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Excretion of Organic Sulfates Following Administration of Adrenalin.

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Several investigators,[1–5] basing their conclusions on experiments carried out *in vitro*, have considered it possible that adrenalin is detoxified in the mammalian body by the oxidative action of enzymes or by autoxidation. Recently however Richter[6] has found conjugation to be the main physiological mechanism by which adrenalin is inactivated in the body. The presence of conjugated adrenalin in the urine of man and the rabbit was shown in his experiments by means of positive tests for adrenalin after hydrolysis with acid. His partially purified specimens gave negative tests for glucuronic acid but positive tests for a sulfate ester.

The following experiment was carried out to furnish quantitative information on the effect of the administration of adrenalin on the excretion of glucuronic acid and organic sulfates.

The urinary sulfates and glucuronates were estimated 24 hours after administration of the

TABLE I.

Excretion of Glucuronic Acid and the Ratio of Inorganic to Total Sulfates in the Urine of Rabbits Following Administration of Adrenalin.

No. of rabbit	Total volume of 1:1000 adrenalin admin., ml	Mode of admin.	Glucuronic acid, mg	Ratio inorganic to total sulfates, %	Comments
1	control	—	10	92	
2	"	—	36	85	
3	"	—	17	90	
4	"	—	59	89	
5	"	—	41	88	
6	1.0	intravenous	36	78	Died 1 hr after final dose
7	1.0	"	40	70	S*
8	1.0	"	18	74	Died 3 " " " "
9	2.0	"	51	73	S
10	2.0	"	10	73	Died 3 " " " "
11	2.0	subcutaneous	27	79	S
12	2.5	"	26	75	S
13	2.5	"	37	77	S
14	5.0	"	48	78	S
15	10.0	"	51	64	Died 30 min " " "
16	10.0	oral	48	85	S
17	20.0	"	48	75	S
18	30.0	"	40	64	S
19	40.0	"	29	56	S
20	50.0	"	0	50	S

S = Survived.

1 Abderhalden, E., and Guggenheim, M., *Hoppe-Seyler's Z.*, 1908, **57**, 329.

2 Green, D. E., and Richter, D., *Biochem. J.*, 1937, **31**, 569.

3 Blaschko, H., Richter, D., and Schlossmann, H., *Biochem. J.*, 1937, **31**, 2187.

4 Bhagvat, K., and Richter, D., *Biochem. J.*, 1938, **32**, 1397.

5 Goodman, L., and Gilman, A., *The Pharmacological Basis of Therapeutics*, The Macmillan Co., New York, 1940.

6 Richter, D., *J. Physiol.*, 1940, **98**, 361.

drug to rabbits, or immediately after death when it occurred within 24 hours. Organic and inorganic sulfates were determined by the turbidimetric method of Treon and Crutchfield,[7] and glucuronic acid by a quantitative procedure described elsewhere.[8] A 1:1000 solution of adrenalin chloride (Parke, Davis and Co.) was employed. It was injected into an ear vein at a rate of 1 ml/30 min. Subcutaneous injections were given in 1.0 ml doses, once every 2 hours, while the compound was given orally (by stomach tube) in 10 ml doses once every 2 hours until the intended dose had been administered. (Precautions to prevent inactivation of adrenalin by reason of the alkaline reaction of the intestine were not taken.)

Experimental results are summarized in Table I. It is evident from the data that adrenalin is responsible for an augmented excretion of sulfate esters in the urine. The intravenous injection of 1 or 2 mg caused a reduction in the percentage of inorganic to total sulfates from a normal average of about 89, to 74%. Doses of 2 to 10 ml injected subcutaneously caused a reduction to 79 and 64%, respectively, while the oral administration of from 10 to 50 ml adrenalin reduced the percentage of inorganic sulfates to 85 and 50, respectively. The excretion of glucuronic acid remained normal after the injection or ingestion of this drug. It is of interest to note that a far greater quantity of organic sulfates was excreted than could be accounted for by conjugation with the amount of adrenalin that had been administered.

Conclusions. In the rabbit the administration of adrenalin is followed by a markedly augmented excretion of organic sulfates. This appears to indicate that this drug is inactivated *in vivo* by conjugation with sulfuric acid. Conjugation with glucuronic acid does not occur. These observations confirm those reported by Richter in 1940.

[7] Treon, J., and Crutchfield, W., Jr., *Ind. Eng. Chem., Anal. Ed.*, 1942, **14**, 119.

[8] Deichmann, W., *J. Lab. and Clin. Med.*, 1943, **28**, 770.

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On the Toxicity of Atabrine.*

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Atabrine (Quinacrine) has lately attracted much attention as an effective substitute for quinine. In animals large doses of atabrine administered orally cause gastro-intestinal and central irritation; intravenous administration causes lowering of the blood pressure, and direct action of the drug on the excised heart results in "paralysis." In man the gastro-intestinal symptoms are reported to be most conspicuous; irritation of the central nervous system occurs but is encountered more rarely.[1]

A consideration of chemical configuration and the mechanism of drug action suggested that the toxic symptoms encountered after administration of atabrine may be due, in

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[1] Findlay, G. M., *Recent Advances in Chemotherapy*, 1939.