

THE PRODUCTION OF HYPERGLYCEMIA BY SUBCUTANEOUS INJECTIONS OF SODIUM ARSENITE IN THE RABBIT.\*

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According to the literature, relative to the action of arsenic in the body, the liver plays an important rôle since in general it serves as a storehouse for the poison, and, in turn, this organ is largely affected. In the metabolism of the liver, carbohydrate, presumably glycogen, is intimately associated. There are few records of the action of arsenic on carbohydrate metabolism. On the other hand arsenic has assumed such importance therapeutically in recent years as to warrant investigation of the influence of this poison upon obvious phases of carbohydrate metabolism, one of which serves as the subject for the present communication.

Saikowsky (1) found that non-fatal doses of arsenious and arsenic oxides caused an increase in the weight of the liver, fatty degeneration, and loss of glycogen, and that the latter conditions were even more evident than in phosphorus poisoning. The fat of the liver was greatly increased, the glycogen present only in traces. As the doses employed by Saikowsky were large, Chittenden and Blake (2) repeated the experiment with small repeated doses of arsenious oxide. Their results indicate a diminution in the weight of the liver and the amount of liver fat and an increase in glycogen. However, in one rabbit they obtained a complete disappearance of glycogen from the liver. In another animal they found a pronounced fatty degeneration of the liver, and an increase in liver weight and liver glycogen. From such results it is difficult to

\* The data are taken from the dissertation presented in 1925 to Yale University by Alice Dimick in candidacy for the degree of Doctor of Philosophy.

draw conclusions, but the data are sufficiently suggestive to indicate an action on carbohydrate metabolism which is probably related to the dosage. After the completion of the present work a paper appeared by Van Dyke (3) yielding comparable results with intravenous injections of sodium arsenite. Since in some respects our results treat of different phases than those covered by Van Dyke, it seems desirable to record them here briefly.

TABLE I.

*Influence of Minimum Fatal Dose of Arsenious Oxide on Blood Sugar and Hemoglobin.*

Rabbit I, weight 2 kilos. Injected subcutaneously 8 mg. of  $As_2O_3$  per kilo.\*

Day.	Hemoglobin.	Blood sugar, mg. per 100 cc.	Remarks.
	<i>per cent</i>		
1	90	111	
2	78		
3	75	101	
4			
9 hrs. after injection.	82	260	Injected 16 mg. $As_2O_3$ . Soft, unformed feces.
22 " " "	101	75	
33 " " "	80	77	Animal paralyzed. Heart beat very shallow and slow. Animal died.

\* M.F.D. for rabbits = 8.33 mg.  $As_2O_3$  (Sollmann (4)).

## EXPERIMENTAL.

*Methods.*

In this investigation normal, full grown rabbits were selected, irrespective of sex or weight. The animals were maintained upon a diet consisting of carrots and oats. In order to obviate the influence of food upon the blood sugar content the rabbits were not fed on experimental days until the last blood sample for the day had been collected. The animals always had access to water.

Blood was drawn from an ear vein. Blood sugar and hemoglobin estimations were made by the methods of Folin and Wu and of Newcomer respectively.

TABLE II.

*Effect of Subcutaneous Injection of Arsenious Oxide upon Blood Sugar Content and Hemoglobin.*

Rabbit II, male, weight 1.9 kilos. Injected subcutaneously 3.7 mg. of  $As_2O_3$  per kilo.

Day.	Hemo- globin.	Blood sugar, mg. per 100 cc.	Sugar in urine.	Remarks.
	<i>per cent</i>			
1	69	153	Negative.	
2	76	140	"	
1 p.m.				Injected 7 mg. $As_2O_3$ .
5 "	70	211	Trace.	
7 "	64	175		
3				
8 a.m.	71	167		
10 "	67	162	Trace.	
2 p.m.	70	156		
4				
10 a.m.	65	169	Negative.	
5				
10 a.m.	58	154		

TABLE III.

*Influence of Single Injection of Arsenious Oxide on Blood Sugar Content and Hemoglobin.*

Rabbit IV, female, weight 2.28 kilos. Injected subcutaneously 4 mg. of  $As_2O_3$  per kilo.

Day.	Hemo- globin.	Blood sugar, mg. per 100 cc.	Sugar in urine.	Remarks.
	<i>per cent</i>			
1	65	158		
10.15 a.m.				Injected 9 mg. $As_2O_3$ .
11.15 "	55	290	Negative.	
1.15 p.m.	61	457	"	
3.15 "	58	339	No urine.	
2				
9.15 a.m.	58	347	Negative.	
11.15 "	57	134	"	
3				
9.15 a.m.	55	150		

The arsenic was injected as sodium arsenite in aqueous solution in varying doses, both single and repeated.

*Influence of Single Large Doses of Arsenite.*

According to Sollmann (4) the minimum fatal dose of  $\text{As}_2\text{O}_3$  for rabbits is 8 mg. per kilo. This quantity was injected into one animal which died in less than 48 hours. The effect upon blood sugar may be seen from Table I. In Tables II and III the influence of approximately one-half this dose may be seen. From these experiments it is evident that a marked hyperglycemia is present within a few hours.

*Influence of Repeated Large Doses of Arsenite.*

In Table IV may be found the effect of repeated doses of approximately one-half the minimum lethal dose. It will be noted that the hyperglycemia promptly appears after each injection and that it quite rapidly falls to near the normal limits.

*Influence of Repeated Small Doses of Arsenite.*

Tables V and VI are illustrative examples of the effect of repeated small doses of sodium arsenite. It will be observed that the influence of the small doses is much less marked than with the larger doses. With the smallest dose there may or may not be an increased blood sugar content.

DISCUSSION.

In attempting to interpret the observations herein recorded, it may be recalled that in arsenic poisoning a condition exists which may resemble the changes found in phosphorus and chloroform poisoning. In these conditions it is assumed that carbohydrate metabolism is involved. In how far arsenic may be included in the category with phosphorus and chloroform is still uncertain. Allen (5) states that "phosphorus and arsenic in exceptional instances cause glycosuria; and since their action is largely upon the liver, the glycosuria may perhaps be due to a sudden dropping of glycogen by the poisoned hepatic cells." Begemann (6) also found that arsenious acid diminishes alimentary glycosuria.

Masing (7) has shown that arsenic reduces the oxidation in the liver but without increasing the carbohydrates.

The striking feature of the experiments submitted here is the marked hyperglycemia in certain instances without the appear-

TABLE IV.

*Influence of Repeated Injections of Arsenious Oxide upon Blood Sugar Content and Hemoglobin.*

Rabbit III, male, weight 1.8 kilos. Injected subcutaneously 4 mg. of  $\text{As}_2\text{O}_3$  per kilo.

Day.	Hemo- globin.	Blood sugar, mg. per 100 cc.	Sugar in urine.	Remarks.
1	71	124		
2	80	132		
9.20 a.m.				Injected 6 mg. $\text{As}_2\text{O}_3$ .
10.20 "	80	197		
12.20 p.m.	79	388		
2.20 "	76	343	Trace.	
4.20 "	73	246		
6.20 "	69	110		
3				
9.20 a.m.	77	117	Trace.	
12.20 p.m.	76	120		
4				
9.20 a.m.	73	152		
5				
9.20 a.m.	79	140		
6				
9.20 a.m.				Injected 5 mg. $\text{As}_2\text{O}_3$ . Diarrhea.
10.20 "	70	157		
12.20 p.m.	80	248		
3.20 "	77			
7				
9.20 a.m.	94			
2.20 p.m.	68	127		Animal died 2 days later.

ance in the urine of more than insignificant traces of sugar. Kidney function as indicated by urinary volume and appearance did not appear to be altered. In some instances, however, a considerable quantity of albumin was present, pointing to a detrimental influence upon the renal organs.

Examination of the livers for glycogen revealed its presence in only very small quantities. In view of these facts the most obvious explanation of the action of arsenic upon this phase of carbohydrate metabolism is increased glycogenolysis resulting in hyperglycemia which is emphasized by an effect upon the kidney

TABLE V.

*Influence of Repeated Injections of Arsenious Oxide upon Blood Sugar Content and Hemoglobin.*

Rabbit V, female, weight 2.2 kilos.

Day.	Hemoglobin.	Blood sugar, mg. per 100 cc.	Sugar in urine.	Remarks.
1	58	91		
2				
12 p.m.				
6 "	56	126	Negative.	Injected 1 mg. $As_2O_3$ per kilo. Slight trace of albumin.
3				
12 p.m.	63	120	Negative.	
4				
12 p.m.	63	122	Negative.	Trace albumin. Injected 1 mg. $As_2O_3$ per kilo.
5	64	141	Negative.	
6	58	95	"	Injected 2 mg. $As_2O_3$ per kilo.
7	62	168	"	No diarrhea.
8				
10	77	198		Injected 3 mg. $As_2O_3$ per kilo.

whereby the renal threshold for sugar is increased. The blood sugar content is far above that usually provocative of a distinct glycosuria. That the hyperglycemia is not due to a marked concentration of the blood is indicated by the lack of significant changes in the hemoglobin content.

TABLE VI.

*Influence of Repeated Injections of Arsenious Oxide upon Blood Sugar Content and Hemoglobin.*

Rabbit VI, male, weight 2.5 kilos.

Day.	Hemo- globin.	Blood sugar, mg. per 100 cc.	Sugar in urine.	Remarks.
1	<i>per cent</i> 89	69		
2				
12.10 p.m.				Injected 1 mg. As <sub>2</sub> O <sub>3</sub> per kilo.
6.10 "	96	94	Negative.	
3				
12.10 p.m.	92	114	Negative.	
4				
12.10 p.m.	86	96	Slight trace.	
12.20 "				Injected 1 mg. As <sub>2</sub> O <sub>3</sub> per kilo.
5				
12.20 p.m.	91	104	Slight trace.	
6				
12.10 p.m.	79	113	Slight trace.	
12.20 "				Injected 2 mg. As <sub>2</sub> O <sub>3</sub> per kilo.
7				
12.20 p.m.	85	109		
10	82	126		Injected 3 mg. As <sub>2</sub> O <sub>3</sub> per kilo.

## CONCLUSIONS.

Arsenious oxide injected subcutaneously into rabbits produces a marked hyperglycemia which is in general proportional to the dosage employed. It is probable that the renal organs are involved also since this hyperglycemia causes little or no glycosuria.

It is also probable that the hyperglycemia is due to increased glycogenolysis since the liver of the experimental animal contains only traces of glycogen.

## BIBLIOGRAPHY.

1. Saikowsky, D., *Virchows Arch. path. Anat.*, 1865, xxxiv, 73.
2. Chittenden, R. H., and Blake, J. A., *Tr. Connecticut Acad.*, 1888, viii, 106.
3. Van Dyke, H. B., *J. Pharmacol. and Exp. Therap.*, 1925, xxvi, 287.
4. Sollmann, T., *A laboratory guide in pharmacology*, Philadelphia, 1917, 322.
5. Allen, F. M., *Glycosuria and diabetes*, Boston, 1913, 535, 744.
6. Begemann, H., *Arch. internat. pharmacod.*, 1912, xxii, 97.
7. Masing, E., *Arch. exp. Path. u. Pharmacol.*, 1912, xxxvii, 491.