In the present study, improvement in glucose tolerance was seen in the placebo, chlorpropamide and tolbutamide groups. This improvement was not associated with an increase in insulin secretion luring the glucose tolerance test. Improvement in glucose tolerance unassociated with increased insulin secretion has been reported by many groups (*8–13, 28*). The discrepancy is most likely due to timing of the test after initiation of drug therapy. An increase in insulin secretion during oral or intravenous glucose tolerance tests is observed when the tests are performed after 1–8 weeks of therapy. Despite this improvement in glucose tolrance, tests done after three months of therapy in diabetics almost invariably show no increase in insulin output when compared with the initial test. Indeed four of the studies (*6, 14, 16, 26*) which demonstrated increased insulin output during glucose tolerance test after short term therapy with sulfonylureas could not demonstrate the same finding when the tests were repeated after three months of therapy. In this present study, the first follow up test was performed after one year of therapy.

The absence of an increased insulin output to account for the improved glucose tolerance would suggest that the sulfonyureas have some extrapancreatic effects which facilitate the disposal of a glucose load. Several mechanisms have been postulated: (a) an acquired loss of insulin antagonism (*6*); (b) an increased biological activity of the endogenous insulin (*29*); (c) an enhancement of the sensitivity of the beta cell wthout affecting its total response (*30*) and/or (d) an increased secretion of insulin coupled with an increased degradation by the liver of the secreted insulin (*9*).

Before attributing the improvement of glucose tolerance in diabetics on long term sulfonylurea therapy to extrapancreatic effects of the drugs, two "pancreatic factors" must be considered. These are the influence of sulfonylureas on glucagon secretion and on early phase of insulin secretion after a glucose load. Experience is too limited to speculate on the role of glucagon in the mechanism of action of the sulfonylureas. In normal humans, oral administration of chlorpropamide (*31*) and gliburide (*32*) did not suppress plasma glucagon levels whereas, in the only reported study in dabetics, therapy with chlorapropamide for 12 days in six maturity onset diabetics reduced levels of circulating glucagon levels (*33*).

Recent observations of the regulation of diabetes in dogs and man using an artificial pancreas suggested the importance of the early phase on insulin secretion (*34, 35*). An absent or reduced early phase would decrease the effectiveness of insulin whilst a restored first phase could lower the subsequent hyperglycemia after a glucose load without increasing the late phase of insulin secretion. In the present study the time of peak insulin was not corrected by diet with or without drug therapy. Three other groups reported similar findings (*10, 26, 28*) whilst another three groups reported a correction of the delay in the peak insulin (*8, 16, 30*). In one of the latter groups (*16*), a highly significant rise in the early phase of insulin release was shown at five minutes after rapid intravenous glucose administration to diabetics on drug therapy.

Previous studies on the effect of phenformin on glucose tolerance tests in diabetics showed improvement of glucose tolerance associated with a decrease in insulin secretion (*5, 25*). Recently, the suggestion was put forth that phenformin's primary action is to enhance peripheral glucose assimilation, and that the changes in insulin secretion are secondary to this (*36*). The present study demonstrated neither an improvement in glucose tolerance nor a decrease in insulin secretion. The discrepancy may be due to the subjects used and the dose of phenformin given. In the two studies quoted, all subjects were obese and a higher dose of phenformin was used. In addition, the subjects were studied after a very short period of therapy.

The need to re-evaluate periodically the necessity of long term therapy with oral hypoglycemic agents in diabetics was recently raised (*37, 38*). The present study also raises the same question because a group of chemical diabetics on placebo therapy did not differ significantly from another group on drug therapy as far as glucose tolerance was concerned. Two points need to be emphasized. First, the chemical diabetics treated wth drugs were on a fixed dose of drug, no attempt being made to regulate the hyperglycemic closely. Second, on an

References at end of article.