fall in the protein content suggesting that widespread liver damage caused by A-methopterine. Although the methods employed in these investigations could not determine whether A-methopterine exerts its action by blocking the biosynthesis of co-enzyme A, or by inhibiting this latter's acetylating effect, it would appear likely that, given the doses used, both mechanisms were involved to a substantial degree. This hypothesis would seem to be supported by the fact that, in animals that were treated with either panthotheine (an intermediate product in the biosynthesis of co-enzyme A) or with adenosintriphosphate, the effect of A-methopterine on the acetylating processes was much smaller.[4].

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The effect of disulfiram on the metabolism of normetanephrine-1-^{14}C in the guinea pig

(*Received* 14 *April* 1960)

THE oxidation of acetaldehyde is inhibited, both *in vivo* and *in vitro* by disulfiram*, a drug used in the treatment of alcoholism.[1] The oxidation of β-substituted acetaldehydes, which are intermediary metabolites of the catecholamines and related compounds,[2] may also be inhibited by this substance. This possibility was investigated in the guinea pig using normetanephrine, the O-methyl derivative of norepinephrine.

Normetanephrine-1-^{14}C, with a specific activity of 1·0 μc/μmole, was synthesized from vanillincyanohydrin-1-^{14}C by reduction with $LiAlH_4$.[3] Female guinea pigs weighing between 350 and 450 g were injected with 100 μg of this substrate and their urines collected during a 24 h period over $CHCl_3$. A portion of the combined urines was extracted with 4 vols. of alcohol–acetone (1 : 1) and the extract applied to a strip of Whatman no. 1 filter paper and developed overnight in *n*-butanol–acetic acid–water, (4 : 1 : 1). The dried chromatogram was scanned in a gas flow counter coupled with a recording device. The relations of the separated radioactive metabolites are shown in scan *A*, Fig. 1. The major

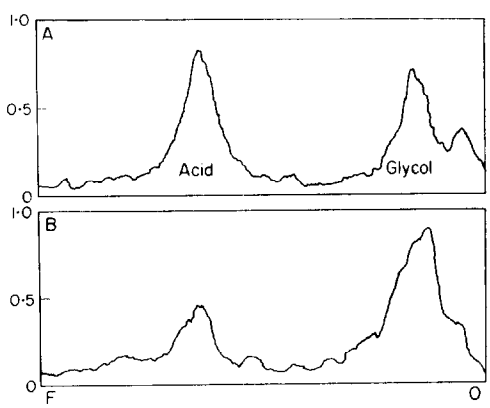

FIG. 1. Distribution and relative amounts of radioactive metabolites on the scanned chromatograms of urines from guinea pigs given normetanephrine-1-^{14}C. Scan *A*: untreated animals. Scan *B*: animals injected intraperitoneally with 200 mg of disulfiram per kg daily for 3 days prior to the administration of normetanephrine-1-^{14}C. Descending chromatography in *n*-butanol–acetic acid–water (4 : 1 : 1). *O* and *F*: origin and front.

* Disulfiram (tetraethylthiuram disulfide) was kindly supplied by Ayerst Laboratories.

radioactive metabolite at $R_f = 0{\cdot}65$ was identified as vanillylmandelic acid (VMA) by distribution coefficients and chromatographic behavior. The second major peak at $R_f = 0{\cdot}2$ represents primarily a compound which can be adsorbed onto an anion exchange resin (Dowex 1X2), but not a cation exchange resin (Dowex 50X16). This anionic compound had an R_f of 0·55 in *iso*propanol–7 N NH_3 (4 : 1). After incubation at 55 °C for 8 hr with sulfatase (Mylase P), a compound was obtained which had the R_f of 0·67 in both butanol–acetic acid and *iso*propanol-ammonia systems. A product with identical chromatographic properties was prepared by reduction of VMA (K & K Laboratories) with $LiAlH_4$. Axelrod *et al.*[4] have shown that 3-methoxy-4-hydroxyphenylglycol sulfate, a compound with similar properties, is a major metabolite of norepinephrine in the rat. The evidence suggests that the peak at R_f 0·2 represents the glycol sulfate. The remaining compounds closer to the origin are unidentified.

The effect of disulfiram on the metabolism of normetanephrine-1-^{14}C was determined in a comparable group of guinea pigs. Disulfiram was prepared as a suspension of 50 mg/ml of propylene glycol–water (1 : 1), and injected intraperitoneally daily for 3 days in a dose of 200 mg/kg. About 6 h after the last dose, 100 μg normetanephrine-1-^{14}C were injected intraperitoneally and the urines collected and processed as before. Chromatography of the urinary extract showed a substantial decrease in VMA relative to the total radioactivity in the urine (scan *B*, Fig. 1). A concomitant increase in the peak representing the glycol sulfate also appears to have taken place. This finding, confirmed by subsequent experiments, suggests that oxidation of the intermediate glycol aldehyde to VMA is inhibited by disulfiram and, as a consequence, formation of the corresponding alcohol is enhanced. This study has been extended to include preliminary experiments with other biologically active amines. In disulfiram-treated rats, significant quantities of tryptophol[5] and tyrosol can be detected in their urines after administration of tryptamine and tyramine. Evidently, disulfiram can inhibit the oxidation of several β-substituted acetaldehydes. This work was supported by a grant (M-1434) from the United States Public Health Service.

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