THE UNIVERSITY OF BUCKINGHAM

CLORE LABORATORY

Institute of Translational Medicine

The diabetes debate

Commissioner for Health, Tonio Borg supports Europe's concerns about diabetes and the importance of preventative measures

I fully share the European Parliament's concern about the alarming increase in diabetes – mostly in type II diabetes – in Europe and worldwide.

I also fully support the goals of the European Parliament Resolution of March 2012 on addressing the EU diabetes epidemic which is now to be implemented across Member States, notably through National Diabetes Plans.

The good news is that type II diabetes is largely preventable. It is linked to nutrition and physical activity – two of the common risk factors which play a role in many chronic diseases.

Indeed, according to the World Health Organisation (WHO), 44% of the global diabetes burden is attributable to obesity, and 27% to physical inactivity.

More than half of the adult population in the European Union is overweight or obese.

The situation for children is equally worrying. In the EU, 1 in 3 children aged 6 to 9 years is overweight or obese. This is a considerable increase from 2008 – just 5 years ago – when the figure was 1 in 4 children.

And, according to the most conservative estimate, from the International Association for the Study of Obesity more than 20,000 obese children in the EU now have type II diabetes, while over 400,000 have impaired glucose tolerance.

These figures illustrate vividly why it is important to invest in preventing diabetes from an early age.

The Commission, in partnership with Member States and stakeholders, has a strong record of addressing nutrition and physical activity.

We work with stakeholders through the EU platform on diet, physical activity and health, generating commitments for action to address obesity.

I should add that the International Diabetes Federation is an active member of the Platform.

The European Commission, together with the Member States, is now shaping a new Action Plan on childhood obesity. If we succeed in reducing childhood obesity now, we will prevent many thousands of children from developing diabetes II later in life.

Taking action to address the determinants of diabetes is an important part of our response in the long run. But our action does not stop here. Prevention is not enough. We also need to support people living with diabetes today.

And while many of the decisions on how health systems respond to the diabetes epidemic fall to Member States, there are areas where the EU can add value to support and underpin national activities.

This month at the Health Council, I will be discussing with Health Ministers the potential for further EU added-value action on the prevention, care, research and information on chronic diseases.

This follows from a thorough reflection process on chronic diseases with Member States and stakeholders which we have carried out.

Early next year, I will launch a Joint Action with Member States on chronic diseases, under the EU Health Programme to support Member States in their efforts to improve prevention and management of chronic conditions.

I am pleased to inform you that this Joint Action will single out work on diabetes – and on no other disease.

In this context, work to the barriers to prevention, screening and treatment of diabetes will be developed over the next three years.

Indeed, according to the World Health Organisation, 44% of the global diabetes burden is attributable to obesity, and 27% to physical inactivity.

This work will improve cooperation among Member States regarding actions on diabetes, and help develop common guidance, for example on training of health professionals or improving literacy to empower people with diabetes.

In this context, we will support Member States' National diabetes plans – this is an important issue stressed in the Parliament Resolution – by fostering the exchange of good practices and by producing guidelines on the essential elements of such diabetes plans (which Member States then can adapt to their circumstances).

In addition, thanks to the European Parliament, the Commission services are right now shaping a pilot project for developing and implementing successful prevention strategies for type II diabetes.

All this is new work developed in the past few months. As you know, however, we are not starting from scratch.

Through the Health Programme, we have supported a number of projects specifically on diabetes – including work on good practice on paediatric and adolescent diabetes prevention, and diabetes information and reporting.

The Commission has also financed many research projects on diabetes and obesity. In fact, during the past 6 years of the 7th Framework Programme for Research and Technological Development, the Commission has invested €270m on obesity and diabetes related research.

The increasing burden of diabetes calls for a serious and sustained debate on how we can adapt our health policies, improve our health and social systems and increase public awareness of the challenges ahead.

To take this forward, I will convene an EU summit on chronic diseases in April 2014. This will review the results of EU action so far, and discuss how and where further EU action can support Member States, stakeholders and citizens.

Diabetes remains at the very centre of this debate, and I hope diabetes stakeholders will play a strong and active role as we take forward action on chronic diseases over the years to come.

Article taken from a speech given at the meeting of the EU Diabetes Working Group at the European Parliament, 12th November 2013, Brussels Belgium.

http://ec.europa.eu/commission_2010-2014/borg/docs/speech_12112013.pdf

Diabetes, Obesity and Alzheimer's – plagues of our time

Mike Cawthorne, Director of the Institute of Translational Medicine at the University of Buckingham, on the need for better and more effective treatments for diabetes, obesity and Alzheimer's.

The most recent estimate of the world diabetes population published by the International Diabetes Federation is 381 million – up by 11 million since 2012. Half of these people with diabetes don't know they have the disease and typically at diagnosis subjects have had diabetes for 10 years.

Expenditure on healthcare of diabetes is more than $471 billion (~ €351 billion) which is more than 10% of the total healthcare costs of adults aged 20-79. However, healthcare costs contribute less than half of the cost of diabetes. To this must be added items such as increased insurance premiums, inability to work, carer costs and early death.

In Europe there are approximately 55 million people with diabetes of which 38% are unaware that they have the disease. However, rates vary significantly from country to country, thus France, UK and Italy are all between 7 and 8% of adults; Spain, Germany and Russian Federation more than 10%.

More than 90% of diabetics are so-called type-2 diabetics where the disease develops over time as a result of increased resistance to the person's own insulin. This puts pressure on the insulin producing cells in the pancreas to produce more insulin. However, these cells have also been damaged and over time fail, at which stage the person will require insulin injections. However, up until that time diabetes is largely a silent disease and the person with diabetes does not suffer any obvious consequence if they do not control their diet or fail to take their oral medication.

Types of diabetes

There are two main types of diabetes:

- Type 1 diabetes is an autoimmune disorder, typically developing in childhood, which requires insulin injections to treat. The trigger that initiates the development of autoimmunity (where the person's immune system recognises the insulin producing cells as foreign and sets out to destroy them) is not known but both a viral infection and early exposure to cow's milk have been suggested.

- Type 2 diabetes affects more than 90% of all people with the disease. It used to be referred to as adult onset diabetes but with the high prevalence of childhood onset obesity it is becoming increasingly common in children and adolescents. There are two separate lesions in type 2 diabetes – insulin resistance, which is a failure of tissues to respond adequately to the subject's own insulin, and defective insulin secretion. These two lesions interact. Patients initially are recommended to diet and exercise, which inevitably fails in the majority. Oral therapy is then used but over time it is likely these patients will require exogenous insulin following pancreatic islet failure.

- The third form of diabetes is gestational diabetes. Failure to control blood glucose during pregnancy predisposes the mother to develop diabetes in later life. More alarmingly, it also programmes the offspring to have a higher risk of obesity and diabetes, and, in particular, be prone to themselves exhibiting gestational diabetes. Therefore, the condition is a multi-generational programming mechanism that is a tendency to diabetes can be inherited by epigenetic modification. Data on hyperglycaemia in pregnancy is unavailable for many parts of the world.

Complications of diabetes

Heart disease and stroke – adults with diabetes have a 2-4 times greater risk of both heart disease and stroke.

High blood pressure – up to 70% of diabetes sufferers have high blood pressure. Indeed, investigation of elevated blood pressure is probably the most common reason for diagnosis of diabetes.

Blindness – diabetes is the leading cause of blindness in adults

Kidney failure – diabetes is the leading cause of kidney failure, accounting for up to 50% of new cases,

Nervous system – about 60-70% of people with diabetes have mild to severe forms of nervous system damage. Male impotence occurs in up to 50% of diabetes sufferers.

Amputation – diabetes is the major cause of non-traumatic lower limb amputations.

Treatment of Type 2 diabetes

The main oral drug used for treating type 2 diabetes is metformin. This drug was first synthesised in the 1920's, tested in clinical trials in 1956 and marketed in Europe in the late 1950's but not marketed in the United States for another 40 years. Generally an algorithmic approach is used to treat diabetes, with drugs being added as patients fail to maintain control of glucose levels. There is a growing realisation that this staging methodology is inadequate and fails to prevent pancreatic islet cell failure. Indeed some drugs might even accelerate islet cell failure.

A treatment goal based on health matters rather than financial cost would aim to provide durable control of blood glucose together with protection from islet cell failure. Potentially this requires a combination of drugs to improve insulin sensitivity in liver, fat and skeletal muscle, to slow absorption of nutrients from the gut, and agents to protect the insulin producing cells from damage and to promote the genesis of new islet cells.

Existing drugs, such as the thiazolidinedione insulin sensitisers, metformin and the GLP-1 mimetics used together would provide the best therapeutic option and should delay or prevent the development of complications. However, new drugs are needed that address the fundamental pathophysiology of diabetes.

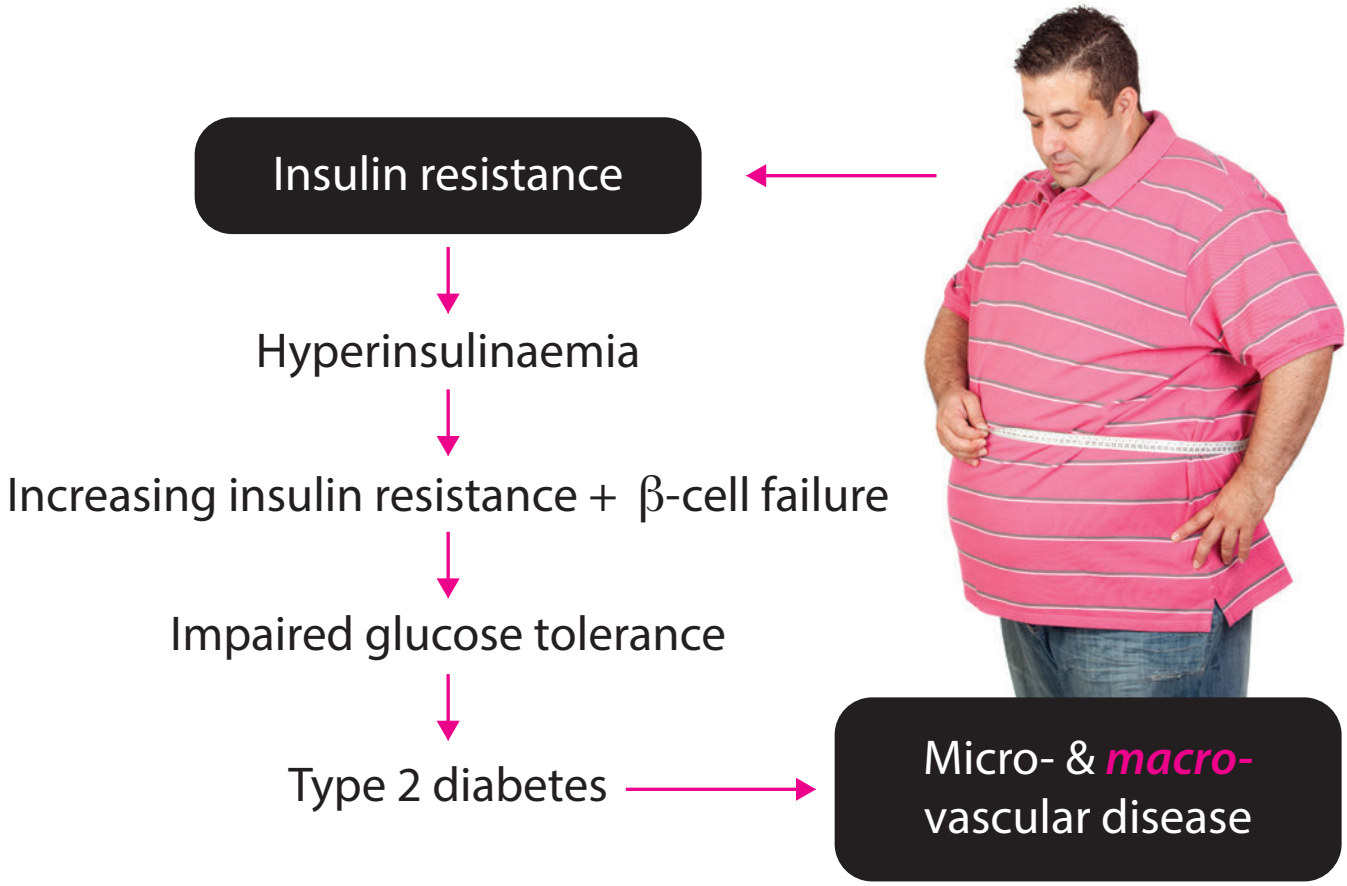
Prevention of Type 2 diabetes

Currently there is no cure for type 2 diabetes. Current drugs and those in the pipeline are merely palliatives. Consequently there is a growing recognition for the need to prevent the development of type 2 diabetes. This is particularly the case for children and adolescents. A major factor is obesity, which results in insulin resistance and compensatory hyperinsulinaemia to overcome the resistance ultimately leading to islet cell exhaustion.

A particularly worrying component of the diet is fructose. Fructose or fruit sugar is 50% of sugar and has a high relative sweetness. As well as in sugar it is present in high fructose corn syrup (used as a sweetener in soft drinks), honey, molasses, maple syrup and fruit juices, particularly apple and pear.

Fructose used to be used in food stuffs for diabetics. In ignorance it was used to provide sweetness without giving glucose. However, there are no limiting steps on fructose metabolism. In animal studies feeding fructose results in the development of insulin resistance and hyperglycaemia. In a study in normal volunteers conducted in the 1980's, this author showed that consumption of a box of diabetic chocolates a day for 10 days resulted in mild insulin resistance. Consequently the consumption of extra large portions of soft drinks or fruit juices can provide more than

Type 2 diabetes: the role of insulin resistance and β-cell failure



100g of sucrose, which is more than 50g of fructose. Steps need to be taken to reduce the sugar (particularly fructose) content of drinks as well as in some cases reducing the overall consumption of sweetened drinks.

Obesity is almost certainly the single most causative factor in the diabetes epidemic. It is also now the major causative factor in cancer in Europe with the decline in tobacco consumption. People have been recommended to diet and exercise for at least two decades but obesity incidence rates continue to rise even in children and adolescents. Drug treatment for obesity has generally been frowned upon with good reason, as the majority of drugs were centrally acting inhibitors of food intake and side-effects were common, resulting in drugs being withdrawn.

Scientists now at the Institute of Translational Research at the Clore Laboratory pioneered the idea of treating obesity (and type 2 diabetes) by activating increased energy expenditure by brown adipose tissue. This tissue's prime role is to produce heat and is highly active in babies to keep them warm but its activity declines, particularly if there is no requirement to produce heat to stay warm. It was thought that it was totally inactive in adult men. However, recent work using imaging techniques has demonstrated that patches of brown adipose tissue exist and a new era of studies to develop thermogenic agents as exercise mimetics has begun.

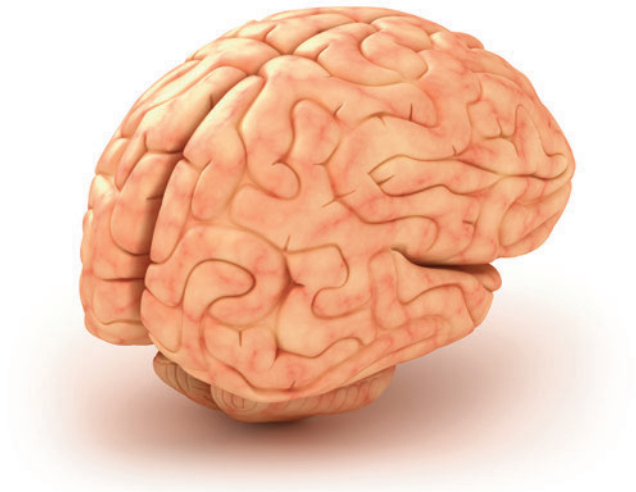
Is Alzheimer's type 3 diabetes?

Until recently it was the view that insulin had little effect on the energy metabolism of the brain. It was thought illogical that something as important as the brain would be dependent in any way on when a person last ate a meal. This was because the brain is a particularly energy intensive organ consuming approximately 25% of the body's total glucose. However, it was first discovered that astrocytes and microglial cells, which are major

Institute of Translational Medicine

- More than 500 peer reviewed publications by staff in disease areas
- Institute staff made major contribution to the development of insulin sensitiser drugs
- Institute staff pioneered brown adipose tissue research and the development of thermogenic drugs
- More than 100 man years of pharmaceutical industry research
- Undertake pre-clinical proof of concept studies for industry, including measurements of food intake, body composition, energy expenditure, glucose tolerance, insulin sensitivity
- Specialised techniques include microarrays, immunohistochemistry, confocal microscopy, FACS analysis and cell sorting, perfused tissues and organs, isolated tissue and cell studies and in silico pathway analysis

communicating cells in the brain, are insulin sensitive and later that the insulin receptor had a wide distribution in the brain. 18Fluorodeoxy-glucose positron emission tomography studies demonstrated that insulin had a role in regulating global brain glucose utilisation in humans, most markedly in the cortical regions. Other studies have demonstrated that insulin plays a key role in neuroplasticity, neuromodulation and neurotrophism – the process of neuronal growth, stimulated by neuronal differentiation and survival.



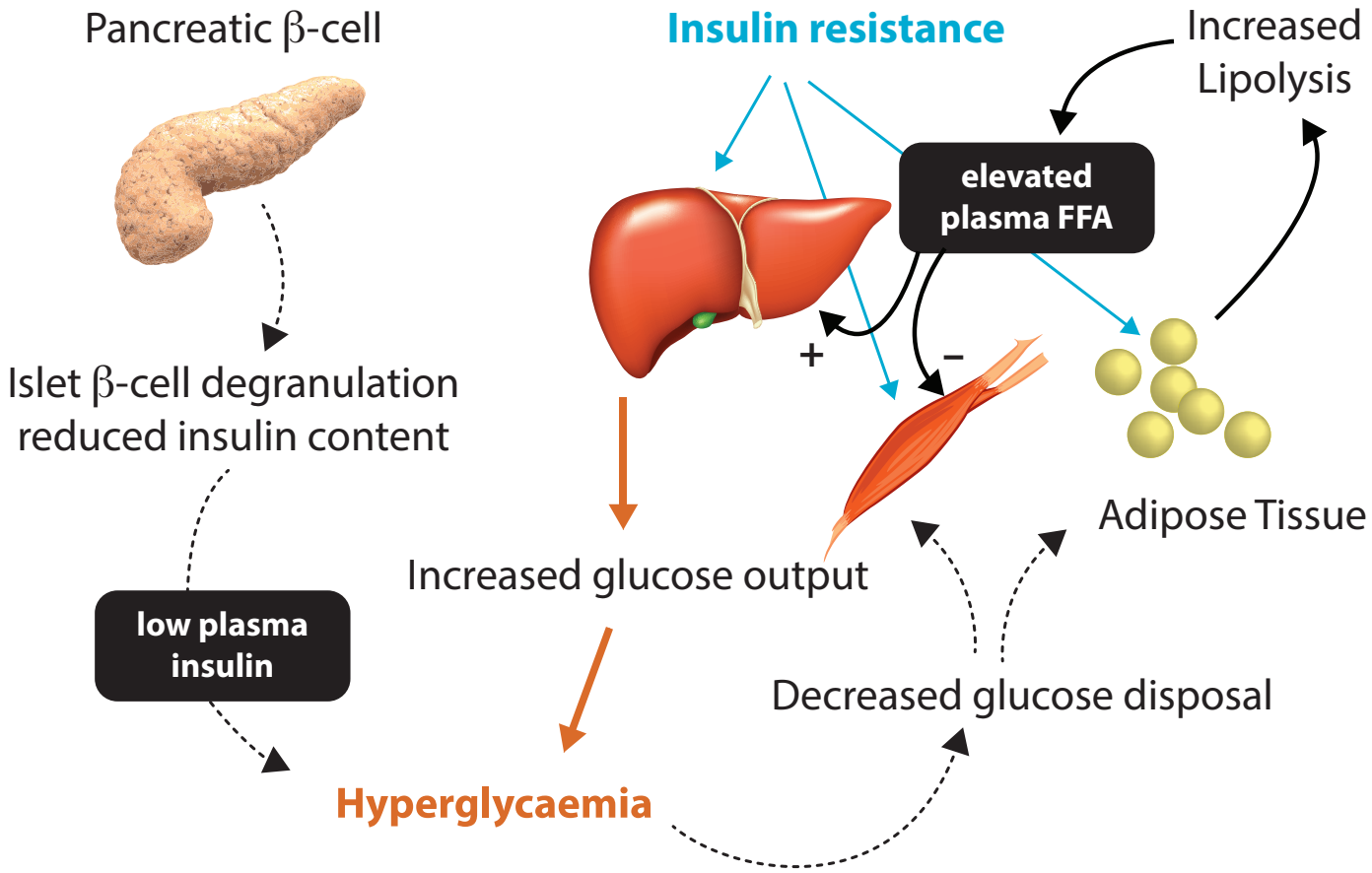
Does the brain develop insulin resistance?

Epidemiology studies demonstrate that the risk of developing Alzheimer's disease is increased by 50% in subjects with diabetes.

The key question is does the brain develop insulin resistance? Recent studies using post-mortem brain from patients with Alzheimer's but without diabetes showed markedly reduced responses to insulin signalling pathway in the hippocampus and to a lesser degree in the cerebella cortex. In the hippocampus the biomarkers of insulin resistance increased progressively from normal cases through mild cognitive impairment cases to Alzheimer's disease regardless of diabetes. However, there is no evidence that the brain in Alzheimer's disease is hyperglycaemic unlike peripheral tissues in diabetes. Thus an appropriate term to describe the state of Alzheimer's disease brain is insulin-resistant brain. This is analogous to insulin resistance syndrome, which is a feature of several peripheral tissue disorders. Insulin resistance in peripheral tissues could promote insulin resistance in the brain by reducing brain insulin uptake and by raising brain levels of amyloid β.

A second reason why peripheral resistance to insulin may affect the brain has been proposed. This is that toxic ceramides generated by the disturbed lipid metabolism in insulin-resistant liver pass into the circulation and transit across the blood brain barrier into the brain. There they

Insulin resistance and β-cell dysfunction drive abnormalities in glucose and fat metabolism



induce inflammation leading to both a second-pronged attack on central insulin action causing insulin resistance and cell death.

These studies lead to the view that drug treatments that improve either or both central and peripheral insulin resistance are potential treatments or at least delay the progression of mild cognitive impairment to Alzheimer's disease. In fact two anti-diabetes drugs have already been shown to have some beneficial effects. They are metformin and the thiazolidinedione rosiglitazone and a third drug pioglitazone has been proposed for a large clinical trial.

However, none of these drugs are a perfect treatment. Many patients do not tolerate easily metformin as a result of gastrointestinal side-effects and the thiazolidinedione insulin sensitiser drugs produce weight gain and water retention. There is, therefore, a need for a concerted effort to discover drugs that act to cause insulin sensitisation in the brain and liver. Such drugs are a potential treatment for Alzheimer's patients possibly when coupled with nasal delivery of insulin, which has been shown to improve learning and memory in clinical trials. The greater need, however, is to develop strategies that will delay the onset and progression of mild cognitive impairment towards Alzheimer's. For this drugs are not the answer unless one had diagnostic assays that were highly predictive, since it would be unethical to give drugs with inherent risks to people who might not develop the disease. However, if non-toxic plant-derived substances with similar insulin sensitiser action could be identified, these could be made available to the public.

Drug from plants

80% of people with type 2 diabetes live in low and middle income countries. In high income countries, diabetes is more prevalent in the lower social economic classes and in people who have migrated from low and middle income countries.

The development of diabetes in many countries is linked to urbanisation. For example, whereas the rate of diabetes in France is 7.5%, the rate in Reunion is 16.5%. In Barbados, the Prime Minister has stated that all of the economic gains post-independence have been lost to the development of chronic metabolic disease of which diabetes is a major component. It follows, therefore, that many countries and their populations will never be able to afford treatments available in the developed world, particularly those that medical opinion leaders are advocating.

A potential solution to the problem is the identification of plant-based treatments which after extraction could be put together in combinations to provide locally grown, defined plant extracts that would ideally mirror, or more realistically approximate to, developed world drug treatments. These plant-based treatments could be used as preventative therapies in the developed world for both diabetes and Alzheimer's. For example, the effects of the diabetes drug metformin, which has also produced benefits on cognitive impairment, can be mirrored in animal studies by an extract of the plant bitter melon. The fruits of this plant, which contain the active principle, are eaten in a number of countries.

Other edible plants have provided some evidence of efficacy similar to that shown by insulin sensitiser drugs.

Professor MA Cawthorne
Director, Institute of Translational Medicine
University of Buckingham
Hunter Street
Buckingham
Bucks MK18 1EG
Tel: +44 (0)1280 820309
Fax: +44 (0)1280 820135
E-mail: mike.cawthorne@buckingham.ac.uk

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