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Effects of Acetylsalicylic Acid on Excretion of Endogenous Metabolites By Man.* (27193)

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Much of the current information on the biochemistry of salicylate has recently been reviewed by Smith(1). Despopoulos(2) has suggested the possibility that the salicylate inhibition of "active accumulation" of p-amino hippuric acid (PAH) may be due to disruption of mitochondrial metabolism. Yu and Gutman(3) have observed a paradoxical effect of varying doses of salicylate on excretion of uric acid by man. On the basis of these types of studies it seemed important to determine whether salicylate would affect the excretion of endogenous metabolites in man since many of these metabolites are "actively transported". The effect of varying amounts of acetylsalicylic acid on excretion of creatinine, urea, uric acid, amino nitrogen, inorganic phosphate, sodium, potassium and chloride was studied.

Procedure and methods. A group of 25 college and medical students (males) served as experimental subjects. Urine samples were collected by voiding after hydration with water until urine flow ranged between 4-20 ml/min. Base line studies were obtained on all subjects as previously described by Wu and Elliott(4). Analytical methods used include alpha amino nitrogen by Yemm and Cocking(5), amino acid chromatography by Hardy(6), flame photometric determination of sodium and potassium(7) and uric acid analysis by the methods of Caraway(8) and Liddle(9).

A series of 4 control samples of urine was collected from each subject and 0.6 or 1.8 g of acetylsalicylic acid (aspirin) were given by mouth. Urine samples were then collected at 15-20-minute intervals for 4 hours.

Results. Fifty-four experiments with varying oral doses of acetylsalicylic acid were performed. The findings are as follows: *sodium, potassium and chloride.* The drug caused a decrease in sodium and chloride excretion in every subject studied except one, following both the 0.6 and the 1.8 g amounts of the drug. The data in Table I show that both amounts had essentially the same effect. Excretion rate data in meq/min for a typical experiment are plotted in Fig. 1. Potassium excretion was not affected in these experiments. *Amino acids.* Aminoaciduria was found in every subject following administration of 1.8 g of the drug. Average increase in excretion rate was 202%. Data from one of these experiments are shown in Fig. 2 and Table I. *Uric acid.* Varying degrees of uricosuria resulted from administration of 1.8 g of drug in all but 3 subjects. Small doses (0.6 g) caused varying retention of uric acid in all subjects so that ex-

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TABLE I. Results.

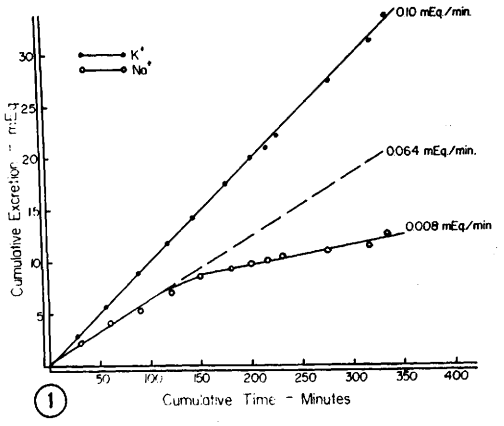
Determination		No. of subjects	Mean change as % control	Range, % control	S.D.	"P" value
Uric acid	a	18	56	23- 91	19	<.001
	b	16	151	74-220	45	<.001
Sodium	a	15	44	8-100	27	<.001
	b	16	45	14-100	26	<.001
Chloride	a	14	50	10-100	23	<.001
	b	14	56	19-100	27	<.001
Amino N	a	17	148	57-450	103	>.05
	b	16	274	100-900	184	<.01
Creatinine	a	18	97	78-100	14	>.3
	b	17	92	50-115	16	>.05
Potassium	a	15	108	35-310	66	>.6
	b	16	111	37-300	66	>.5
Phosphate	a	15	124	56-280	75	>.2
	b	16	129	50-400	87	>.1

a = .6 g acetylsalicylic acid.
b = 1.8 g " " .

perimental rates ranged from 23-91% of control values (Table I). *Inorganic phosphate.* There was wide variation in excretion of inorganic phosphate and the data are not statistically significant. *Creatinine.* There was variation in excretion of creatinine. The excretion rate was reduced in 5 of 18 subjects following 0.6 g of acetylsalicylic acid and in 7 of 17 subjects following 1.8 g. There was a small increase in rate in 2 subjects following the large amount of drug. These data are summarized in Table I.

Discussion. Since salicylate has been shown previously to affect the energy available from oxidative phosphorylation reactions, it seems reasonable that the excretion rate of any substance excreted by "active transport" would be altered by the presence of acetylsalicylic acid. The data presented tend to support this hypothesis. It is of particular interest that the decreases in sodium excretion data are statistically significant while the potassium excretion data are not. These findings, combined with the significant decrease in chloride excretion, suggest an adrenal steroid effect which may be the result of interference by salicylate with conjugation of steroids in the liver. This would cause a net increase in blood level of active adrenal cortical hormones that might account for the effect on electrolyte excretion.

If uric acid excretion is dependent on tubular secretion as suggested by Yu and Gutman (3), the paradoxical effect of varying doses of salicylate on uric acid excretion might also be explained by the effect of salicylate on the energy cycle in the renal tubule cell. In this case we would assume that the small dose would be sufficient to block active tubular secretion resulting in a decrease in uric acid excretion rate, while the larger amount of salicylate would have a more profound effect on the energy requiring reabsorptive processes of the renal tubule cell. This would be in agreement with our finding of aminoaciduria in every subject administered larger quantities of acetylsalicylic acid. Paper chromatographic analysis for amino acids in the urine samples from these subjects indi-



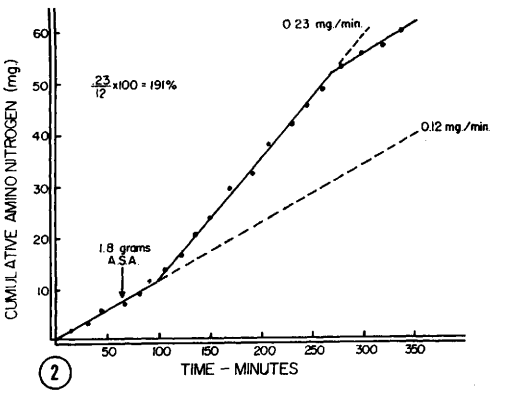


FIG. 1. Effect of 0.6 g of acetylsalicylic acid on renal excretion of sodium and potassium. Dashed line is the extrapolation of sodium excretion rate from control period. The drug was administered 90 min. after start of experiment.

FIG. 2. Effect of 1.8 g of acetylsalicylic acid on renal excretion of endogenous amino acids.

cated that the increase in alpha amino nitrogen was due to a generalized failure of the reabsorptive mechanisms rather than inhibition of a specific transport system for groups of amino acids as described by Beyer(10).

The finding of variable potassium excretion appears to differ from the report by Robin, *et al.*(11) that hypokalemia occurs during salicylate poisoning. However, this hypokalemia was thought to be a manifestation of the respiratory alkalosis caused by salicylate rather than a specific function of salicylate.

Summary. 1. Both small and large amounts of acetylsalicylic acid have a marked inhibitory effect on renal excretion of sodium and chloride. 2. Uricosuric amounts of acetylsalicylic acid block the renal reabsorptive mechanisms for amino acids. 3. The findings of Yu and Gutman concerning the paradoxical effects of salicylate on uric acid excretion are confirmed.

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Fate of Radioactive Glucosamine Administered Parenterally to the Rat.* (27194)

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Glucosamine is found in many animal tissues, in glycoproteins and mucopolysaccharides. It has been shown that radioactively labeled glucose is converted to protein bound glucosamine(1,2,3). Furthermore, liver extracts are capable of transforming glucosamine to acetyl glucosamine-6-phosphate(4). However, few studies have been made of utilization of glucosamine by the intact animal. Boas and Foley(5) administered glucosamine intravenously to rats and found that the added glucosamine was rapidly cleared from the blood and that the hexosamine content of a number of tissues was increased.

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Recently, glucosamine-1-C^{14} has become available in amounts which make possible studies in laboratory animals. Preliminary studies indicate that glucosamine-1-C^{14} administered parenterally to rats is rapidly incorporated into the serum glycoproteins without degradation(6). This report concerns the distribution of radioactivity in various tissues of the rat following administration of radioactive glucosamine.

Methods. Three male Holtzman rats ranging in weight between 350 and 450 g were fed a stock diet of laboratory chow. During the experiment, the animals were kept in individual all glass metabolism cages(7) which permit collection of expired air, urine and feces. Feed and water were supplied *ad libitum*. One hundred microcuries of radio-