HETEROGENEITY WITHIN TYPE II AND MODY DIABETES

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ABSTRACT

The heterogeneity within Type II diabetes (NIDDM) and within Maturity-Onset type Diabetes of Young people (MODY), a subset of NIDDM which is inherited in an autosomal dominant fashion, is discussed. Aspects of the definition and phenotypic expression of MODY are reviewed. Within NIDDM there are differences in patterns of inheritance between subgroups. HLA antigen associations are not found in most NIDDM populations but exist in three specific population groups with Type II diabetes. Within NIDDM and within MODY there are differences in the magnitude of insulin responses to glucose, differences in target tissue responsiveness to insulin in vivo, and differences in receptor and post-receptor effects of insulin. Structurally abnormal variant and biologically defective insulin molecules have been found in some Type II diabetic patients and in members of certain MODY families. The presence or absence of obesity may mark heterogeneous groups of Type II diabetic patients, in addition to the importance of obesity in uncovering an insulin secretory defect by causing insulin resistance. There is heterogeneity in susceptibility to vascular disease within NIDDM and MODY. The natural history of carbohydrate metabolism and of insulin secretory responses to glucose in early Type I diabetes and in MODY with low insulin secretory responses are illustrated and similarities and dissimilarities compared and contrasted. Failure to recognize young patients with MODY may contribute to incorrect diagnosis, management, and assignment of prognosis of this form of diabetes in the young by many practicing physicians.
The recognition that Type I or insulin-dependent diabetes (IDDM) and Type II or noninsulin-dependent (NIDDM) differ from each other not only phenotypically but also in etiology and pathogenesis led the National Diabetes Data Group (NDDG) to devise the present nomenclature and classification of diabetes mellitus.\textsuperscript{37} These were adopted by the World Health Organization.\textsuperscript{58} As suggested by the NDDG report, the classification should be reexamined periodically to reflect improved understanding of the disease, to stimulate further research, and to be of help to practicing physicians.

Various speakers in this Symposium will address in detail the heterogeneous nature of Type I and Type II diabetes on the basis of genetic, immunologic and environmental factors and discuss similarities and dissimilarities between these two entities. I will give a simplified overview of the heterogeneity of Type II diabetes and emphasize Maternity-Onset type Diabetes of Young people (MODY), a subset of NIDDM in which there is heterogeneity in pathogenesis as well. Similarities and dissimilarities between MODY and conventional NIDDM will be reviewed on the one hand, and between MODY and Type I diabetes on the other hand. In addition, I will demonstrate that abandonment of the term MODY, or a similar term, as a subgroup within the classification of NIDDM, as adopted by the NDDG report,\textsuperscript{37} fails to recognize this heterogeneity within NIDDM, and more importantly may contribute to incorrect diagnosis, management and prognosis of this form of diabetes in the young by many practicing physicians.

Evidence abounds for heterogeneity within Type II diabetes (Table 1). Genetic factors as expressed by patterns of inheritance differentiate subgroups within NIDDM. MODY is consistent with autosomal dominant inheritance\textsuperscript{2,3,10,14,15,26,56,57} while most NIDDM is not inherited in this way. Further evidence for genetic heterogeneity within Type II diabetes comes from HLA antigen association. In contradistinction to Type I diabetes, HLA antigen associations have not been found in most populations with Type II diabetes. On the other hand, in three specific population groups an HLA antigen has been associated with NIDDM (Pimas, HLA-A259; Xhosas, HLA-A26; Fijians, HLA-Bw6.\textsuperscript{50} No association has been found between specific HLA antigens and MODY\textsuperscript{1,10,12,38,43,44} in spite of an earlier report to the contrary.\textsuperscript{2}

Before proceeding, I would like to review briefly some aspects of the evolution of our definition and the phenotypic expression of MODY. In 1960 we first reported that impaired glucose tolerance, diabetic glucose tolerance and fasting hypergycemia occurring in young patients could be normalized by sulfonylurea therapy.\textsuperscript{17} In 1964, exactly 20 years ago here in Toronto at the Vth Congress of the International Diabetes Federation, we first used the term "maternity-onset type diabetes of young people" for the nonprogressive or slowly progressive diabetes occurring in children, adolescents and