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Tackling the epidemic of diabetes – Need for a multidisciplinary approach

Referring to the worldwide diabetes epidemic, the World Health Organization (WHO) issued the following statements: 'the statistics are frightening; the burden on healthcare system is overwhelming; and the cost in human suffering and lives due to diabetes and its complications is heartbreaking'. Nowhere is the truth of these statements most obvious than in India which today has the dubious distinction of having become the diabetic capital of the world. With an estimated 23 million diabetics today and the numbers set to increase to 57 million by 2025 (ref. 1), diabetes is fast emerging as one of the top health concerns of the country notwithstanding the continued presence of communicable diseases like malaria and tuberculosis. In these days of rapidly expanding technology, everyone, whether it be a physician, a scientist or a government policy maker, finds it difficult to sift through the exploding new information on diabetes. In the special section of this issue of *Current Science* devoted to diabetes, we have attempted to compile reviews from experts on current concepts and recent advances on a few selected areas which, in our opinion, will bear significant impact in expanding our present day knowledge on diabetes epidemic, prevention, treatment and research.

Diabetes mellitus is presently a burden not only on the individuals affected by the disease but also on society, particularly the national health systems. The principles of management of diabetes, particularly in developed countries, have been identified and largely publicised. In contrast, despite considerable progress in the tools available to manage the disease and the varied resources used, the situation of the diabetic patient is far from enviable, in terms of quality of life and life expectancy. Governments in various countries of the developed world today consider diabetes as an ideal example to empower the 'disease management concept' in which the emphasis would be on the continuum of care rather than on episodes of illness or disability. The increasing prevalence of diabetes in developing countries like India reflects the changes in lifestyle, excessive energy intake and reduced physical activity which always accompany economic development. This contributes to the rapid explosion of diabetes in India[2]. Ramachandran *et al.* (**page 1471**) have summarized the Indian scenario with respect to the burden of diabetes and its complications.

Type 2 diabetes may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance. For the overwhelming majority of persons with typical Type 2 diabetes, a single gene variant cannot explain its occurrence. Rather, the genetic component of the disease is the result of multiple genes acting together and modified by environmental factors. Scientists have identified some gene variants that contribute to Type 2 diabetes. There is also hope in that the information gained from genetic studies of diabetes will indicate key pathways involved in the control of blood glucose levels, and that this will lead to the development of new drugs for treating this disease. Again, if we understand the genetic factors involved, this will allow us to begin to search for the important environmental or lifestyle factors that convert genetic risk to overt disease. Susceptible individuals may then be able to modify their lifestyle accordingly and thereby reduce their risk of developing diabetes. Torben Hansen (**page 1477**) has presented an overview of recent genetic studies of Type 2 diabetes with special reference to the classical studies on monogenic forms such as maturity-onset diabetes of the young (MODY).

Abnormalities in glucose and lipid metabolism, obesity, and high blood pressure occur together in the same individuals more than by chance so as to suggest that they are somehow interrelated. In fact, this cluster of abnormalities has come to be known as a syndrome, going by a variety of names, including Syndrome X, the Deadly Quartet, Metabolic syndrome and the Insulin Resistance Syndrome. A common thread connecting the various features of the syndrome together is insulin resistance, i.e. a reduced sensitivity in the tissues of the body to the action of insuln. When insulin resistance exists, the body attempts to overcome this resistance by secreting more insulin from the pancreas. This compensatory state of hyperinsulinemia (high insulin levels in the blood) is used as a marker for the syndrome. The development of Type 2 diabetes occurs when the pancreas fail to sustain this increased insulin secretion. As suggested by Misra and Vikram (**page 1483**), insulin resistance syndrome which was originally conceived as a cluster of a few risk factors now appears to represent an interface of several complex metabolic alterations and diseases. The fact that Indians are more insulin resistant[3,4] and more vulnerable to the insulin resistance syndrome[5] warrants in-depth molecular biology and genetic studies on this condition in Indians.

The greatest cause of mortality in Type 2 diabetes is atherosclerotic vascular disease and its sequelae. Between 75% and 80% of adult patients with diabetes die of macrovascular complications. Links between endothelial dysfunction, atherosclerosis and diabetes have been increasingly recognized. One of the earliest discernible atherogenic changes in diabetes is endothelial dysfunction, which is characterized by inhibited vasodilation, vascular smooth-muscle proliferation, increased thrombogenesis and proatherogenic cellular processes. Once clinical cardiovascular disease develops, patients with Type 2 diabetes have a poorer prognosis for survival than normoglycemic patients with cardiovascular disease. Mohan and colleagues (**page 1497**) review the current status of various traditional and newer variety of cardiovascular risk factors in patients with Type 2 diabetes.

Diabetes is one of the leading causes of blindness, and in the western world, the risk of blindness to persons with diabetes is 25 times greater than that of the general population. This problem is internationally recognized as evidenced by this year's World Diabetes Day theme: 'Reducing the burden: Your eyes and diabetes'. Decreased vision due to diabetes can be caused by several mechanisms, and there is an urgent need to accelerate basic research directed toward discovering the cellular and molecular basis of diabetic retinopathy. Recent advances in structural, cell and molecular biology can be applied more widely to gain a better understanding of retinal cell basement membrane biology, pericyte–endothelial cell interactions, three-dimensional structure of retinal enzymes, and regulation of retinal gene expre-

ssion. More information about retinal metabolic pathways and how these pathways are regulated, as suggested by Balasubramanyam, Rema and colleagues (**page 1506**) could possibly lead to the development of biological modifiers or pharmacologic agents that would be useful in preventing or treating diabetic retinopathy.

The glycation or Maillard hypothesis proposes that the complications of diabetes are a direct consequence of accelerated, cumulative modification of proteins and other biomolecules by glucose or its metabolic intermediates during hyperglycaemia in diabetes. The Maillard hypothesis identifies glucose as the culprit in diabetes. The hypothesis is attractive because it explains the development of similar complications in both Type 1 and Type 2 diabetes, despite the differences in aetiology of these diseases. It also explains the development of complications in kidney, nerve, retina and vasculature, tissues in which glucose transport is relatively independent of insulin, but which are rich in long-lived proteins, such as collagens, elastin and myelin. It is now well established that advanced glycation end products (AGEs), although not a freestanding entity, are one of the determinants for the origin of diabetic complications. Schmidt and colleagues (**page 1515**) have summarized recent findings on the receptor for advanced glycation end products (RAGE) which raises hopes for developing new therapies against AGEs and RAGE to ameliorate disease progression. Chandalia and Krishnaswamy (**page 1522**) thoroughly review the historical perspectives of glycated hemoglobin (GHb), different methodologies for GHb estimations, their clinical relevance and applications.

The dramatic increase in the number of classes of oral antidiabetic agents has provided physicians with more tools to help patients manage Type 2 diabetes. The mechanism of action of an agent, its side effect profile, and the potential for various nonglycemic benefits apart from the primary glucose lowering, may help determine which is the best drug for an individual patient. Chakrabarti and Rajagopalan (**page 1533**) present a review of oral antidiabetic agents, some old and some new, with a perspective on developing newer drugs having multiple beneficial actions.

The war against diabetes through the development of new drugs is an ongoing continuous process. The therapies include novel classes of drugs as well as new insulin sensitizers and new stimulators of insulin secretion. Unfortunately, the speed with which our knowledge of diabetes and its effects is expanding is not matched by the availability of new drugs. Kadhe and Arasan (**page 1539**) present the promising advances in drug delivery of oral hypoglycemic agents with special reference to improvised formulations of glipizide and metformin.

Ever since the technologies in molecular biology made possible the development of human insulin, it appeared that animal insulins have slowly lost their place in the therapeutic armamentarium. Indeed, in many countries animal insulin is no longer available. As human insulin is very much more expensive than animal insulins, they are clearly unaffordable by people in many developing countries. The article by Mohan (**page 1544**) points out the 'pros' and 'cons' of animal and human insulins and makes a plea to continue animal insulins at least till human insulin becomes affordable.

The impetus behind the discovery of insulin in 1922 was the need to lower blood-sugar levels to prevent death from diabetes. With insulin as the only treatment for Type 1 diabetes (insulin-dependent diabetes), using it effectively to control blood-sugar levels became the challenge of the 1980s and 1990s. The question whether complications can be prevented by good diabetes control was finally resolved by the Diabetes Control and Complications Trial (DCCT)[6] and United Kingdom Prospective Diabetes Study (UKPDS)[7]. Eighty years after insulin was first made available as a treatment for diabetes, today clinicians have a range of insulins including designer insulin and analogues and delivery systems so that treatment can be tailored to suit the lifestyles of individuals with diabetes. Using these tools we can achieve the goals helping patients feel better and avoiding the distressing long-term complications of diabetes. David Owens and colleagues (**page 1548**) elaborate on the recent developments in insulin therapy and delivery systems.

A number of studies during the past decade have investigated the comorbidity of mental illness and diabetes. Studies that used structured diagnostic interviews found that the mean prevalence of current depression in diabetic subjects was 14.0% in controlled studies and 15.4% in uncontrolled studies. These rates are at least three times the 3%–4% prevalence of major depressive disorder found in the general adult population of the United States[8]. Sridhar and Madhu (**page 1556**) explain how psychosocial and cultural issues can influence outcomes of diabetes management and the importance of training health professionals in psychosocial skills.

The authors who have contributed to this special section have decades of experience in their respective fields and readily accepted to contribute the articles when we approached them. We sincerely thank all of them for submitting their articles on time. A special word of appreciation to P. Balaram, Editor, *Current Science*, who conceived the need for such a compilation on diabetes. We hope that this special section on current concepts in diabetes will be useful to scientists, physicians, pharmacueticals companies, government policy makers and to the diabetes community as a whole.

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