose control and improvement in insulin sensitivity results. So it's worth bearing that in mind, but the question that people ask is if we treated Type 2 diabetes with insulin sensitisers, might we in some way alter the natural history of the disease?—and one big study that addresses this is the ADOPT study. It's another of these pharmaceutically-sponsored studies, and again the patients were randomised to different agents, but the pattern is rather similar to that which you saw earlier, initial improvement, but then over the four or five years of the study, there was a tendency for overall control to drift off. But at the end of the study, the drift off was rather greater with the sulphonylurea, glycuride, than it was with the insulin sensitiser, rosiglitazone. Now, some concern, by the time they got to four years, there weren't so many patients left on the study. We haven't heard anything further from this study about what the effects were down the line, but I think these are tantalising results which do raise the question of whether an approach on insulin resistance in Type 2 diabetes might have some beneficial effect long term. Having said that, I don't think this one study has been sufficient to alter my practice to a significant extent, still tend to stick with metformin as the first agent, of course, it is an insulin sensitiser, and then sulphonylurea second, but it's nice to have the alternatives, like thiazolidinediones available.

The last little bit is on the insulin resistance or metabolic syndrome. And I've talked already about the development of this concept, the promotion by Gerald Reaven, and of course it has caught on to a remarkable extent, and people well outside the areas of diabetes and metabolism know things about the metabolic syndrome, even if they don't know too much about other aspects of diabetes or endocrinology, and that's a good thing. Making sense of the pathophysiology is not particularly straightforward. Unfortunately there isn't a neat underlying metabolic abnormality or underlying genetic abnormality that can explain the insulin resistance, and explain the association with hyperlipidemia, high blood pressure, and can explain the high incidence of vascular disease, so it's not neat in that way. And just to show you a—not complicated but probably confusing slide—this is something called factor analysis, not able to get down to pathophysiology, people have done associations of all the different features. As some of you know, there are quite a few other features have been pulled into the metabolic syndrome label, and they've

grouped all these together to see if that would result in an understanding, and I think the answer is that it hasn't really. It's resulted in them grouping into, a lot of things into three large groups, but it really doesn't explain, I think, anything very much else. So I'll move on from that, and mention something about the definition of this syndrome and epidemiology, and our failure to explain it easily in pathophysiological terms hasn't stopped us defining it and describing it epidemiologically.

Here are the definitions, at least three of them that we use, modified World Health Organisation, the National Cholesterol Education Programme in the US, and the International Diabetes Federation. Only one of them actually has a direct measurement of insulin resistance. They're all rather similar, so that for example, the IDF definition says that you have to have central obesity, an increased waist/hip ratio, plus two of four other features, and the four other features are a slightly raised fasting plasma glucose, slightly raised blood pressure, slightly raised triglyceride, and a low HDL. And if you use some of these definitions, what you find is that the metabolic syndrome is very common. So here are North American data, subjects over the age of 50 years, using the National Cholesterol Education Programme criteria; subjects over here on the left with normal fasting glucose, about 26% of them have the metabolic syndrome; whereas over on the right, if they have diabetes, nearly all of them have the metabolic syndrome. The percentages with different definitions vary a little bit, and in Europe the figures would be slightly lower, presumably related to slightly less obesity, but you can see it's very common.

But what does it really mean? Is it of any significance?—and I think in trying to answer this question, one can ask a series of other questions, such as, does this insulin resistance syndrome predict the development of Type 2 diabetes? Does it predict the development of cardiovascular disease? Is it a better predictor than individual risk factors or other groups of risk factors? And anyway, is there a specific treatment of the condition, perhaps through modifying insulin resistance?

Well, here are some of the data. Here's the Strong Heart Study. This is a study of North American Indians aged over 50, followed up for four to eight years, those on the left who didn't have the metabolic syndrome, those on the right who did, and the incidence of diabetes in those who had the metabolic syndrome, much, much higher than those who didn't; whereas the incidence of cardiovascular disease in those with the metabolic syndrome was no different. So predictive of diabetes, but not predictive of cardiovascular disease.

On the other hand, here's another North American study—Atherosclerosis Risk in Communities Study—over 50-year-olds without cardiovascular disease or diabetes, and they used carotid intimal medial thickness as a surrogate for vascular disease, so the thickness of the intima of the carotid arteries does predict vascular disease, and that was what was used in this study. A huge number of patients. Those who had hypertension alone had about 14 microns of intimal medial thickness; those who had high triglycerides alone had about 16 microns of intimal medial thickness; those with hyperinsulinaemia, six. If you put these three features together, you've got a much greater than expected intimal medial thickness, maybe suggesting that this association of the different individual features of the metabolic syndrome, when they were occurring together, they were in some way interacting in a special way to cause this abnormality which is predictive of vascular disease.

Can we explain some of the conflicting data with regard to cardiovascular disease risk in metabolic syndrome? Well, here's a recent attempt from Scandinavia, which took, on the right-hand panel here, some patients aged 60 to 74, with and without the metabolic syndrome—no difference in cardiovascular disease mortality; whereas if you took younger patients, 40 to 59, those who didn't have the metabolic syndrome were not dying as quickly as those who had it. So maybe the idea that, if it was started at a younger age group, a greater length of time for the abnormality to act, maybe that was explaining some of the difference.

So I think we can summarise this bit and say that the insulin resistant syndrome is predictive of Type 2 diabetes. It's less clear if it predicts cardiovascular disease. It's also, and I haven't shown you any data here, it's also uncertain if it's a better predictor than individual or groups of risk factors, so that if you compare it with various risk tables like, based on the Framingham study, it doesn't do, it generally tends to do a little bit less well, and one of the obvious reasons is, if you take things like Framingham risk, it takes smoking into account. The insulin resistant syndrome does not take smoking into account at all, and yet it's perhaps the most powerful risk factor that there is for vascular disease.

Well, I suppose the pragmatic question is, would attacking insulin resistance in this condition, whatever's actually causing it, make a difference? We don't have a nice study of patients with the insulin resistant syndrome. We do have this study, this is the proactive study, the third of the large pharmaceutical studies that I've shown you tonight, using pioglitazone, one of the thiazolidinediones, an insulin sensitiser, giving it to patients with Type 2 diabetes, most of whom will have the insulin resistant syndrome, but finding that over the three years of this study, although the lines began to diverge a little bit in terms of the primary end point, they did not reach statistical significance, it was essentially a negative study.

Now, they used a rather complex composite end point, and I suspect somebody's in the drug firms head might still be rolling down the corridor. If they'd chosen a different endpoint, they might have got a different result, but this is what they chose and this is the result that they got. It didn't have any effect over-

all on that main endpoint, so we can't really say that targeting insulin resistance in the metabolic syndrome, that there is evidence specifically that it works. There's more research to come on this.

So, what about the insulin resistant syndrome overall, then?—well, I would put it to you that it has helped raise awareness of multiple vascular risk and the association with glucose metabolism. It has brought diabetologists and cardiologists closer together; it's made diabetologists become multiple risk factor interventionists; it's, I think, reminded cardiologists that there are things they can usefully do outside the cath lab. It's emphasised the need to consider intervention strategies to prevent Type 2 diabetes, although this country and most countries are woefully inadequate in what they're doing in this regard. It's not clear that it provides a better prediction of cardiovascular disease in other models, and it's not clear at the present time that identification of the syndrome is useful in treatment, so I would not suggest that the general practitioners amongst you should be making a point of labelling people with metabolic syndrome. I think the conventional risk factors that you're assessing are still the ones where there's an evidence base, and that at the present time is what you should be doing, although it is possible that could change.

So, ladies and gentlemen, I think it's time to stop. I hope that this evening, I have persuaded you that insulin resistance is something that you should be aware of, and there's maybe some bit of it that's relevant to you in your different aspects of practice. Thank you very much.

Professor Atkinson:

Thank you very much, Patrick. I'm sure you'll agree to take some questions?

Professor Bell:

Oh, yes.

Professor Atkinson:

And first of all, while you're all warming up, if I can ask you, somebody comes into the surgery tomorrow morning, and they say, well I have a bit of a family history and I really don't want to get this Type 2 diabetes, and I've read about the Finnish study, what should I actually do? How can I stop this happening, what's the best thing that I can do?

Professor Bell:

Maintain normal weight, which is easy to say, and take lots of exercise, which is easy to say. I mean, there's evidence for both of those, and also for those people who can't lose the weight, there is, I think, pretty good evidence that keeping fit is also very good, even if you're not losing the weight. Now, the real question is, how do you get people to do those things?—and I think that's a much more difficult question. The Finns were able to manage it clearly.

Professor Atkinson:

What did they actually do?—what did they get advised to do?

Professor Bell:

Well, I think they had very frequent review with the various people that were running the study. They had expert dieticians, they had expert physicians, they had expert nurses. I suspect there was some psychological and group work in the Finnish study as well, I can't just remember that precisely, but they threw a lot at it, and I don't see much evidence that we're really throwing a lot at it at the moment. I'd better stop there before I say something controversial, but if somebody asks me another relevant question, I'm sure I could say something controversial!

Audience member:

Thanks very much Patrick, a great talk. Just following on from that point, if somebody comes into the surgery, and you have to tell them that the results are back and they've got diabetes, Type 2 diabetes. It seems that the counsel, from what we should be doing at this stage, is hit them hard, and give them metformin and so on, and traditionally in general practice we've taken a much more leisurely view, and said, let's see if we can get your weight down, let's see if we can get the exercising, let's see what that does to the figures, and then bringing the metformin in and the other drugs in, but are we then controlling that disease, or effectively showing it as green [?] diet or exercise, we shouldn't throw them[?].

Professor Bell:

We certainly shouldn't. I think the difficulty is that we know that diet and exercise can be quite effective. The question, I suppose, really that you're asking is, how long do we leave it?—and I don't think we should leave it too long. I think we need to get our decision—now, some places would say, would feel that the response to diet and exercise is so poor, that they would throw the metformin almost in from the beginning anyway. Now, I still can't quite bring myself to do that, and would still like to give them maybe a couple of months to just see how they're going. The difficulty is that, at our own clinic, with a time between review appointments, is often such that we don't see them again for a while, we don't always have the good communication with primary care to make sure, you know what we're thinking, and we know what you're doing, and so on, but I would have thought we should be taking early decisions about pharmacological therapy, after a month or two.

Audience member:

Yeah, but it seems to me that this is the message coming through now, is that we should, exercise and diet are very important, but don't delay at all the drug therapy, and this is really a general practice/primary care problem. We're seeing these patients mostly, I

think, and we should be looking after them, and perhaps, I tend to agree with what you say there, I'd be reluctant to just get in with the medication right away, and the virtue of giving the diet and exercise a go is, even to demonstrate to the patient, I think, that that can, it may not, it will not be the whole answer, but to give them sight of what effect that can have.

Professor Bell:

I think there is an issue about emphasising the primacy of diet and exercise, because no matter what we do with drugs, if the patient's really bad with the diet, we're going to struggle, and I think a period on that alone emphasises our view that it is an important modality of treatment. I don't think there's going to be a problem unless glucose is very high clearly, but we're talking about patients whose glucose is not too bad. I think a month or six weeks, or maybe eight weeks, is not a great problem, but we can't really afford to let it go too long.

Professor Randal Hayes:

About this question of, how do you get people to do things, it's a story from long ago now, a chap came into the clinic in about December, he was 29 and 19 stone, and he saw one of my juniors, and he started him off on a diet, and by March he was 21 stone! These are the ones that they sent to me, so we went through the diet and I think he might have been [?] Ulster, but I started talking to him about exercise, and he said, "I can't do it, doc—a bad back, I can't do the weights".

So I tried to persuade him that wasn't the kind of exercise we were talking about, and that he should walk, maybe for 20–30 minutes four days a week, just enough to get him out of breath. I sent him off with no great expectation. In June he came back, 16 stone, and blood glucose normal and cholesterol well down, and I said to him, have you been walking?—and he said, "Walking, doctor, I'm out with the band five nights a week!"

Professor Atkinson:

No answer to that!

Professor Hayes:

If we really are …something that works, he was a big drum player, so that if we really want to do this, we have to get them out, and beating big drums.

Audience member:

I'm thinking down the line, of the two-year-old diabetic child, who will have diabetes for the rest of his life, ahead of him or her, does it help the child or the parents, or can you see a time when a test or something could be done to say, this child will suffer insulin resistance?

Professor Bell:

Well, there are a few answers to that. I don't think there's an easy test that any of us would recommend in that situation, either in non-diabetic kids to pick up diabetes, or in the diabetic kid to pick up insulin resistance. If you compare the diabetic, Type 1 diabetic patients to non-diabetic folk, they are slightly insulin-resistant on average, but I don't think any of us would do an assessment of insulin resistance in that situation, and I think it's more about an awareness of the different things that might affect insulin resistance as they go along, rather than their intrinsic insulin resistance. I'll not get into the whole debate about whether Type 1 diabetes and Type 2 diabetes are the same disease, and that there is a link of insulin resistance that brings them together, that's maybe a discussion for another evening.

Professor Atkinson:

Time for another couple of quick questions, I think.

Dr Carol Wilson:

We see a lot of diabetics, so a lot of people who go through the cath lab, I suspect up to 20% are probably diabetic, roughly, but we talk to them about their cardio disease, but occasionally get round to talking about their diabetes to them, and my feeling is that out there, patients generally don't have a great, this is perhaps too much of a generalisation, but they don't have a tremendous understanding of what diabetes is beyond blood sugar, and what it potentially means for them in the long term, and a lot of them still have the touch of diabetes when there's full-blown diabetes, and it's how we get round that education, by not wanting to scare patients, making them realise the implications of this, long term.

Professor Bell:

I think a couple of points—the touch of diabetes certainly is a bad view to have, and I think all of us have been guilty of not wanting to alarm patients at the time of diagnosis and not putting it down to them too heavy. It's a bit easier for us probably in a hospital context, because usually by the time they come up to us, the shock at least of the Type 2 diabetes is over, and it is possible for us to lay it down a bit heavier and tell them that they're going to be needing maybe, most of them will be needing insulin in six or eight years, even though this is Type 2 diabetes, so that's one point.

The other point that we have been a bit too glucose-centric, I suppose, is a fair criticism. I guess our defence is that, up until not that long ago, we didn't have such good evidence that controlling the blood pressure and controlling the lipids was so important particularly in Type 2 diabetes. We've got that evidence now, and I think in fairness I'm pretty sure whatever diabetes clinic you looked at now, the emphasis on statins and anti-hypertensives and aspirin, which is another controversy we could talk about, I think it's pretty much there.

Dr Wilson:

I'm not saying that you weren't looking after those, the patients …

Professor Bell:

Well, I'm still taking that as a slight implied criticism, Carol! because if we haven't got the patients along with us, then we're not succeeding, are we?—and that probably is the case, that we, maybe in the consultation, we just haven't got all the messages across, and there probably is, the blood glucose is maybe the thing that we probably still pay most attention to, and it's a fair point, I wouldn't disagree with what you're saying.

Audience member:

Patrick, you started off by saying, 30 years ago you saw patients who had an insulin requirement of 200 units. Do you still see those people, and if so, how would you avoid it? Do you get patients with such insulin resistance?

Professor Bell:

It's a good question, and there are one or two others in the audience who would probably have maybe a better perspective on this than I would have, but let's take out of the consideration the obese patients, of whom we're seeing so many more, either Type 1s or Type 2s, who could easily get up to 200 units of insulin without really trying, because they're very insulin-resistant, I think, because of their obesity, but I think we did see, 30 years ago, relatively normal weight Type 1 patients, and there were a few who were requiring big doses of insulin, and I think some of those, it was probably related to antibodies to pork and beef insulin, but it's certainly, in normal weight patients, it wouldn't be a common phenomenon, and I don't think that antigenicity and antibody formation is a significant problem.

Professor Atkinson:

Patrick, thank you very much.