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Alloxan-Induced Azotemia in the Rat.*

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The production of renal injury by alloxan is well known and was pointed out by Dunn and McLetchie[1] in their original article on the production of alloxan diabetes in the rat. In the dog, the islet tissue is more susceptible to injury than is the kidney and thus smaller doses of alloxan are nearly selectively diabetogenic in this species. With larger doses, as Goldner and Gomori[2] have shown, sufficient renal damage is produced to cause a diabetic uremic syndrome. These experiments were undertaken to determine whether this differential sensitivity was present in the rat, and whether a dose level of alloxan could be found that would produce hyperglycemia without azotemia.

All animals used were male rats of the Long-Evans strain between 45 and 50 days of age at the time of the initial injection, and were allowed free access to the stock diet at all times. Alloxan monohydrate in aqueous solution was used and was injected intraperitoneally on a body weight basis. Animals were sacrificed 72 hours after the initial injection except in those cases where the effects of persistent diabetes were studied, in which case they were sacrificed approximately one month after the initial injection. Blood was obtained from the inferior vena cava and following deproteinization, glucose was determined by the Somogyi[3] micro-method and non-protein nitrogen was determined by the micro-Kjeldahl procedure.

In Table I are presented the data on the blood glucose and blood NPN obtained 72 hours after the initial injection of various amounts of alloxan. It will be seen that with a dosage of 200 mg per kg there was a slight rise in the mean glycemia and the azotemia although all animals did not respond. The degree of elevation of the NPN was somewhat greater than that of the blood glucose, one animal showing a blood NPN of 153 mg %, as contrasted with 34 mg %, the maximum of the control group. At a dose level of 250 mg per kg the mean blood glucose was approximately doubled, being 219 mg %; but the mean NPN was increased approximately four-fold being 115 mg %. With larger doses whether given as a single injection or as repeated smaller injections, both the hyperglycemia and azotemia were more marked. In general the severity of the histopathological changes in the kidney paralleled the degree of nitrogen retention.

That this effect on the nitrogenous constituents of the blood was due to a primary renal injury and was not due to functional renal failure secondary to the severe diabetic state was shown by the fact that the simultaneous administration of insulin prevented the extreme hyperglycemia but did not alter the azotemia.

In another series of animals which received 400 mg of alloxan per kg it was determined that 3 major components of the NPN: namely, urea N, uric acid N, and creatinine N were all elevated. The mean control urea N level was 22 mg % as compared with a mean experimental level of 165 mg %. For uric acid and creatinine the control values were 3.2 mg % and 1.7 mg % respectively as compared with 12.5 mg % and 6.7 mg % for the alloxan-treated group.

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1 Dunn, J. S., and McLetchie, N. G. B., *Lancet*, 1943, **2**, 384.

2 Goldner, M. G., and Gomori, G., *Endocrinology*, 1943, **33**, 297.

3 Somogyi, M., *J. Biol. Chem.*, 1937, **117**, 771.

TABLE I.
Blood Glucose and Non-protein Nitrogen Level in the Rat 72 Hours After the Initial Alloxan Administration.

Alloxan dose per kg	Blood glucose in mg %		Blood NPN in mg %	
	Mean	Range	Mean	Range
Uninj. control	129 (13)*	113-146	27 (8)	23-34
150 mg	118 (13)	85-155	32 (6)	25-39
200 "	151 (11)	108-333	66 (6)	26-153
250 "	219 (10)	123-388	115 (4)	27-215
300 "	381 (6)	156-648	201 (4)	168-235
150 " 2 consecutive days. Total dose 300 mg	354 (13)	129-668	115 (6)	61-233
200 mg 2 consecutive days. Total 400 mg	736 (8)	149†-1030	140 (8)	41-238
150 mg 3 consecutive days. Total 450 mg	549 (8)	189-955	185 (8)	95-347
200 mg 2 consecutive days plus 2 units protamine insulin daily	140 (8)	41-238	177 (5)	83-245

* The figure in parentheses indicates the number of observations in the group.
† Only one value below 600 mg %.

TABLE II.
Blood Glucose and Non-protein Nitrogen Level in Rats with Alloxan Induced Diabetes of One Month's Duration.

	Blood glucose in mg %		Blood NPN in mg %	
	Mean	Range	Mean	Range
Uninjected controls (7)*	122	76-143	27	22-30
Persistent diabetics (8)	431	381-510	41	24-70
Recovered diabetics (5)	132	111-153	30	27-31

* The figure in parentheses indicates the number of observations in the group.

In Table II are presented the data obtained from animals 31-34 days following the administration of 400 mg of alloxan per kg. It will be seen that even in those animals in which there was a persistent diabetes, there was only slight residual azotemia. The mean blood NPN in this group was 41 mg % as compared with 27 mg % for the controls or as compared with 140 mg % for animals 72 hours after the injection of the same amount of alloxan. This would seem to indicate a high degree of functional recovery of the kidney. In those animals in which diabetes was not persistent there was a complete functional recovery of the kidney insofar as the NPN was completely normal.

Summary. In rats of the Long-Evans strain there is no difference between the diabetogenic and nephrotoxic dose of alloxan as judged by hyperglycemia and azotemia. Even when diabetes persists there is nearly complete functional recovery of the kidney.