nylureas and the biguanides is that many patients are subjected to the expense and potential hazard of long-term treatment to attain a relatively limited goal—freedom from hyperglycemic symptoms—while the agents are used under conditions in which their efficacy is restricted and is only rarely adequately assessed.

The foregoing comments should not be misinterpreted. There are a number of adult-onset diabetics in whom the use of the sulfonylureas can produce further improvement in the range of fluctuations of blood glucose over that resulting from the correction of obesity. These agents may also be effective in some nonobese adult-onset diabetics. We do not eschew the use of sulfonylureas in efforts to prevent symptomatic hyperglycemia, or to achieve an approximation of normal fluctuations in blood glucose. In both instances, however, the consequences of effective weight reduction should first be demonstrated if obesity is present. If the addition of a pharmacologic agent is required, the relative merits either of insulin or of a sulfonylurea must be considered. We do not believe that the biguanides have an established place in the treatment of diabetics.

Many physicians are reluctant to accept the fact that the sulfonylureas and the biguanides are not appropriate agents in circumstances in which rapid correction of the metabolic abnormalities is required. An obvious instance is when ketonemia develops either in association with an acute infection or following the institution of therapy for an unrelated disease that requires the use of agents that can impair endogenous insulin secretion and/or decrease its apparent effectiveness. In these circumstances insulin is indicated, since neither the sulfonylureas nor the biguanides provide significant protection against the development of ketoacidosis. Even in the more common situation in which the previously untreated patient presents with marked polydipsia, polyuria, and weight loss without ketonemia, one cannot predict with any certainty whether the patient will respond to sulfonylurea or biguanide therapy. Under these circumstances, and particularly if there is an associated illness that predisposes to dehydration, it is wiser to use insulin for the acute correction of hyperglycemia and the relief of symptoms. Nonetheless, many physicians attempt trials at treatment with the sulfonylureas or the biguanides with a resulting delay in effective therapy that in some instances may contribute to the development of hyperglycemic nonketotic coma.

The use of insulin to achieve acute improvement does not imply that the patients will necessarily require exogenous insulin once they have been stabilized for a significant period. When there is a demonstrated requirement for the addition of a pharmacologic agent to correct symptomatic hyperglycemia, there is a curious reluctance to employ insulin in the management of adult-onset diabetics. This stems, in part, from the misconception that these patients are invariably insulin hypersecretors and that insulin resistance is a major factor in the pathogenesis of this syndrome. The bulk of the present evidence (which Kipnis has admirably reviewed[21]) clearly indicates that most adult-onset diabetics exhibit an impaired insulin secretory mechanism when compared with appropriately matched age, sex, and weight groups. Moreover, although obesity in both the normal and diabetic individual is associated with an apparent decrease in the biologic effectiveness of insulin, the diabetic state per se does not appear to be associated with any significant degree of insulin antagonism (if one excludes specific circumstances such as