Editorial

A decade of diabetes research and development

Tony Townsend
Department of Family Medicine, Faculty of Medicine & Health Sciences, Al Ain

The first editorial for this journal appeared in the first issue in October 1993. Professor Roger Ferguson wrote about the prospects and challenges for diabetes in the 90's and commented that 'better ways of influencing patterns of behaviour and compliance and of motivating lifestyle changes are the only hope for fulfilling the promise of diabetes demise in the 21st century'.[1] It is timely, at the beginning of the 21st century, when the promise of the demise of diabetes seems further away than ever, to reflect on some of the accomplishments of diabetes research in the last decade.

During the last 10 years our understanding of the aetiology, natural history and management of diabetes (in particular type 2 diabetes) has taken an exponential leap forward. This is largely due to those professionals who have dedicated themselves to research activities which will benefit many of the 154 million people estimated to have diabetes now, and even more of the 300 million predicted to be affected by diabetes in 2025.[2,3] Of course, it is not possible to summarise all of the major achievements of diabetes research during the last 10 years in a few paragraphs, but, from the perspective of a generalist family physician, some of the highlights will be discussed in the following paragraphs.

There is a much better, but still incomplete, understanding of the aetiology of diabetes mellitus. The relative contributions of genetic predisposition, developmental influences and environmental triggers leading to the disturbed metabolic homeostasis that characterises diabetes are more clearly understood.[4,5,6] The role of insulin resistance in the aetiology of type 2 diabetes has been clarified,[7-13] the contribution of β-cell dysfunction has been elucidated and the complex inter-relationship of insulin and leptin resistance to hypertension, obesity and diabetes is gradually being unravelled. The leptin receptor gene has been cloned and mapped. Hypothalamic leptin receptor mutations, impaired leptin signalling systems and impaired access of leptin into the central nervous system are thought to lead to dysfunctional body weight homeostasis. In these situations hypothalamic neuropeptide Y levels are elevated with resultant hyperlepti-naemia and leptin resistance.[14,15] Zimmet and his colleagues have animal and human data suggesting that leptin resistance and hyperleptinaemia rather

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Correspondence to : Tony Townsend, Whangamata Medical Centre, 103 Lincoln Road, Whangamata, New Zealand.

than, or synergistically with, insulin resistance and hyperinsulinaemia may play a central role in the development of the cardiovascular risk factors that constitute the metabolic syndrome.[16]

A revised classification based on a better understanding of the aetiology of diabetes has now been widely accepted.[17,18] This differentiates between clinical stages and aetiological types of diabetes. Clinical stages include impaired glucose tolerance or impaired fasting glucose, non-insulin requiring diabetes and insulin requiring diabetes (for control or for survival). The aetiological types include type 1 diabetes which is characterized by beta-cell destruction, usually leading to absolute insulin deficiency; type 2 diabetes which includes diabetes characterized by insulin resistance and insulin secretory defects; a number of specific syndromes which include diabetes associated with specific genetic defects, endocrinopathies and drugs and gestational diabetes. Future classifications will almost certainly include reference to the metabolic syndrome which has been defined as glucose intolerance or diabetes and/or insulin resistance together with at least two of the following components; raised arterial blood pressure, raised plasma triglycerides, central obesity or microalbuminuria.[18]

New diagnostic criteria have been produced.[17,18] There has been general acceptance of the lowering of the threshold of fasting glucose levels for diagnosis to $\geq$7.0 $mmol^{-1}$ and introduction of the category of impaired fasting glucose (fasting levels $\geq$6.1 and <7.0 $mmol^{-1}$). However debate continues about the importance of the oral glucose tolerance test in both clinical and epidemiological practice.[19,20,21] There are some indications that fasting hyperglycaemia (IFG) is associated with beta-cell dysfunction while impaired glucose tolerance (IGT) is associated with the insulin resistance syndrome.[22]

An increase in the number of epidemiological studies, recognition of the prevalence of previously undiagnosed diabetes with the revised criteria and calculations based on the changing patterns of diabetes in developing countries have led to more accurate predictions of the enormous impact of diabetes on different populations. The greatest impact is expected to occur in the Middle East and India with increases between 1995 and 2025 of 193% and 195% respectively.[2] In each of these regions there will be more than 50 million people with diabetes by 2025. There have been landmark trials confirming the importance of tight glycaemic control in both type 1[23] and type 2 diabetes.[24,25,26,27]

New therapeutic agents are being introduced to assist in glycaemic control. The most promising of these are peroxisome proliferator-activated receptor (PPAR) agonists such as rosiglitazone[28] and rapid-acting insulin secretagogues such as repaglinide.[29] The thiazolidinediones (the first of the PPAR agonists) appear to not only act as insulin sensitizers but also to lower blood pressure and protect against impairment of endothelial dysfunction.[30] There is also evidence that they inhibit beta-cell destruction in insulin-resistant Zucker diabetic fatty rats when administered before the development of diabetes.[31] Despite concerns about liver toxicity, the thiazolidinediones offer an alternative or additional mode of therapy for diabetes and several other chronic diseases in the near future.[32] Insulin secretagogues are taken before

meals and aid in the disposal of mealtime glucose load without continued stimulation of pancreatic beta-cells in the post-prandial period.[29] They can be used to achieve good glycaemic control with less risk of producing hypoglycaemia.

There has been confirmation that early detection and management of diabetic complications lead to decreased morbidity and mortality.[33] Two particularly important clinical developments in the last decade have been the observation that reduction of systolic blood pressure significantly lowers the risk of developing diabetic complications[34] and the increasing use of tests to detect microalbuminuria leading to the subsequent long-term protection against the development of nephropathy not only in hypertensive diabetic patients but also in normotensive patients by treatment with angiotensin-converting enzyme inhibitors.[35]

As most of the developments have occurred within the last decade there can be little doubt that the sharing of information about diabetes and diabetic care is fundamentally important. With all that has happened in the last decade, it would take a brave, or perhaps foolish, person to predict what might be important in the next ten years. However, three areas appear to be of particular relevance in the prevention and management of type 2 diabetes. Firstly, greater emphasis should be placed on those social and behavioural changes which should help in the primary prevention of type 2 diabetes and of the cardiovascular complications of the metabolic syndrome.[36] The interim results from the Finnish Diabetes Prevention Study claim to demonstrate the efficacy and feasibility of a lifestyle intervention programme for people who have impaired glucose tolerance.[37] Secondly, early detection and treatment of insulin and leptin resistance should be initiated before the development of the metabolic and physiological disturbances (in particular hyperglycaemia, hypertension, hypertriglyceridaemia and endothelial dysfunction) which lead to most of the complications.[38] And thirdly, better therapeutic regimes will improve glycaemic control without the risk of serious hypoglycaemia.

Not only is diabetes rapidly becoming a global burden but also there are still many unanswered questions about prevention and management. As one third of all diabetic patients will reside in this part of the world by 2025, health professionals must continue to be informed about new developments. The journal has a central role to play in the dissemination of information. I encourage all health professionals who have an interest in diabetes research or who work with diabetic patients to consider how each can best share their experience and knowledge, thereby contributing to improving the care of those members of our community whose lives are affected by this illness.

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