INTRODUCTION AND HISTORICAL BACKGROUND

In 1933 Himsworth and Kerr\(^8\) used the plasma glucose response to an oral glucose plus intravenous insulin challenge to divide patients with diabetes mellitus into two types—designated as being either insulin sensitive or insulin insensitive. Based upon the available clinical information, patients classified by Himsworth as being insulin sensitive seem most comparable to individuals who would be designated as having insulin-dependent diabetes (IDDM) by today's criteria.\(^12\) In contrast, the group of patients who would be classified today as having noninsulin-dependent diabetes mellitus (NIDDM) share the characteristics of those designated by Himsworth as being insulin insensitive. Several years ago,\(^16\) we reviewed available information as to the ability of insulin to stimulate glucose uptake in patients with diabetes mellitus. At that time we indicated that resistance to insulin-stimulated glucose uptake characterizes patients with NIDDM, but that it could also exist in patients with IDDM. However, in the latter instance the resistance appeared to be related to degree of metabolic control, and it seemed to us that insulin sensitivity was normal in patients with IDDM well-controlled on insulin. Interest in the role played by insulin resistance in the pathogenesis of diabetes mellitus has increased greatly since publication of our earlier review. This has been associated with the development of new techniques for the assessment of insulin-stimulated glucose uptake in patients with diabetes, resulting in the appearance of a considerable amount of new information as to the characteristics of insulin action in patients.
The purpose of this presentation will be to critically review available data, and to use this information in an attempt to define the effects of IDDM and NIDDM on insulin-stimulated glucose disposal.

INSULIN-STIMULATED GLUCOSE UPTAKE IN IDDM

IDDM is characterized by absolute hypoinsulinemia, and efforts have been made to use animal models rendered insulin deficient in order to gain insights into this syndrome. It is always dangerous to extrapolate from animal models, and it is obvious that there are great differences between a human being with IDDM and a rat with streptozotocin-induced insulin deficiency. On the other hand, there is considerable information concerning the impact of insulin deficiency on insulin-stimulated glucose uptake in both dog and rat, and these data seem worthy of review. Thus, in this section an attempt will be made to document the effects on insulin-stimulated glucose uptake in both experimentally-induced insulin deficiency in animal models and in patients with IDDM. Furthermore, an effort will be made to relate these data to the pathogenesis of IDDM.

Animal Studies

Evidence published from our group has demonstrated that resistance to insulin-stimulated glucose disposal can develop in dogs secondary to alloxan-induced insulin deficiency. However, insulin resistance did not occur unless the alloxan-induced diabetes was severe in magnitude. Furthermore, insulin treatment restored insulin-stimulated glucose uptake to normal in dogs with severe alloxan-induced diabetes. Essentially identical findings have been more recently reported by Caruso et al., supporting the view that insulin resistance develops when dogs are made insulin deficient and that the resistance disappears following control of hyperglycemia with insulin.

The appearance of resistance to insulin-stimulated glucose secondary to experimentally-induced insulin deficiency is not limited to dogs, as the same phenomenon has been described in association with streptozotocin-induced diabetes in the rat. Furthermore, in this animal model of IDDM it has been shown that the ability of insulin to maximally stimulate glucose transport by isolated adipocytes is also markedly reduced. Thus, there is considerable evidence that experimentally-induced insulin deficiency in animals leads to a reduction in insulin-stimulated glucose uptake, and that the insulin resistance disappears following insulin replacement and control of hyperglycemia.