outer layer of the membrane is thought to be continuous with the endoplasmic reticulum; in such cases, it has been calculated that about one-tenth of the nuclear surface is in direct contact with the cytoplasmic matrix through pores, and the remaining surface is in indirect contact with it through the enclosed cavities of the endoplasmic reticulum (13). Such a close relationship between the nuclear membrane and endoplasmic reticulum is not apparent in the germ cells of the larva *Heliothis obsoleta*.

Summary. 1. Electron microscope studies on thin sections of germ cells of the larva *Heliothis obsoleta* have revealed the presence in the nuclear membrane of pore-like structures which are spaced about 1300 A apart. The pores are approximately 280 A in diameter and are surrounded by a relatively dense wall about 320 A in diameter. Thus, the diameter of the pore plus the surrounding wall is approximately 920 A. 2. The pores appear to be of a size that would permit the passage of large molecules through the nuclear membrane.

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Ineffectiveness of Sulfonylureas in Alloxan Diabetic Rats.* (22297)

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In explanation of the mechanism whereby the sulfonamide derivative, 1-butyl-3-p-aminobenzenesulfonylurea (BZ55) produces hypoglycemia in animal and man, Franke and Fuchs(1), Bertram, Bendfeldt and Otto(2) and Achelis and Hardebeck(3) postulate that the sulfonylurea interferes with the production of glucagon. In support of this hypothesis, these investigators refer to studies by others who demonstrated that some sulfonamide derivatives may reduce the blood sugar of alloxan diabetic animals(4,5). Further, Achelis and Hardebeck state that the sulfonylurea used by Franke and Fuchs(1), and by Bertram, *et al.*(2), produces a decrease in the blood sugar of some alloxan diabetic rabbits though they do state their impression that there may be no decrease in the blood sugar of severely diabetic alloxanized rats. In view of the paucity of data concerning this question, it became pertinent to determine whether or not the sulfonylureas are hypoglycemic in the alloxanized diabetic rat.

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Method. Male rats, weighing from 150 to 250 g were given a subcutaneous injection of 180 mg alloxan per kilogram as a 5% solution. Forty-eight hours thereafter, those animals which developed glycosuria were maintained on 1 unit protamine-zinc insulin† per day. Approximately 1 month later, the insulin was discontinued for 2 days, and after an overnight fast, 15 rats which exhibited a significant glycosuria were selected for study. A group of 15 normal male rats weighing from 150 to 250 g were used as controls after an overnight fast. Both groups of rats were given a gavage of 100 mg 1-butyl-3-p-tolylsulfonylurea‡ per kilogram body weight as a 2% solution in 0.5% sodium bicarbonate, adjusted to pH 8.0. Immediately before and at hourly intervals for 5 hours after the gavage, blood samples were taken from the clipped tails into 0.1 ml pipettes. The blood sugar concentration was determined by the Nelson procedure(6). The blood sugar concentration for each interval after the gavage was expressed as the per cent of the pre-gavage level for each animal.

Results. The mean ± SE response of the blood sugar concentration to the ingestion of tolylsulfonylurea by the normal and alloxan diabetic groups of rats is illustrated in Fig. 1. The mean ± SE initial blood sugar concentration was 83.0 ± 3.0 mg in the normal group and 352 ± 17.5 mg% in the alloxan diabetic group. Whereas the normal rats developed a statistically highly significant diminution in the blood sugar level within 1 hour after the ingestion of the sulfonylurea which persisted for four hours, no significant change in the blood sugar occurred in the diabetic rats.

Discussion. The administration of tolylsulfonylurea to fasted alloxan diabetic rats does not produce any significant change in the blood sugar whereas normal rats exhibit a marked hypoglycemia under similar conditions. Since the administration of alloxan results in necrosis of the beta cells of the Islets of Langerhans and a consequent cessation of insulin production, the hypoglycemic response to the ingestion of tolylsulfonylurea must be related to the availability of insulin. Further, the absence of any hypoglycemic response in the diabetic rats suggests that the hypoglycemic response of the normal rat cannot be due to an inhibition of glucagon production or utilization. Likewise, the hypoglycemic response of the intact animal cannot be due to some acute non-specific hepatotoxic action of the sulfonylurea since such action would be present in the alloxanized as well as the normal animal.

The above indicates that the response of normal animals is due to an increase in the availability of insulin. Such an increase may result from either an increased production of insulin consequent to direct stimulation of the Islets of Langerhans or to a decreased destruction of insulin consequent to an inhibition of the enzyme which catalyzes the destruction of insulin (insulinase), or to both factors. That the inhibition of insulinase plays a role in the response to the sulfonylurea by normal rats is revealed in the observation that the tolylsulfonylurea is a non-competitive inhibitor of insulinase *in vitro* and *in vivo*(7).

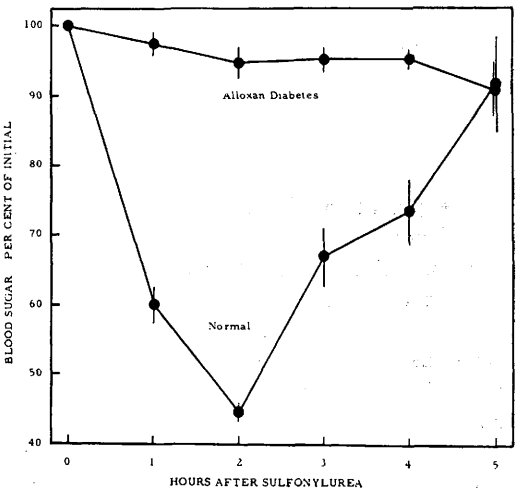

FIG. 1. Effect of tolylsulfonylurea on blood sugar of normal and alloxan diabetic rats. Blood sugar concentration at each hourly interval is expressed as % (mean ± SE) of initial concentration.

† We are indebted to the Eli Lilly Co. for generous supplies of insulin.

‡ We are indebted to Dr. C. J. O'Donovan of the Upjohn Co. for generous supplies of 1-3-butyl-p-tolylsulfonylurea ("Orinase").

Summary. Oral administration of 100 mg 1-3-butyl-p-tolylsulfonylurea per kg body weight to normal rats results in a marked hypoglycemia within one hour which persists for 4 hours. No significant change occurs in blood sugar of similarly treated alloxan diabetic rats.

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Effect of CO_2 on Blood Lactic Acid in Cats.* (22298)

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Fenn and Asano(1) have observed in cats an increased acidity or fall in the alkali reserve of the blood during CO_2 inhalation, which could not be explained by movements of sodium, potassium, or chloride between tissues and plasma, and Shaw and Messer(2) have similarly observed a fall in the bicarbonate level during CO_2 breathing.

These experiments were undertaken to help clarify these findings and to identify if possible the acid mobilized by CO_2.

Procedure. The effect of high CO_2 tension on blood lactic acid was investigated in cats. Each animal was anesthetized by intraperitoneal injection of dial with urethane. Urethane has been found to raise the blood sugar, but not the lactic acid and allows for a large and rapid effect of adrenalin on the blood lactic acid(3). Four different gas mixtures were used, 10%, 20%, 30%, and 40% CO_2 in oxygen. Thus in every case the experimental animal was assured of a sufficient supply of oxygen to avoid any possibility of anoxic lactic acid formation. The desired gas mixture was inhaled by the cat from a spirometer through respiratory valves and a tracheal cannula. Blood samples were taken from the right carotid artery and were immediately deproteinized with trichloroacetic acid to stop glycolysis. After the tracheal and arterial cannulation, heparin was injected (10 mg/kg of body weight). One sample was always taken just before the onset of CO_2 inhalation. The lactic acid was determined colorimetrically by the method described by Barker and Summerson(4).

Results. The findings of these experiments are illustrated in the accompanying graphs. Increments of lactic acid in m. eq./liter above the rather variable initial blood level are plotted against time after the beginning of CO_2 inhalation. To save space, a logarithmic time scale has been used. In the graphs on the left, the different concentrations of CO_2 were inhaled for 10 minutes, (solid lines) after which the cat breathed air, (dotted lines) while in those of the right, the CO_2 was inhaled for one hour or more and a few curves are continued as dotted lines during recovery breathing air. The initial levels of lactic acid corresponding to each curve are indicated by points with appropriate symbols plotted just to the right of each graph.

With 10% CO_2 there is often a slight fall, but never a definite increase in lactic acid. The increase with 30% and 40% CO_2 is on the average somewhat greater than with 20%. The cats were unable to take 40% CO_2 for

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