Preface

Diabetes is one of the most prevalent chronic disorders worldwide with significant personal and financial costs for patients and their families, as well as for society. Different types of diabetes exist with distinct aetiologies and pathogeneses. No age group seems to be spared, and some populations are more affected than others. Northern Scandinavia, for instance, and other more defined geographical areas such as Sardinia, have particularly high incidence rates of Type 1 (insulin-dependent) diabetes mellitus. In these populations, Type 1 diabetes seems to be increasing to the extent that as many as 1% of newborns will develop Type 1 diabetes during their lifetimes. The more common form of diabetes, Type 2 (non-insulin-dependent) diabetes, may affect 3–5% of the Western population. In Native Americans and certain Indian and Polynesian populations, more than 50–60% of the 40- to 50-year-olds suffer from Type 2 diabetes. Adopting a Western diet and lifestyle appears to be a threat to certain populations not previously affected by diabetes.

In both Type 1 and Type 2 diabetes, inadequate amounts of secreted insulin are associated with an inability to control blood sugar levels. Obesity and hypertension are risk factors for Type 2 diabetes. Insulin therapy is a rather inadequate replacement therapy for the Type 1 diabetic patient. And, in Type 2 diabetes, a programme aimed at lowering the blood sugar with a combination of diet and exercise is preferable to either insulin injections or oral hypoglycaemic agents. The relative failure of replacement therapy in Type 1 diabetes and of the management of Type 2 diabetes is reflected by an increased mortality due to cardiovascular disease and other diabetic complications including retinopathy, nephropathy and neuropathy in these patients.

Despite the serious consequences of diabetes, the underlying factors which lead to the development of this disorder are far from understood. Rapid advances are currently being made to unravel some of the mechanisms. In fact, rare cases of monogenic non-insulin-dependent diabetes have been found to be due to defined mutations in the genes for insulin and the insulin receptor and, most recently, in the glucokinase gene. These cases explain the

aetiology of but a few Type 2 diabetes patients and do not seem to contribute much to understanding the complex development of Type 1 diabetes, which is associated with immunopathological phenomena. The possible role of autoimmunity in this type of diabetes may require that we first gain a better understanding of the development of the immunological system in man and, in particular, how tolerance to self-antigens is induced in utero and maintained after birth. Numerous questions therefore remain to be answered before it is possible to diagnose, classify and properly treat diabetes, based on knowledge of its aetiology. Multi-disciplinary interactions and novel biomedical research approaches and tools seem necessary to enhance progress. There may, however, be a disparity between the progress made in medical biology in general and the progress made specifically in understanding diabetes. Where is our understanding of diabetes situated in relation to the frontiers of research in medical biology?

An interdisciplinary approach to answer this question was the purpose of the Third JDF World Conference on Diabetes Research, professionally and successfully organised by the Juvenile Diabetes Foundation International in Monte Carlo, Monaco, 8–10 March 1992. The Third JDF World Conference was long in planning. The objective of the meeting was to review the state-of-the-art of research, not only in diabetes, but in all areas that might be relevant to research in diabetes. For many of the participants, therefore, diabetes was not the subject of their own research. The aim of the Programme Committee from the very beginning was to organise a conference on diabetes without the “old boys network”—to identify areas of scientific research which may not yet have had an impact on diabetes. The areas selected were relevant to diabetes and its complications; however, that relevance may not yet have been applied to research in diabetes and incorporated in the rapid progress that is taking place there. It was felt that a conference covering many of the frontiers of medical biology with clinical and basic scientists from other fields might bring into focus, or even help to answer, critical questions that need to be addressed in order to

understand the aetiology and pathogenesis of diabetes and its complications.

The format of this conference was also somewhat unusual. The nine different work groups were given as much time as possible to themselves to permit comprehensive discussions without the formalities and time restrictions of conventional meetings. The theme of interdisciplinary interactions was important, and plenary lectures, given by eminent scientists served as focal points for these interactions.

An overview of diabetes was given by C. Ronald Kahn (Joslin Diabetes Center, Boston, Mass., USA) in his lecture on Diabetogenes and the Environment in the Pathogenesis of Diabetes. Retrovirus Disease, including the devastating consequences of AIDS and the many phenomena that need to be explained to understand the pathogenesis of this disease, was reviewed by Luc Montagnier (Institut Pasteur, Paris, France). Sir Walter Bodmer (Imperial Cancer Research Fund, London, UK) examined the Basic Biology of Disease to indicate the rapid progress in understanding the genetic component of diseases such as familial polyposis in specific molecular terms and to provide approaches to the diagnoses and understanding of disease mechanisms. The Progress in Understanding Hereditary Diseases was reviewed by Sir David Weatherall (John Radcliffe Hospital, Oxford, UK) who described the ever increasing complexity of the molecular biology of the globin gene and the phenotypic diversity of diseases involving the same gene. He discussed the rapid scientific progress and simultaneously successful clinical applications which the field of molecular medicine has accomplished. Finally, Sir Gustav Nossal, (Walter and Eliza Hall Institute, Royal Melbourne Hospital, Victoria, Australia) addressed some of the fundamental, but least understood, functions of the immune system in his lecture on Immunologic Tolerance. The exquisite ability of the immune system to distinguish between self and non-self is now best studied with an array of molecular and cellular approaches; however, the possible mechanisms of tolerance induction to self-antigens remain, in part, unresolved. The understanding of tolerance must be fundamental to autoimmune disorders such as Type 1 diabetes.

This supplement to *Diabetologia* represents the highlights of the deliberations within each of the nine work groups. The reports were prepared by rapporteurs in close interaction with the group chairpersons and the participants. First drafts of the reports were prepared at the site to ensure rapidity of publication. Consequently, each report is somewhat different, but provides both the necessary background as well as recent highlights and views of the future for each of the nine topics. Existing knowledge of genetic mechanisms in both Type 1 and 2 diabetes is reviewed in Work Group 1: Genetic Control. Observations of mutations in the glucokinase gene in Type 2 were reported with a summary of recent information and

the use of new technologies. The possibility of obtaining genetic information in inbred experimental animal models which could be applied to man was discussed. The spectrum of therapies used in the management of diabetes at present and potential future management approaches, including pancreas and islet transplantation, were discussed in detail by Work Group 2: Treatment of Diabetes Mellitus. The need for better understanding of how to treat pre-Type 1 diabetic patients as well as for more sensitive biochemical and genetic markers to identify subjects at increased risk for developing diabetic complications was stressed.

Novel approaches to studying the brain were discussed by Work Group 3: Neurotrophic Interactions in the Nervous System. Recent evidence that growth and trophic functions are central to development and maintenance of brain function is a clear-cut example of a new approach into the many unanswered questions about the effects of diabetes on the brain. The rapid changes that take place in ion movements across plasma membranes and the molecular basis of ion movements was discussed in Work Group 4: Ion Channels. Certain ion channels may be critically involved in cells which are abnormal in diabetes and basic research has proven advantageous to our improved understanding of the role of ion channels in insulin release. Complete Beta-cell channel characterisations will be necessary before the field of diabetes can take advantage of detailed characterisation of channel structure for rational and specific drug design.

Atherosclerosis which is accelerated in diabetes, is responsible for marked morbidity and mortality in diabetic patients. The Process of Atherogenesis, reviewed as cellular and molecular interactions in Work Group 5, clearly indicated new directions which can now be applied to this condition in diabetes. Evidence that atherosclerosis is a specialised, chronic, inflammatory, fibroproliferative process may help to explain the extreme sensitivity of diabetic patients to this complication. It is interesting to note that one of the recommendations of this work group is the need for systematic studies to compare lesions of atherosclerosis in diabetic patients to those of non-diabetic humans. This should have been done a long time ago!

In Work Group 6: Cellular and Molecular Biology of the Beta Cell several highlights of recent advances involving insulin gene transcription factors, processing of proinsulin as well as specific features of the Beta cell in terms of stimulus-secretion coupling were reviewed. The possibility of dissecting the mechanisms that regulate insulin secretion by systematic gene transfections in non-insulin-producing cells, may offer future directions which will help reveal basic mechanisms that need to be understood before we will be able to explain diabetes due to Beta-cell failure. This conclusion was also evident in Work Group 7: Autoimmune Tolerance and Type 1 Diabetes which provided a succinct and up-to-date account on possible mechanisms of tolerance both in man and experimental

animals. It is an exciting prospect that the understanding of tolerance should make it possible to explore novel therapeutic approaches to arrest autoimmune responses. This is of considerable importance as novel assays for HLA susceptibility genes, a second diabetes gene, and rapid and precise high-capacity assays for islet GAD65 antibodies may improve the prediction of Type 1 diabetes. Therefore Consequences of Disease Prediction was added as Work Group 8. The reading of this report should be mandatory for all who contemplate establishing programmes for the screening of diabetes. The history of screening and counselling programmes of other, mostly monogenic diseases, are not encouraging and should serve as a warning to all to think carefully and approach this process differently for diabetes. This report clearly delineates problems in disease prediction, in general, and for diabetes, in particular.

Finally, the report of Work Group 9: Molecular Design, entitled Structural Biology and Diabetes: Molecular Pathogenesis and Rational Drug Design, provides an extremely useful account of the recent advances in structural molecular biology and molecular design relevant to drug discovery. It is evident that the rapid development of this field may facilitate the development of new drugs to treat and perhaps prevent diabetes.

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