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Hepatic Vascular Occlusion Following Lethal Doses of Salmine Sulfate.

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Previous studies have shown that the intravenous injection of salmine sulfate (a protamine) causes anaphylactoid shock.[1] The production of emboli may play a role in this phenomenon.[2] This hypothesis was based on 1. The demonstration *in vitro* of salmine-induced protein precipitation and in some cases hemagglutination in the blood of various species. 2. The addition of salmine sulfate to blood perfusing the normal liver or lung resulted in obstruction to flow. 3. Similar addition of salmine sulfate to saline solutions perfusing these organs failed to diminish flow.

In no experiments previously reported has the blood flow through any vascular bed been studied in animals killed with lethal intravenous doses of protamine. The present experiments were undertaken with a view to testing *in vivo* the assumed vascular occlusive effects of salmine sulfate. Since the nature of the postulated emboli appeared to preclude their direct microscopic demonstration, liver perfusion studies were made after administering protamine solutions intravenously. The rat and guinea pig were chosen because of the difference in the effect of salmine on their bloods.[2] Although salmine sulfate causes a precipitate of plasma protein in the blood of both, hemagglutination is produced only in the rat.

Method. Rats (220-260 g) and guinea pigs (225-300 g) were anesthetized by the intraperitoneal injection of 5 mg of 5% pentobarbital sodium/100 g of body weight. With the onset of respiratory failure produced by the injection of 10-50 mg of 2% salmine sulfate* per 100 g into the portal vein of the anesthetized animal, cannulation of the portal vein and the thoracic inferior vena cava was performed. Physiological saline at 37°C ± 1°C was delivered from a Mariotte flask to the portal cannula at pressures varied progressively from 2-42 cm of saline. The rate of flow of the perfusion fluid at various pressures has been employed as the criterion of the occlusive effect. Respiratory failure was induced in the control animals by ether, pentobarbital, or pneumothorax.

Results and Discussion. The results of experiments on 22 animals are given in Table I. Perfusion rates in salmine-treated rats and guinea pigs are significantly and consistently lower than in the controls. The observations with portal pressures of 4 to 8 cm of saline should be especially emphasized, for these constitute the range of normal pressures.[3] At portal pressures of 4 and 8 cm, average control rates of 5 and 11 cc of saline per minute were observed in the rat. In the treated animals no appreciable flow occurred at these pressures. In the rats given 50 mg per 100 g no flow could be induced using pressures as high as 42 cm. In the guinea pig comparable but less pronounced reduction in flow occurred. It can be concluded that lethal intraportal doses of salmine sulfate produce a vascular occlusive effect on the hepatic circulation of the animals studied.

The difference between the degree of vascular occlusion in the rat as compared to the guinea pig parallels the difference noted in *in vitro* studies of the effect of salmine sulfate on the blood of these animals. Both hemagglutination and protein precipitation occur in the rat, whereas only protein precipitation was noted in the guinea pig.

Among the factors which may be causally related to this impedance to flow are the lodgment of multiple small emboli, local cellular edema, and/or local vasospasm. The present studies do not directly differentiate the relative importance of these factors. But when

1 Thompson, W. H., *Trans. Roy. Acad. Med. in Ireland*, 1900, **18**, 426.

2 Shelley, W. B., Hodgkins, M. P., Visscher, M. B., PROC. SOC. EXP. BIOL. AND MED., 1942, **50**, 300.

* Kindly placed at our disposal by Eli Lilly and Company of Indianapolis, Indiana.

3 Trowell, O. A., *J. Physiol.*, 1942, **100**, 432.

TABLE I.
Perfusion Rates Through Portal Circulation of Isolated Livers of Rats and Guinea Pigs after Intraportal Administration of Salmine Sulfate at Various Dose Levels.

Animal	No. of animals	Dose of salmine sulfate mg/100 g	Perfusion flow rate—cc/min Perfusion pressure: 2 cm	4 cm	8 cm	16 cm	32 cm	42 cm
Rat	4	Control	1	5	11	25	50	50
	3	10	0	0	1	4	26	39
	2	20	0	0	0	1	15	27
	2	50	0	0	0	0	0	0
Guinea Pig	4	Control	4	8	20	34	51	62
	3	10	0	1	9	17	45	70
	2	20	0	1	5	17	33	60
	2	50	0	0	4	17	39	51

considered in conjunction with our previous observations, they are consistent with the hypothesis that embolus formation plays a role in the toxicity of intravenously administered salmine sulfate. No studies have been made to evaluate the importance of direct histotoxic effects.

Conclusion. 1. Vascular occlusion, as shown by perfusion studies, occurred in the livers of rats and guinea pigs receiving lethal doses of salmine sulfate. 2. This effect was of greater magnitude in the rat than in the guinea pig.

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Metabolism of Glycolic and Glyoxylic Acids.*

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In the metabolism of both glycine and fatty acids it has been proposed that 2 carbon acids are formed which in turn take part in the formation of glucose or the acetone bodies. The purpose of this communication is to present further information on the metabolism of 2 compounds, glycolic acid ($HOCH_2$—COOH) and glyoxylic acid (O:HC—COOH) either of which might be involved in the above transformations.

Methods. Three types of experiments were performed. (1) Liver glycogen formation studies were done by administering the test substances by stomach tube to adult male rats which had been previously fasted for 48 hours. Glycogen was determined by the method of Good, Kramer and Somogyi.[1] (2) Urine acetone body excretion studies were made by administering the test substance by stomach tube over a 4-day period to fasting adult male rats which previous to fasting had been maintained on a high fat-low protein diet. Daily urine collections were made from individual rats and acetone bodies were determined by the method of Van Slyke.[2] (3) Blood acetone bodies were studied in rats which were taken from the stock diet and immediately fed the test substances by stomach tube. The rats were anesthetized with amytal and bled from the large abdominal vessels and blood acetone bodies were determined by the method of Barnes and Wick.[3]

Results. Liver glycogen after administering either glycolic acid or sodium glycolate, the

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1 Good, C. A., Kramer, H., and Somogyi, M., *J. Biol. Chem.*, 1933, **100**, 485.

2 Van Slyke, D. D., *J. Biol. Chem.*, 1917, **32**, 455.

3 Barnes, R. H., and Wick, A. N., *J. Biol. Chem.*, 1939, **131**, 413.