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Rate of Urinary Arsenic Excretion After Giving Acetarsone ("Stovarsol") and "Carbarsone" by Mouth.*

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As part of the necessary pharmacological evaluation of a new drug[1] before it should be tried even in controlled clinical experimentation, its rate of absorption (if given by mouth) and excretion should be studied. If possible this should be done on normal human volunteers in order that any deleterious effects may be noted to be guarded against when used in patients. Especially is this procedure important in order to judge the danger of cumulative effect before venturing to employ arsenical compounds on repeated administration in human therapy.

Except for the bare statement that 3-acetylamino-4-hydroxyphenylarsonic acid (acetarsone N.N.R. or "stovarsol") is excreted in the urine after oral administration,[2] we have not been able to find any information regarding its absorption or excretion, in spite of the fact that it has considerable toxicity[3] and has been widely exploited in human therapy with some incidence of poisoning.† The present study was undertaken to supply this deficiency in part. Since our laboratory investigation of a considerable number of arsenical compounds revealed several which would seem on experimental evidence to be superior to acetarsone in treating amebiasis, we decided to include in this study the one upon which we had the most satisfac-

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1 Leake, C. D., *J. Am. Med. Assn.*, 1929, **90**, 1632.

2 Findlay, G. M., "Recent Advances in Chemotherapy," Phila., 1930, p. 92.

3 Anderson, H. H., and Leake, C. D., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 267.

† It is our opinion that drug houses should be held responsible for the untoward effects of new drugs in human therapy, if commercial exploitation is made without the previous publication from disinterested sources in reputable scientific journals of data obtained in the pharmacological evaluation of such drugs, especially in regard to toxicity and rate of excretion.

tory data. This was 4-carbaminophenylarsonic acid,‡ previously shown on comparison with acetarsone to have a lower toxicity on oral administration, but more amebacidal action *in vitro,* and with a calculated therapeutic index about 8 times as great.[4]

Excretion in the urine is evidence of absorption from the gut following oral administration. The rate of excretion (assuming all the arsenic to be excreted that is absorbed) then would be, for these compounds, an index of the rate of alimentary absorption, and might give some indication of the degree of systemic action to be expected. Direct determination by stool examination of the amount of arsenic not absorbed from the gut is too difficult to be practical. But we intend to control our data on the rate of excretion in the urine, as an index of the rate of absorption of these compounds from the gut, by comparison with the rate of excretion following the intravenous injection of known amounts, and by determining in animals the ratio between the average lethal dose of each compound when given by mouth or intravenously.

The method of analysis was essentially the same as that followed by Young and Muehlberger in studying the excretion of tryparsamide.[5] Following Kjeldahl digestion of aliquot urine samples with sulphuric and nitric acids and neutralizing with sodium hydroxide and sodium carbonate, the arsenic present was titrated by iodine using starch as an indicator.

In one subject undergoing a course of treatment with acetarsone for amebiasis, a total of 11 tablets, each containing 0.25 gm. of the drug, were given over a period of 6 days. Of a total of 0.756 gm. of arsenic administered, 29% was recovered from the urine in 14 days following the beginning of treatment. In a second subject receiving 14 tablets of acetarsone (for amebiasis) over a period of 7 days, 17% of the 0.952 gm. of arsenic administered was recovered during the 10 days after treatment began. In a normal human (A) receiving two 0.25 gm. tablets of acetarsone containing 0.138 gm. of arsenic, 20% was recovered in 72 hours after giving the drug, but in a second subject (L) given the same amount, only 7% was found in 29 hours following oral administration. Two months later, these same 2 normal subjects were each given 0.5 gm. "carbarsone"

‡ Deutsches Reichpatent, 213155; U. S. P. No. 937929 (issued to Paul Ehrlich and A. Bertheim, 1909); supplied by the Lilly Research Laboratories. For convenience in expression we propose to call this substance "carbarsone."

[4] Leake, C. D., Koch, D. A., and Anderson, H. H., PROC. SOC. EXP. BIOL. AND MED., 1930, **27**, 717.

[5] Young, A. G., and Muehlberger, C. W., *J. Pharmacol. Exp. Therap.*, 1924, **23**, 461.

by mouth, containing 0.135 gm. of arsenic. From subject L, 13% of the arsenic was recovered from the urine after 42 hours, while only 8% was found in the urine of the other subject (A) after 52 hours. The rate of excretion of the 2 drugs in the normal subjects is shown graphically in Fig. 1.

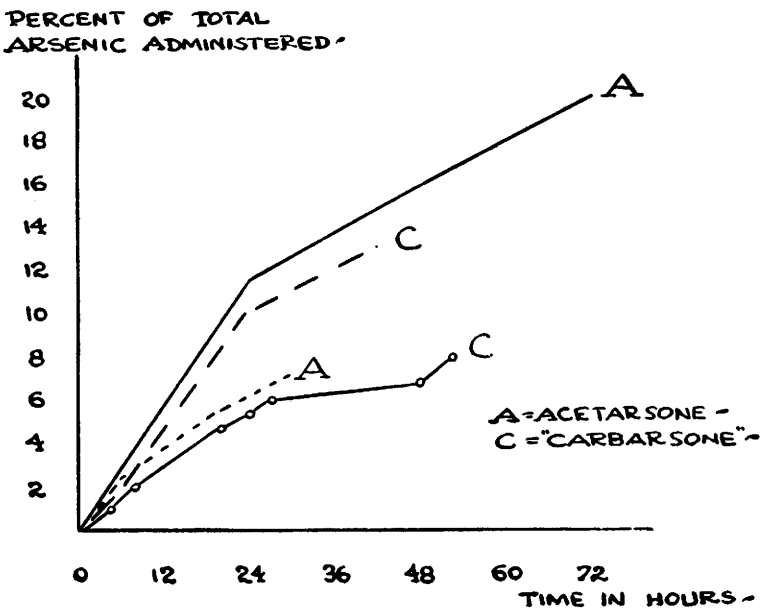

FIG. 1.
Rate of urinary excretion of arsenic after oral administration of acetarsone and "carbarsone" in normal humans.

The fact that in the normal subjects from 10 to 30% of the recovered arsenic appeared in the urine within 6 hours after ingestion is evidence of fairly prompt absorption. Although 60 to 75% of the total arsenic found in the urine was eliminated within 24 hours after ingestion, the delay in the excretion of the remainder recovered may be explained on the basis of delayed absorption as the drug passes down the gut. Nevertheless this delay presents an element of danger in connection with the possibility of cumulative systemic effect on repeated administration. Especially is this liable with "carbarsone", where the substituted amino group in the para position to the arsenic suggests possible deleterious action on the optic tract.[6] Even though this drug would probably not be used in human therapy (for amebiasis) in oral doses larger than 0.5 gm. per day for 10 days

[6] Young, A. G., and Loevenhart, A. S., *J. Pharmacol. Exp. Therap.*, 1924, **23**, 107.

(the total of which would equal a frequently used single intravenous dose of tryparsamide, a closely related compound), careful watch for eye symptoms would be a necessary phase of the treatment. No symptoms of any sort were noted in our normal subjects.

Summary. 3-acetylamino-4-hydroxyphenylarsonic acid (acetarsone N.N.R. or "stovarsol") and 4-carbaminophenylarsonic acid ("carbarsone") are rather slowly excreted in the urine after oral administration. In one normal human subject 20% of the ingested arsenic in 0.5 gm. acetarsone was recovered in the urine in 72 hours, but only 8% of the arsenic of the same dose of "carbarsone" after 52 hours. In another normal human, 7% of the arsenic received in the same dose of acetarsone was found in the urine in 24 hours, while 13% was recovered from the same amount of "carbarsone" in 42 hours. Even though relatively small absorption from the bowel is indicated by these experiments, "carbarsone" should be used cautiously in human therapy until it is established whether or not it is liable to injure the optic tract.

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Iodoxybenzoate as a Test Reagent for Free Phenolic Hydroxyl Groups in Organic Compounds.

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While attempting to study the pharmacological action of oxidation products of morphine, I tried to induce rapid oxidation of the drug by means of ammonium iodoxybenzoate. The salts of iodoxybenzoic acid have been studied by Loevenhart and his associates[1] and their oxidizing properties are well known. Upon treating morphine salts with an aqueous solution of ammonium iodoxybenzoate the straw to garnet color characteristic of a morphine solution on eremacausis develops within a few moments. No other opium alkaloid, except apomorphine, seems to yield color with this reagent. Codeine is monomethyl morphine, with the methyl group replacing the hydrogen of the phenolic hydroxyl group of morphine. This

[1] Loevenhart, A. S., and Grove, W. E., *J. Pharmacol. Exp. Therap.*, 1911, **3**, 101; Arkin, A., *Ibid.*, 1911, **3**, 145; Young, A. G., and Yeomans, J. B., *J. Am. Med. Assn.*, 1926, **87**, 746.