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Effect of Intrasplenic Injections of Alloxan in the Rat.*

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Alloxan is usually effective in producing diabetes in experimental animals whether it is administered subcutaneously or intramuscularly,[1] intraperitoneally,[2] intravenously[3] or enterally.[4] This drug has a greater diabetogenic action when given to rats which have been fasted 2 or 3 days.[5] Furthermore, the selective action of alloxan, in destroying certain cells of the pancreatic islets, takes place within a few minutes following its administration.[6,7]

Since the action of alloxan is limited to such a short period of time following its administration, the present study has been undertaken in order to determine whether the liver might be responsible for the inactivation of this substance. Intrasplenic injections permit the alloxan to pass through the liver before it reaches the pancreas.

Material and Methods. One hundred and twelve adult male rats of the Long-Evans strain were used in this study. The animals were given intrasplenic injections of a 25% solution of alloxan and the dosages used were 50, 88, 125 or 150 mg/kg. The rate of injection, controlled by a micrometer syringe, varied in the different animals but the most satisfactory rate tried was 1/100 cc/min. Control rats received either intraperitoneal or subcutaneous injections of alloxan in the same amounts and at the same injection rate as was injected intrasplenically.

The rats were placed in metabolism cages for urine collections on the eighth and fifteenth days, respectively, following the injection of alloxan. Only rats with a 2-4+ urine sugar were considered to be diabetic. At the end of the 15-day period samples of tissue were taken for histological examination. Both the splenic and duodenal portions of the pancreas and pieces of liver were fixed in Bouin's solution.

Results. Considerable variation was seen in the response of the rats to the intrasplenic as well as the intraperitoneal injections of alloxan. Certain animals were not able to tolerate the toxic effects of the drug, regardless of the route of administration and differences in the injection rate and the amount of alloxan administered accounted for some variation. The data for the animals which were not fasted before they received the alloxan are shown in Table IA. The rate at which the injections were given is not indicated on the table. In most instances, however, the control rats received intraperitoneal injections of the same amount of alloxan, at the same rate, as did the animals which were given injections intrasplenically. The smaller amounts of alloxan were usually more effective in producing diabetes when injected rapidly into the spleen than when given intraperitoneally. However, if 125 mg/kg were injected rapidly into the spleen, the animals usually died. Death in such cases was probably due, in many instances, to infarcts in the liver. The lobes of such livers showed a marked necrosis, although the crown region was generally normal.

Animals which received the drug intrasplenically tolerated it much better when injections were made at a slower rate (1/100 cc/min.) but a given amount of alloxan was

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TABLE I.
Effect of Alloxan Injections.

	Mg alloxan/kg body weight						
	A Non-fasted				B Fasted 2 days		
	50	88	125	150	88	125	150
A. Intrasplenic							
1. Diabetic	1	2	4			7	2
2. Non-diabetic	8	1	1	3	3	1	
3. Died	1	5	16	1			
B. Intraperitoneal							
1. Diabetic			7			6	2
2. Non-diabetic	4	4	6	2	3	4	
3. Died	2	3	3				
C. Subcutaneous							
1. Diabetic						8	
2. Non-diabetic						4	

less effective in producing diabetes.

A more uniform response was obtained and no deaths occurred when the rats were fasted 2 days before they were injected slowly with alloxan (Table IB). In the rats studied, 88 mg of alloxan per kg was not sufficient to elicit diabetes when given intrasplenically or intraperitoneally, while 150 mg resulted in a severe diabetes when injected by either method. When 125 mg/kg was given, diabetes was produced in 7 out of 8 rats when injected intrasplenically, in 8 out of 12 rats when injected subcutaneously, and in 6 out of 10 rats when given intraperitoneally. Within the limitation of the number of animals used in this study it was noted that diabetes in the latter group of animals was not so severe as in the other 2 groups.

The islets in both the splenic and duodenal portions of the pancreas were examined histologically in an attempt to determine whether one portion of this gland might be more susceptible to the alloxan. Islet damage, however, was not localized in any particular region of the pancreas.

Comment. Since alloxan injected intrasplenically is just as diabetogenic as when given subcutaneously, indications are that this drug is not inactivated specifically in the liver. However, when administered intrasplenically, alloxan appears to be slightly more effective in producing diabetes than when given intraperitoneally. A possible explanation for this variation is that after the latter method of administration, the alloxan is absorbed over a large area of the peritoneal cavity and is thus diluted to a greater extent before reaching the pancreas.

Summary. The present observations indicate that alloxan is just as effective as a diabetogenic agent when given intrasplenically as when given subcutaneously. Similar amounts of alloxan given intraperitoneally result in many instances in a milder diabetes. It appears that alloxan is not inactivated specifically in the liver.