

In the dog, both Orinase and its sodium salt were studied. They were equally effective in maintaining a lowered blood sugar, but the water-soluble salt decreased the blood sugar more rapidly. A single dose of 25 mg/kg of the sodium salt decreased and maintained the blood sugar of a normal starving dog at a level 25 to 30 percent below controls for at least 24 to 32 hours. When 100 mg/kg was given, a decrease of about 40 percent was observed for at least 32 hours (Fig. 2). Although 600 mg/kg produced a blood sugar depression no greater than 100 mg/kg, this dose caused death within 20 hours.

Rabbits that were given 400 mg/kg of the sodium salt of Orinase responded with maximum blood sugar depressions similar to those obtained with 100 mg/kg in dogs. The rate of recovery from hypoglycemia in these rabbits, however, was comparable to that in dogs that were given only 5 to 15 mg/kg. The lethal dose for rabbits was approximately 3500 mg/kg and, as in dogs, death was not the result of hypoglycemia.

Determinations of the plasma level of the drug in dogs that were given oral doses at levels of 5, 15, 25, 100 and 600 mg/kg indicated that at the peak plasma levels, about 10 percent of the dose can be found in the plasma (Fig. 2). The times required to clear the plasma of the drug were about 24, 48, and 72 hours for doses of 5, 25, and 100 mg/kg, respectively.

Chronic toxicity studies in several species are now in progress (12). Weanling rats of both sexes have been fed the drug for 8 weeks at approximately 100, 200, and 400 mg/kg, and no significant weight changes were seen when compared with controls. At 4 weeks, no change in the hemograms was apparent, but a moderate enlargement of the thyroid gland was observed in all rats that were given the higher doses.

The mechanism of action of Orinase has not been resolved at the present time, but it does affect the mechanisms involved in the deposition of liver glycogen in the fasting rat. The effect of Orinase on pancreatic function and on the peripheral action of endogenous insulin and glucagon is under study.

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5. Orinase is the Upjohn trademark for its brand

of 1-butyl-3-*p*-tolylsulfonylurea. Supplied by Farbwerke Hoechst and J. B. Wright and D. A. Lytle, department of chemistry, the Upjohn Company.

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Insulin-Sparing Sulfonamides

An orally administered sulfonamide has been found to lower the blood sugar in normal individuals and in patients with "mild" diabetes (1). Toxic effects have been minimal or absent.

The present report (2) summarizes some observations of clinical interest in ten patients who have received one or both of two such sulfonamides (3). Six were "severe" diabetics, and four were "mild" diabetics. Three of the former and one of the latter have been studied under precisely controlled conditions on the metabolic ward.

Three of the five "severe" diabetics had very significant decrease in insulin requirement and/or lowering of blood or urine sugar on a constant dose of insulin. Two grams or more of sulfonamide per day were required to produce this effect. One "severe" diabetic on chemically constant intake had a significant increase in glycosuria during sulfonamide administration. The fifth "severe" diabetic had essentially no demonstrable effect.

Three middle-aged obese diabetics had more than 50-percent reduction in insulin requirement with sulfonamide administration of less than 2 g daily. One mild diabetic, maintained on chemically constant intake (without insulin), had a 50-percent reduction in blood sugar level during the day on which she received a single dose of 3 g of sulfonamide. A very diabetic glucose-tolerance curve reverted to normal following a single dose of 6 g of sulfonamide in one "preclinical" diabetic.

Twenty-four-hour iodine-131 uptake by the thyroid was diminished to less than 5-percent during intensive sulfonamide administration in three severe diabetics. With reduction in dosage, the uptake returned to a normal level.

In the three "severe" diabetics who responded favorably, a reciprocal relationship between blood free sulfonamide and blood sugar levels was noted.

In two "severe" juvenile diabetics, one of whom had profoundly favorable modification of the diabetic state, and the other of whom had a significant increase

in glycosuria during sulfonamide administration, all of the administered sulfonamide could be accounted for in the urine. In the former, the greater portion of urinary sulfonamide was conjugated; in the latter, the greater portion was free.

Decrease in circulating granulocytes was noted during the administration of very large dosages of sulfonamides. Marrow findings were interpreted as showing maturation arrest (William Chew). The blood count returned to normal when medication was decreased or stopped.

The foregoing observations confirm the results recently reported by German investigators in patients with "benign" diabetes. In addition, the sulfonamides favorably modify the diabetic state in some severe diabetics. Significant differences in free and conjugated sulfonamide excretion, respectively, have been noted in severe diabetics who do and who do not respond favorably to sulfonamide. This suggests that differential metabolism of administered sulfonamide may be partly or completely responsible for the type of therapeutic response.

Large dosage may result in toxic manifestations. Reduction of dosage, thus far, has been associated with disappearance of such manifestations.

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2. We wish to acknowledge the technical assistance of Marjorie Coelho, George Fukayama, Florence Olson, and Evalyn Jones.
3. The two sulfonamides that have been used are BZ-55 (N₁-sulfanilyl-N₄-n-butyl-carbamide) and Orinase (a compound identical with BZ-55 except for the substitution of a methyl for the amino group on the benzene ring). Orinase was administered in doses ranging from 1 to 6 g/day. BZ-55 was administered in doses ranging from 1 to 16 g/day. Grateful acknowledgment is made to C. J. O'Donovan of the Upjohn Company for supplies of both preparations and to W. R. Kirtley of the Lilly Research Laboratories for supplies of BZ-55.

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Black Pigment Concentrating Factor in the Fiddler Crab

The production of both a body-lightening and body-darkening blood-borne factor by a crab has not been demonstrated although such antagonistic hormones are known in other crustaceans (1). All crabs that have been examined with the exception of three species of the genus *Sesarma* blanch following eyestalk removal (2).