90. *Effect of Prolonged Administrations of Mesoxalate on Diabetic Condition of Alloxanized Rats*

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Success was obtained in maintaining alloxan diabetic rats in practically the same condition for long periods by feeding them on a diet with a high protein and high fat content prepared by Houssay and Rodriguez.¹⁾ These rats were subjected to 6 months' administration of sodium mesoxalate to observe changes in their diabetic condition.

Methods. The rats were of the Wister species. They were bred in a room temperature of 20–25°C on a daily diet of dry yeast 1 g, dry skim milk 6 g, casein 1.2 g, salad oil 1 g, cod liver oil 0.12 g, and salt mixture 0.4 g. They were allowed to drink water freely. Alloxan monohydrate 80 mg/kg in a 5% solution was injected through the tail vein.

From among these diabetic rats, 60 which showed a constant urine sugar excretion and a blood sugar level of over 200 mg% when hungry were selected for experimentation. These diabetic rats were divided into 3 groups at random: the control group and two other groups treated with sodium mesoxalate 200 mg/kg daily and 50 mg/kg per day orally for 6 months.

After the end of 6 months' observation the rats were sacrificed, liver glycogen quantitatively determined, and a histological study made of the pancreas. The quantitative determination of urine sugar was made by the Fujii-Benedict method and that of blood sugar by the Hagedorn-Jensen method by taking the peripheral venous blood. The quantitative determination of glycogen was made by taking a liver slice of 100–200 mg and producing by hydrolysis with alkali and acid and then applying the Hagedorn-Jensen method. The histological stain of the pancreas was made by the Gomori method.

Results. Nine rats out of 20 in the group given 200 mg/kg/day showed no glycosuria within 1 month, while urine sugar completely disappeared after about 2 months' administration of the drug in 7 rats out of 20 in the group given 50 mg/kg/day. On the other hand, all rats in the control group showed glycosuria for the 6 months experiment period. On the basis of the disappearance of glycosuria, decrease of urine volume, increase in body weight and normalizing of fasting

Fig. 1. Changes in body weights and urine sugar amounts excreted for one week in alloxan diabetic rats which were treated and untreated with sodium mesoxalate. Each line represents the mean for 20 animals tested.

Fig. 2. Increase in the liver glycogen concentration after 6 months' administration of sodium mesoxalate in alloxan diabetic rats. Each bar represents the mean for 3-8 animals.

blood sugar (less than 150 mg%), it was established that 9 rats out of 20 in the 200 mg/kg/day group and 7 rats out of 20 in the 50 mg/kg/day group were cured and that 1 rat out of 20 in the 200 mg/kg/day group and 3 rats out of 20 in the 50 mg/kg/day group were to some extent improved. Experimental results in all rats tested²⁾ are summarized in Fig. 1.

Glycogen content of the liver was observed after 6 months' administration of the drug in these alloxanized rats.

After 5 hours of fasting, no significant difference was seen in liver glycogen content between the untreated diabetic rats and the mesoxalate-treated and cured rats. But after 16 hours of fasting a clear difference was apparent, the liver glycogen of the treated rats being far in excess of that of the untreated rats as shown in Fig. 2.

The histological study³⁾ revealed that there was a greater increase in the number of β -cells of Langerhans' islets in the rats treated with mesoxalate as compared with the control group.

In particular, some in the group administered a large dose, i.e. 200 mg/kg/day, showed an increase of β -cells almost the same as in normal rats. However, there was a degranulation and vacuolization in the cells appeared, although to a lesser extent than in the untreated animals. In this case it is interesting to note that part of the β -cells becomes considerably stained with hematoxylin.

Summary. There was a marked improvement in symptoms in alloxan diabetic rats after the prolonged oral administration of 50–200 mg/kg per day of the drug. The blood sugar level was normalized, urine sugar excretion disappeared, and body weight gradually increased in about half the rats tested. The liver glycogen content of rats which were treated for long periods was significantly increased in comparison with untreated animals. In the histological investigation of those rats it was found that there was a tendency of marked proliferation of β -cells in Langerhans' islets of the pancreas in treated rats whereas there was no such change in the untreated diabetic rats.

References

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