Although the molecular mechanism of action of these agents is not understood, several pertinent observations have been made, Hellman and associates (1971) concluded that labeled tolbutamide is restricted in its action to the extracellular space and does not need to enter the β cell. The invoked release of insulin is immediate and is intimately related to the action of glucose; the drug may sensitize the cell to the normal secretagogue (Widstrom and Cerasi, 1973). Sulfonylureas do not increase the secretion of glucagon.

Extrapancreatic effects of the sulfonylureas have been noted in various organs, and certain of these may potentiate the effects of insulin. A reduction in the hepatic uptake of endogenous insulin has been described (Marshall *et al.*, 1970). Tolbutamide enhances the antilipolytic action of insulin in adipose tissue. This appears to be related to an altered effectiveness of cyclic AMP rather than to any change in metabolism of the cyclic nucleotide (Brown *et al.*, 1972; Fain *et al.*, 1972), and an inhibitory effect of the drug on cyclic AMP-dependent protein kinase has been observed (Wray and Harris, 1973). Other reports indicate a variety of influences on cyclic AMP metabolism in different tissues (Brooker and Fichman, 1971; Kuo *et al.*, 1972; Lasseter *et al.*, 1972); their significance is difficult to assess.

Duration of action, fate, and excretion. The sulfonylureas are absorbed from the gastrointestinal tract and hence are effective when given by mouth. The most important difference among the sulfonylureas, for clinical purposes, is in their duration of action; in increasing order they are tolbutamide, acetohexamide, tolazamide, and chlorpropamide.

Tolbutamide can be detected in the blood within 30 minutes after oral administration; peak concentrations are reached within 3 to 5 hours. The drug is bound to plasma proteins. Tolbutamide is oxidized in the body to butyl-*p*-carboxyphenylsulfonylurea, which is a major excretory product. The half-life of tolbutamide is about 5 hours. Two or occasionally three doses are required daily.

Acetohexamide is rapidly absorbed, and maximal hypoglycemic activity is observed about 3 hours after ingestion. The total duration of action is 12 to 24 hours. Much of the activity is ascribable to a metabolite, *hydroxyhexamide*, which has a plasma half-life of about 6 hours; the parent compound, acetohexamide, has a plasma half-life of 1½ hours. In persons with normal renal and hepatic function, more than 80% is excreted, largely as metabolites, in 24 hours. Two doses are usually required daily.

Tolazamide is slowly absorbed; the onset of hypoglycemic action occurs at 4 to 6 hours and persists at a significant level up to 15 hours after a single dose. Tolazamide is metabolized to a number of hypoglycemic substances that are largely excreted by the kidney. For most patients controlled by tolazamide, a single daily dose is sufficient; a few patients require administration of the drug twice daily.

Chlorpropamide is also rapidly absorbed from the gastrointestinal tract and is bound to plasma proteins. In contrast to tolbutamide, chlorpropamide is not metabolically altered to any significant degree and is excreted very slowly in unchanged form. The half-life of a single dose is about 36 hours, or seven times as long as that of tolbutamide. With daily doses of 250 to 500 mg, blood concentrations may not be expected to reach a plateau before 3 or more days. Chlorpropamide is administered in a single daily dose.

Toxicity. O'Donovan (1959) analyzed the incidence of side effects to *tolbutamide* in 9168 cases. The total incidence of side effects was 3.2%; the drug was withdrawn in 1.5% of the patients. The reactions have been classified as hematological (0.24%), cutaneous (1.1%), and gastrointestinal (1.4%). Of the 22 subjects exhibiting hematological abnormalities, 19 had a transient leukopenia; in 9 instances, the leukocyte count returned to normal despite continuation of the drug. Paresthesia, tinnitus, and headache may also occur.

The total incidence of untoward reactions is about 6% for *chlorpropamide* (hematological, 0.6; cutaneous, 3; gastrointestinal, 2; and jaundice, 0.4%). The jaundice is of the cholestatic type and is usually transient. Hyponatremia has been reported in a small number of patients treated with tolbutamide and chlorpropamide.

Experience with *acetohexamide* and *tolazamide* suggests that the frequency and the kinds of toxic reactions are similar to those encountered with tolbutamide and chlorpropamide. Hematological (leukopenia, agranulocytosis, thrombocytopenia, pancytopenia, and hemolytic anemia), cutaneous (rashes, photosensitivity), gastrointestinal (nausea, vomiting, rarely hemorrhage), and hepatic