A MODERN DAY PLAGUE?

Mike Cawthorne, Director of the Clore Laboratory for Translational Metabolic Research at the University of Buckingham, on the need for better and more cost effective treatments for diabetes and obesity

he Clore Laboratory was developed as a diabetes and obesity research centre and has been involved in the discovery and development of every promising drug class in diabetes and obesity. It undertakes both basic and applied preclinical research with other universities worldwide and with major pharmaceutical and biotech companies.

The International Diabetes Federation estimated in 2012 that more than 371 million people had diabetes, with half of them undiagnosed. Expenditure on healthcare of diabetes is more than \$471bn (~€357bn), which is more than 10% of the total healthcare costs of adults aged 20-79 years.

In Europe, there are approximately 55 million people with diabetes, of which 38% are unaware that they have the disease. However, 80% of sufferers live in low or middle income countries, with half the number of people (4.8 million in 2012) who die from diabetes being under 60.

Types of diabetes

There are three main types of diabetes:

- Type 1 diabetes is an autoimmune disorder, which requires insulin injections to treat;
- Type 2 diabetes affects more than 90% of all people with the disease. It usually occurs in adults, although with the high prevalence of childhood obesity it is becoming more common in children. 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 can be controlled with oral therapy but over time they are likely to require exogenous insulin following pancreatic islet failure; and
- The third form of diabetes is gestational diabetes. Failure to control blood glucose during pregnancy predisposes the mother

Validated expertise

- More than 500 peer reviewed publications by Clore Laboratory staff in the area of diabetes and obesity;
- Clore Laboratory staff have made major contributions to the development of insulin sensitiser drugs;
- Clore Laboratory staff pioneered brown adipose tissue research and the development of thermogenic drugs; and
- More than 100 man years of pharmaceutical industry research.

to develop diabetes in later life. It also programmes the offspring to have a higher risk of becoming obese and diabetic and, in particular, be prone to gestational diabetes. Therefore, the condition is a multi-generational programming mechanism.

PROFILE

Treatment of Type 2 diabetes

People with diabetes have an increased risk of diseases affecting the heart and blood vessels, kidneys, eyes, nerves, teeth and skin. The main oral drug used for treating Type 2 diabetes is metformin. Generally an algorithmic approach is used with drugs being added as patients fail to maintain control. There is a growing realisation that this staging methodology is inadequate and if one attempts to both control glucose (and lipids) and prevent (or at least delay) pancreatic islet cell failure, then multiple treatments are needed that fully address the pathophysiology of the disease. Potentially, this requires drugs to improve insulin sensitivity in liver and skeletal muscle, slow the absorption of nutrients from the gut and provide islet cell protection.

The Clore Laboratory staff have a wealth of background knowledge and experience in undertaking preclinical studies that allow positioning of drugs into the therapeutic regimes of today and tomorrow.

Prevention of Type 2 diabetes

There is a growing recognition for the need to prevent the development of Type 2 diabetes. A major factor is obesity, which results in insulin resistance and compensatory hyperinsulinaemia leading ultimately to islet cell exhaustion. All anti-obesity drugs to



Methods of preclinical research

- Well validated rodent models;
- Proof of concept studies;

PROFILE

- Body composition measurements: DEXA and NMR;
- Food intake measurements and diet choice;
- Central administration;
- Energy expenditure by indirect calorimetry;
- Oral, intraperitoneal and i.v. glucose tolerance;
- Insulin sensitivity measurements (glucose clamp and nonclamp techniques);
- Transgenic models;
- Hepatic glucose uptake and tissue utilisation rates;
- Pancreatic perfusion;
- Isolated pancreatic islets, hepatocytes and adipocytes;
- Isolated soleus muscle;
- Pancreatic islet cell mass;
- Immunohistochemistry;
- Microarrays, RNA analysis and western blots;
- Confocal microscopy;
- FACS analysis and cell sorting; and
- In silico pathway analysis.

date have either been centrally acting agents to reduce food intake or inhibitors of nutrient (fat) absorption. Side effects have been common and have, in a number of cases, led to the drugs being withdrawn.

⁴As indicated earlier, 80% of people with diabetes (predominantly Type 2) live in low and middle income countries.⁹

Scientists from the Clore Laboratory pioneered the idea of treating obesity (and Type 2 diabetes) by activating increased energy





utilisation by brown adipose tissue. These compounds (β_3 adrenoceptor agonists) failed because of species differences in the β_3 -adrenoceptor and the view that adult man lacked the target tissue. The latter view has now been shown to be erroneous and a new era of studies to develop thermogenic treatments has begun.

Drugs from plants

80% of people with diabetes (predominantly Type 2) live in low and middle income countries. In high income countries, diabetes is more prevalent in the lower social economic classes.

In Barbados, the Prime Minister has stated that all 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 developed world treatments, particularly those that medical opinion leaders are advocating.

A potential solution to the problem is the identification of plantbased treatments that could be put together in combination to provide locally grown, defined plant extracts that would ideally mirror, or more realistically approximate to, developed world drug treatments. The Clore Laboratory is working on a number of such agents, which might also be used in the developed world for preventing the progression to diabetes in people with prediabetes (impaired glucose tolerance).

BUCKINGHAM

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