Limited Effectiveness of Oral Hypoglycemic Agents

If the physician resorts to pharmacologic agents to prevent symptomatic hyperglycemia in adult-onset diabetics before demonstrating the necessity for their use, then one might hope that he would at least document the effectiveness of the agent employed. Since a fixed dosage of 1.5 gm. per day of tolbutamide was employed, the data derived from the UGDP study are not completely applicable. However, all the sulfonylureas have a relatively narrow effective dosage range, and the experience of this study is probably not too unrepresentative of the long-term efficacy of sulfonylureas in adult-onset diabetics in whom significant weight reduction is not achieved. In the UDGP study there was an initial improvement in fasting blood sugar and also in the blood glucose level observed one hour after a glucose load. This improved "control" paralleled the initial and transient weight loss which had occurred in these patients. Subsequently there was a progressive rise in mean fasting blood glucose and over the remaining four plus years it rarely differed from that of the group receiving a placebo by more than 15 mg. per cent (the mean values in both groups being persistently abnormal). The blood glucose level after a glucose load also tended to increase progressively in the patients treated with tolbutamide, and the mean value was rarely more than 20 mg. per cent different from that of the placebo group. At the end of four plus years the mean value in the group treated with tolbutamide was 244 mg. per cent, whereas the value for the placebo group was 251 mg. per cent. Thus, one may question whether the use of tolbutamide under these conditions significantly reduced the frequency with which *abnormal* blood glucose levels were present in these patients, or with which symptomatic hyperglycemia developed.

The mechanisms responsible for the development of refractoriness to sulfonylurea therapy in patients in whom an initial response is observed are still uncertain, and the data on its incidence are difficult to interpret.[20] Values ranging from 0.3 to 30 per cent have been reported, and there is a suggestion that the incidence increases with known duration of diabetes. The uncertainty results, in part, from differences in patient selection, in criteria for failure, and in the extent to which other factors such as weight gain and dosage were considered. Unfortunately physicians exercise little selectivity in administering sulfonylurea or biguanides to adult-onset diabetics, ignore the limitations imposed by obesity, and are slow to raise the question of efficacy. One can only guess at the number of patients presently receiving these drugs in whom their withdrawal would not significantly alter the daily fluctuations in blood glucose levels. Our own experience would suggest that it represents a significant fraction of the patients who have received the drug for a prolonged period and in whom obesity persists.

In general, both physicians and patients are reluctant to stop oral hypoglycemic therapy once it has been instituted. In many instances random blood glucose values of 200 to 300 mg. per cent are observed over a period of months to years before the physician reluctantly concludes that the drug has become ineffective. The usual course under these circumstances is to resort to another sulfonylurea in the hope of finding one that is "effective," and often to combine this with a biguanide. The pernicious aspect of the current misuse of the sulfo-