excreted in relatively large amounts in rat bile. In the guinea pig the minimum molecular weight for significant biliary excretion appears to be about 400 ± 25 and in the rabbit it appears to be about 500 ± 50 .

F. T. A. A., who is on leave from the Department of Biochemistry, Assiut University, U.A.R., is grateful to the British Council for a Scholarship.

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Some Aspects of the Metabolism of ^{14}C -Labelled ($\pm$)-2,3-Dehydroemetine in the Rat

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Female Sprague-Dawley rats of the same age and weight (200 g) were operated upon under sodium pentothal anaesthesia for cannulation of the common bile duct close to the liver, to afford continuous collection of bile. After the operation the animals were placed in restraining cages with access to chow and tap water. They were injected intravenously with ^{14}C -labelled (at the 3'-position) racemic 2,3-dehydroemetine dihydrochloride in freshly prepared saline solution (0.5 ml) at a dose of $4 \mu\text{Ci}/\text{mg}$ per 200 g rat, and samples of bile and urine were collected continuously over a period of 3 days. Faeces were also collected.

Under these conditions radioactivity was detected in the urine and in the bile, which accounted for 33% of the administered dose in 3 days. The rate of excretion of radioactivity in bile and urine diminished rapidly after the first 24 h. The almost complete absence of radioactivity from the faeces suggested that 2,3-dehydroemetine was not excreted through the intestinal wall, as might have been expected from the high yields of radioactivity in the faeces of non-cannulated animals treated with this drug by Schwartz & Herrero (1965).

Ascending t.l.c. (Gelman Instrument Co. chromatography media ITLC type SA) with solvent A [chloroform-acetone-diethylamine (5:4:1, by vol.)] and solvent B [benzene-ethyl acetate-diethylamine

(8:2:1, by vol.)] as described by Randerath (1966), followed by scintillation counting of excised areas of the chromatograms in Bray's (1960) solution, established that the radioactivity in bile in all samples other than those collected in the first hour was not equivalent to free 2,3-dehydroemetine (R_F values 0.88 and 0.63 respectively), but appeared to be some kind of highly polar metabolite (R_F 0).

Treatment of bile with bacterial β -glucuronidase at pH 5 under the conditions described by Robinson, Smith & Williams (1953) released an appreciable amount of radioactivity migrating with the original compound, indicating that an *N*-glucuronide of 2,3-dehydroemetine is formed and excreted via the bile. Two apparent metabolites of 2,3-dehydroemetine are also released, with R_F values 0.60 and 0.20 in solvent A, representing approx. 21 and 12% respectively of the biliary radioactivity. The chromatography of enzyme-treated bile revealed that some 50% of the total radioactivity did not migrate (R_F 0), which suggests that there may be other conjugates or very polar metabolites. To put this to the test, portions of bile were hydrolysed with arylsulphatase from limpets at pH 5, but no sulphate conjugation could be demonstrated in this way.

Urine contained appreciable amounts of free 2,3-dehydroemetine. Chromatography with solvent A led to the detection of radioactive peaks with R_F values 0.56, 0.30 and 0.10, and radioactivity at the origin. Treatment of urine with β -glucuronidase or with arylsulphatase did not change the pattern of detectable radioactive compounds, which indicates that glucuronide and sulphate conjugates of 2,3-dehydroemetine or its metabolites are not present in the urine.

The possibility that 2,3-dehydroemetine might be *O*-demethylated was examined by incubating liver microsomal preparations from control and stimulated sodium phenobarbital-pretreated (80 mg/kg body wt. daily for 3 days) rats *in vitro* with 2,3-dehydroemetine as substrate and the full supporting system described by Jondorf, Simon & Avnimelech (1966), and measuring formaldehyde formed as a product of metabolism. We found no evidence for oxidative demethylation under these circumstances. Further, by incubating each of the microsomal preparations with chromatographically purified labelled 2,3-dehydroemetine under the same scaled-down general conditions and chromatographically analysing the end products of the metabolic reaction, we found that unchanged 2,3-dehydroemetine could be recovered in 95–100% yield.

This appears to indicate that the polar metabolites detectable with our chromatographic procedures were not likely to be *O*-demethylation products.

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This work was supported by the U.S. Public Health Service (Grants CA-02978 and GM-5TOI-26) and by Hoffmann-La Roche Inc. We thank Dr W. E. Scott for gifts of labelled 2,3-dehydroemetine.

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The Absorption, Excretion and Metabolism of Disodium [^{14}C]Cromoglycate in Man

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Disodium cromoglycate, the disodium salt of 1,3-bis-(2-carboxychromon-5-yloxy)-2-hydroxypropane, is used in the treatment of bronchial asthma (Howell & Altounyan, 1967; Kennedy, 1967).

After the oral administration of disodium [^3H]cromoglycate to monkeys, rabbits and rats, 1%, 2% and 4% of the dose was absorbed respectively (G. F. Moss, personal communication). However, intratracheal administration in these three species indicated that disodium cromoglycate was quickly absorbed from the lung (Moss, Jones, Ritchie & Cox, 1970). Intravenous studies (G. F. Moss, personal communication) have shown that this compound is rapidly excreted via the bile and urine in several animal species. Chromatography of bile and urine indicated that all the recovered radioactivity was in unchanged disodium cromoglycate.

The fate of inhaled disodium [^{14}C]cromoglycate has been examined in asthmatic patients. Maximum plasma concentrations (9 ng/ml) were obtained within 15 min of inhaling the disodium cromoglycate (20 mg, 33 μCi), and the half-life in plasma was 81 min. The urinary-excretion findings suggest that drug reaching the lung is rapidly absorbed and excreted. Only 2% of the inhaled dose appeared in the 24 h urine, 84% being recovered in the faeces.

The fate of orally administered disodium [^{14}C]cromoglycate (20 mg, 8 μCi) was examined. The drug was poorly absorbed from the gastrointestinal tract, only 0.4% of the dose appearing in the 24 h urine and 82% being recovered from the faeces. No metabolites were detected chromatographically.

The intravenous administration of disodium [^{14}C]cromoglycate (4 mg, 6 μCi) resulted in approximately equal amounts being excreted in the urine and the faeces. Disodium cromoglycate is highly polar with a molecular weight of 512, and thus satisfies the criteria for biliary excretion (Millburn, Smith & Williams, 1967).

A comparison of our results with the animal data shows that the monkey handles the drug in a similar manner to man.

The work was supported by a grant from the Medical Research Council.

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The Fate of [^3H]Salbutamol in Man

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The catecholamine isoprenaline is an adrenergic β -receptor stimulant. It affects both bronchial smooth muscle and cardiac muscle. It has been widely used by inhalation in the treatment of asthma, its main disadvantages being its short duration of action and cardiac stimulation. The metabolic fate has been examined in man (Morgan *et al.* 1969).

Salbutamol [2-*tert*.-butylamino-1-(4-hydroxy-3-hydroxymethyl)phenylethanol] is a non-catechol adrenergic β -receptor stimulant. Its advantages over isoprenaline are longer duration of action, selective action on bronchial smooth muscle and the fact that it can be taken orally.

The metabolism and excretion of [^3H]salbutamol has been investigated in rat, rabbit, dog and guinea pig (L. E. Martin, personal communication). In these species between 50 and 80% of the dose was excreted in the urine (0–48 h). The *O*-glucuronide (4-phenyl) of salbutamol was identified as the major metabolite in the urine of rat, rabbit and guinea pig. The dog excreted four unidentified minor metabolites in addition to salbutamol.

The fate of orally administered [^3H]salbutamol (4 mg or 8 mg) has been studied in asthmatic patients. Maximum plasma concentrations (0.23 or 0.43 μM) were obtained 2.5–3 h after dosing. The half-life in plasma was 3.5 h. Analysis of plasma samples indicated that 80% of the radioactivity