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Dr R Ratner, Vice-President for Scientific Affairs, MedStar Research Institute, Washington, DC, USA

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Dr J McKnight, Consultant Physician, Western General Hospital, Edinburgh, Scotland. Dr M Fisher, Royal Infirmary, Glasgow, Scotland

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Dr M Strachan, Consultant in Diabetes and Endocrinology, Western General Hospital, Edinburgh, Scotland

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Male contraception – how do we do it? does it work?

Dr R Anderson, Clinical Scientist, MRC Human Reproductive Sciences Unit, University of Edinburgh, Edinburgh, Scotland

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Adrenal androgens – physiological importance of adrenal androgens – rationale for replacement – assessment of effect

Professor VKK Chatterjee, Professor of Endocrinology, Addenbrooke's Hospital, Cambridge, England

Recent Advances in Androgen Replacement – options for testosterone replacement – how does one decide if there is adequate/over replacement?

Professor FWu, Professor of Medicine and Endocrinology, University of Manchester, Manchester, England

Abstracts: Metabolic Therapies for the population Symposium 2005

ABBREVIATIONS Bone mineral density (BMD), dehydroepiandrosterone (DHEA), gonadotrophin-releasing hormone (GnRH),

SESSION I GLYCAEMIA

Chairman: Dr G Leese, Consultant Diabetologist, Ninewells Hospital, Dundee

STANLEY DAVIDSON LECTURE

Chairman: Professor N Douglas, President, Royal College of Physicians of Edinburgh, Edinburgh, Scotland

Relationship between glucose and diabetes complications – How low should we go?

Dr R Ratner, Vice-President for Scientific Affairs, MedStar Research Institute, Washington, DC, USA

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Abstract Plasma glucose levels are very closely regulated in the normal human being, with a very small degree of variation throughout the day and between days. Epidemiologic studies have provided us with categorical cutoffs of glucose to define impaired glucose tolerance and diabetes based upon likelihood of progression and development of microvascular complications, respectively. Additional epidemiologic evidence is pointing towards lower threshold for categorical disease based upon the risk of macrovascular complications. Clinical trial evidence provides us with theoretical goals of therapy primarily based upon reduction in risk of microvascular complications.

It is currently unknown whether macrovascular disease can be substantially reduced by lowering glycaemic targets beyond those attained in the DCCT or UKPDS. Were it not for the limitations of our clinical armamentarium and the risk of hypoglycaemia, there are no reasons why we should not strive for the lowest glycated haemoglobin possible. Our goals of therapy must be tempered by a real cost-benefit analysis. The benefit of lowering glycaemia beyond 7.2% A1c is the reduction in the incidence of microvascular and macrovascular complications. These reductions must be viewed as absolute risk reductions rather than relative risk reductions in order to balance the risks and costs associated with more aggressive interventions.

The development of new, more physiologic approaches to glycaemic control will reduce the potential risks of hypoglycaemia and facilitate our efforts to normalising glucose in subjects with diabetes.

Key words: Aggressive intervention, glycemic targets, microvascular complications, more physiologic approaches, real cost-benefit analysis

Achievable targets for HbA1c – applying targets to individual patients – a UK perspective

Professor D Matthews, Consultant Physician, Radcliffe Infirmary, Oxford, England

Abstract Targets for HbA1c in diabetes cannot be directly adduced from randomised clinical trials. They can only be assessed from epidemiological evidence and are generally set by consensus. The evidence is strongly in favour of the concept of the lower the HbA1c the less the risk of complications. However lowering HbA1c carries with it a finite and progressively increasing risk of hypoglycaemia. Targets therefore have to be a compromise between what is theoretically achievable and what is pragmatically possible. This compromise will differ between patients. Type 2 diabetes early in its genesis is relatively easy to control: at the other end of the spectrum Type 1 diabetes can be a therapeutic nightmare.

New therapeutic manoeuvres do allow us to aim for lower glycaemic targets than were possible ten years ago. However, the science of deciding targets is inexact. The art of negotiating glycaemic control with individual patients is still a necessary and important skill.

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Local glycaemia results – how are we doing?

Dr J McKnight, Consultant Physician, Western General Hospital, Edinburgh, Scotland. Dr M Fisher, Royal Infirmary, Glasgow, Scotland

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Abstract In the last four years, Greater Glasgow has implemented a project based upon the management of Type 2 diabetes in primary care. This is now an established service within a Managed Clinical Network. A key component has been data collection, and Scottish Care Information-Diabetes Collaboration is currently being installed in primary and secondary care centres.

Data has so far been collected through primary care, and in particular using GPASS, which is used by more than 90% of practices in Glasgow. For the calendar year 2004 there were 29,248 people with diabetes, and HbA1c was measured in 90%. The mean HbA1c was 8.1%, and 46% of people had a reading below 7.5%, 26% between 7.5–9.0%, and 19% above 9.0%. Further breakdown of data is available by type of diabetes, gender, age and BMI.

Key words: HbA1c, Managed Clinical Network, type 2 diabetes.

Sponsors: None.

SESSION 2 GLYCAEMIA CONTINUED

Chairman: Dr J McKnight, Consultant Physician, Western General Hospital, Edinburgh, Scotland

Insulin pumps – effects on glycaemic control, advantages and disadvantages of pump therapy, patient selection

Dr S Hurel, Consultant Physician, University College Hospital, London, England

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Abstract Administration of insulin by continuous subcutaneous infusion pump has been available for many years. Early adverse publicity and cost, limited the use of these devices. The technology has advanced significantly. It is clear that for the some patients the use of pumps provides for greater control of their diabetes. The devices must only be used in well motivated and educated patients. There are, however, still considerable funding issues to be resolved.

The talk will cover the background and evidence for pump use. Current models and their clinical application to patients and the methods of funding and future

technologies, will be discussed.

Insulin pump technology continues to evolve. The use of this technology will increase. Closed loop systems are being developed and will be launched in the future. Until an adequate supply of islet cells is available, manipulating insulin delivery, such as is possible with pumps, is the only method of improving control.

Key words: CSII, diabetes, insulin pumps.

Sponsors: None.

Declaration: I have attended 2 educational courses sponsored by MiniMed. I receive no sponsorship or funding from any party related to this technology.

The UK Transplant Programme – UK centres – outcomes following transplantation – who should be referred?

Dr M Press, Consultant Endocrinologist, Royal Free Hospital, London, England

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Abstract Because Type 1 diabetes is an unstable condition, it is not possible to achieve normoglycaemia (and hence prevent complications) without an increased risk of hypoglycaemia. Transplantation of the whole pancreas normalises glycaemic control, reverses complications and prolongs life but is associated with major surgical morbidity. The pancreatic islets (which is all the diabetic patient needs) can be purified in a volume of a few ml and embolised into the liver via the portal vein.

Since a breakthrough at the University of Alberta in 2000, one year insulin independence rates comparable to whole pancreas transplantation have been described. However, the procedure currently requires several donors per recipient and ways need to be found to increase the number of islets which survive the isolation and transplantation procedure. There are also concerns over adverse effects of the immunosuppressive drugs on islet function, and hence on long term outcome. There have now been almost 500 successful islet transplants world-wide. In Britain a consortium of centres is trying to work together to mimic the results elsewhere at a time when whole pancreas transplantation, which has lagged badly behind the rest of the world, is finally beginning to become established.

Key words: Immunosuppressive drugs, normoglycaemia, transplantation of pancreatic islets.

Declaration: No conflict of interest declared.

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Glycaemia and cognitive function long-term – effect of hypoglycaemia and hyperglycaemia on long term cognitive function – in type 1 and 2 diabetes

Dr M Strachan, Consultant in Diabetes and Endocrinology, Western General Hospital, Edinburgh, Scotland

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Abstract The impact of diabetes on cognitive function was first examined as far back as the 1920s. In more recent times, research activity has centred around children and younger adults with Type 1 diabetes and older adults with Type 2 diabetes.

The initial focus in adults with Type 1 diabetes was around the impact of recurrent episodes of severe hypoglycaemia on cognitive function. Cross-sectional studies suggested that adults exposed to five or more episodes of severe hypoglycaemia had significant cognitive decrements compared to individuals who had never experienced such episodes. These data have not been replicated in large, prospective studies, but this may be a consequence of patient selection and duration of follow-up. Nevertheless, there is now considerable interest on potential deleterious effects of chronic hyperglycaemia on cognitive function.

The developing brain is, in theory, much more sensitive to the effects of hypoglycaemia and, indeed, there are data in children to suggest that hypoglycaemia may adversely affect cognitive performance. However, as with adults, there is increasing evidence that hyperglycaemia may cause cognitive decrements in children.

In older adults, there is a large body of cross-sectional and prospective data that demonstrates that Type 2 diabetes is associated not only with an increased risk of cognitive impairment, but also with vascular and Alzheimer's dementia. The mechanisms behind these associations are likely to be multifactorial, but recent data suggest that hyperglycaemia may be important. In a multi-centre, randomised trial, better glycaemic control was associated with specific improvements in working memory function.

Type 1 and Type 2 diabetes are associated with cognitive impairment. While hypoglycaemia may have particular impact in children, there is increasing evidence of the harmful effects of chronic hyperglycaemia on cerebral function.

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Key words: Chronic hyperglycaemia, cognitive function, recurrent hypoglycaemia.

Sponsors: The randomised trial of improved glycaemic control on cognitive function in Type 2 diabetes was funded by GlaxoSmithKline.

Declaration: Dr Strachan has received consultancy fees from GlaxoSmithKline and honoraria for travel and lectures from GlaxoSmithKline and Takeda.

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SESSION 3 ENDOCRINOLOGY

Chairman: Professor B Walker, BHF Senior Research Fellow and Professor of Endocrinology, University of Edinburgh, Edinburgh, Scotland

Which fuels do you burn when? – control of body weight – when do you burn fat and when do you store it?

Dr M Jensen, Professor of Medicine, Mayo Clinic, Rochester, MN, USA

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Abstract The growing prevalence of obesity and the interest in weight loss remedies has stimulated interest in dietary and exercise approaches to maximise fat oxidation. Despite claims for dramatic effects on body fat loss by some diets, the human body has a relatively limited ability to modulate the fuels that are burned.

Unless significant ketosis develops, brain glucose utilisation (~100 g/day) limits how much carbohydrate intake can be restricted before proteins, endogenous or exogenous, are converted to glucose. For most 'diets' the vast amount of the energy deficit is made up by the oxidation of body fat. No diets can 'magically' increase fat loss, and diets that create massive energy deficits generate the majority of initial weight loss from glycogen and protein.

Diets that generate modest energy deficits will result in 'pure' fat loss. When energy intake exceeds energy expenditure the result is fat gain, even if the diet is low in fat. Long term regulation of body composition is dependent upon energy balance and physical activity. Except for highly trained athletes, the energy expenditure of physical activity is provided by a mix of fat and carbohydrate oxidation. There appear to be sex differences in the response to physical activity, but

greater levels of physical activity/energy expenditure allow better regulation of body fat stores.

Energy deficits, whether created by reduced intake or increased expenditure, are largely served by increased fat oxidation. Excess energy intake results in fat gain (after glycogen stores are replete) irrespective of the mix of nutrients consumed. Higher levels of activity can improve the chances of long-term maintenance of healthy body composition.

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Key words: Body fat, diet, exercise, substrate oxidation.

The Atkins Diet? – does the Atkins diet work, and if so, how?

Professor M Lean, Professor of Human Nutrition, University of Glasgow, Glasgow, Scotland.

Abstract Not available at the time of going to press.

SESSION 4 FOCUS ON ANDROGENS

Chairman: Dr P Padfield, Consultant Physician, Western General Hospital, Edinburgh, Scotland

Male contraception – how do we do it? does it work?

Dr R Anderson, Clinical Scientist, MRC Human Reproductive Sciences Unit, University of Edinburgh, Edinburgh, Scotland

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Abstract Male methods of contraception are used by about one third of the world's population, yet there have been no significant developments for decades, and in particular none taking advantage of the steroid chemistry which has revolutionised female-based contraception. It has been known for 60 years that testosterone administration to men will stop spermatogenesis, so why is there no 'male pill' yet?

Landmark studies by WHO 15 years ago demonstrated that testosterone given to large numbers of men profoundly suppressed spermatogenesis sufficient to

result in reliable contraception. Since then, large numbers of studies have explored a wide range of regimens, mostly based on administration of a progestogen, which potently suppress gonadotrophins in men as in women, in combination with testosterone. The progestogen allows a lower and therefore safer dose of testosterone to be administered, and combination regimens are also probably more effective at inducing higher rates of azoospermia. Gonadotrophin-releasing hormone agonists have proved ineffective. While GnRH antagonists appear promising, only very small pilot studies have been performed. We have explored orally-administered desogestrel, and more recently long-acting implants of its active metabolite, etonogestrel. With testosterone implants, these provide highly effective and long-acting spermatogenic suppression. A major hurdle has been the lack of development of improved testosterone delivery methods, but new preparations are now becoming available.

For the first time, commercially-funded studies are now underway providing real hope that this method may become a reality. We will then see how hormonal male methods add to the range of choices available to couples.

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Key words: Contraception, spermatogenesis, testosterone.

Sponsors: The authors studies have been funded by Medical Research Council and the Department for International Development.

Declaration: No conflict of interest declared.

Adrenal androgens – physiological importance of adrenal androgens – rationale for replacement – assessment of effect

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Abstract Dehydroepiandrosterone, is the most abundant circulating adrenal steroid. Its physiological role is not understood and may include acting as a substrate for

sex steroid synthesis, exerting central nervous system effects as a neurosteroid, or antagonising action of glucocorticoids. Following a peak in the third decade of life, there is a progressive age-related decline in DHEA levels in both sexes. Primary adrenal insufficiency (Addison's disease), is associated with glucocorticoid and mineralocorticoid deficiencies which are life-threatening if untreated; however, the associated near-total failure of DHEA synthesis is not usually corrected.

Epidemiological studies have correlated the decline in DHEA levels with various age-related disorders including cardiovascular disease, depression and cognitive decline, low BMD and cancer risk, but not established a causal relationship.

Placebo-controlled trials of DHEA supplementation in normal, ageing subjects have shown an improvement in psychological well-being¹ or enhanced libido, sexual satisfaction and BMD in women.²

In Addison's disease, short-term, placebo-controlled trials of DHEA replacement have shown enhanced sexual interest and satisfaction in women and improved mood, well-being and fatigue in both sexes.^{3, 4} In a longer-term (12 month) trial, beneficial effects on fatigue and well-being were observed, together with increased lean mass and femoral BMD.

In ageing, longer-term studies are needed to determine whether DHEA supplementation can reduce its co-morbidities. DHEA treatment is beneficial in adrenal insufficiency and, if it is safe in long term studies, its addition to conventional hormone replacement may be indicated.

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Key words Addison's disease, ageing, dehydroepiandrosterone.

Sponsors None.

Declaration No conflict of interest declared.

Recent Advances in Androgen Replacement – options for testosterone replacement – how does one decide if there is adequate/over replacement?

Professor FWu, Professor of Medicine and Endocrinology, University of Manchester, Manchester, England

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