in various species has now shown that phenylacetic acid can form conjugates with glutamine, glycine, ornithine, taurine and glucuronic acid, the nature of the conjugates formed being dependent on the species. The taurine conjugate of phenylacetic acid is reported for the first time.

Phenacetylglutamine was found to be the only conjugate in the urine of man and the Old World monkeys, rhesus monkey (*Macaca mulatta*), cynomolgus monkey (*M. fascicularis*), green monkey (*Cercopithecus aethiops*), drill (*Mandrillus leucophaeus*), white-collared mangabey (*Cercocebus torquatus*) and baboon (*Papio cynocephalus*). Both phenacetylglutamine and phenacetylglutamine were formed in the New World monkeys, squirrel monkey (*Saimiri sciureus*) and capuchin monkeys (*Cebus albifrons* and *Cebus nigrivittatus*). Phenacetylglutamine but no phenacetylglutamine was excreted by the lower primates slow loris (*Nycticebus coucang*) and bushbaby (*Galago senegalensis*) and by the following non-primates: rat, rabbit, guinea pig, mouse, hamster, cat, dog, ferret and vampire bat.

The hen was found to excrete mainly N^2N^5 -diphenacetylornithine (phenacetornithuric acid), together with smaller amounts of phenacetylglutamine. The pigeon, however, excreted, not diphenacetylornithine, but two other amino acid conjugates, one of which was readily identified as phenacetylglutamine, but the other did not correspond to the any of the known conjugates of phenylacetic acid. It was eventually identified, by using the mass spectrometer and amino acid analyser, as phenacetyltaurine.

An unknown conjugate had been detected in the urine of several other species, and from its R_f value on radiochromatograms this also appears to be phenacetyltaurine. It has been found in substantial amounts in the urine of the slow loris, bushbaby and ferret and in small amounts in the urine of the dog.

It is noteworthy that, as far as the glutamine and glycine conjugations of phenylacetic acid in primates are concerned, only glutamine conjugation occurs in man and the Old World monkeys, both glutamine and glycine conjugation occur in New World monkeys and only glycine conjugation occurs in the lemurs. A similar distribution of conjugation in primates has been found for indol-3-ylacetic acid (M. E. Evans, R. L. Smith & R. T. Williams, unpublished work; see Williams, 1971).

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The Biliary Excretion of Amphetamine and Methamphetamine in the Rat

By J. CALDWELL, L. G. DRING and R. T. WILLIAMS.
(Department of Biochemistry, St Mary's Hospital Medical School, London W.2, U.K.)

Both amphetamine and methamphetamine are excreted by the rat mainly in the urine (Dring, Smith & Williams, 1970; Caldwell, Dring & Williams, 1971), the major metabolic reaction being aromatic hydroxylation. The biliary excretion of these drugs in the rat has now been examined and, although the faecal excretion of these drugs is low (4-5% of the dose for amphetamine and 2% for methamphetamine), there is an appreciable biliary excretion of the metabolites of these drugs.

[^{14}C]Amphetamine sulphate (7.5 mg/kg) and [^{14}C]methamphetamine hydrochloride (7.5 mg/kg) were administered intraperitoneally in water to bile-duct-cannulated rats (Abou-El-Makarem, Millburn, Smith & Williams, 1967). The bile and urine were collected for 24 h and analysed for the ^{14}C -labelled metabolites by paper chromatography, radiochromatogram scanning and scintillation counting. In the case of amphetamine 69 and 16% of the dose of ^{14}C were excreted in the urine and bile respectively in 24 h, whereas with methamphetamine the values were 54 and 18%. The metabolites of amphetamine in the urine and bile respectively were: amphetamine, 24 and 1%; total 4-hydroxyamphetamine, 38 and 15%; hippuric acid, 6 and 0.1% of the dose. Similarly the metabolites of methamphetamine were: methamphetamine, 16 and 0.5%; amphetamine, 22 and 2%; total 4-hydroxymethamphetamine, 6 and 1%; total 4-hydroxyamphetamine, 4 and 1%; total 4-hydroxynorephedrine, 2 and 13% of the dose.

The main metabolite of amphetamine in bile was 4-hydroxyamphetamine glucuronide (12% of the dose) and that of methamphetamine was 4-hydroxynorephedrine glucuronide (12%). These two conjugates could be expected to be excreted in the bile in significant amounts, since their molecular weights (327 and 343 respectively) are in the lower range suggested by Millburn, Smith & Williams (1967) for extensive biliary excretion in the rat. The low faecal excretion and appreciable biliary excretion of certain metabolites of these drugs show that they can undergo an enterohepatic circulation in the rat. This suggests that on repeated administration of methamphetamine in the rat an accumulation in the body of 4-hydroxynorephedrine, which has been postulated as a false transmitter at nerve endings, might occur.

[^{14}C]Amphetamine was a gift from Smith, Kline and French Laboratories, Philadelphia, Pa., U.S.A.

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The Metabolism of [^{35}S]Homosulphanilamide

By L. C. K. WONG,* P. MILLBURN and R. T. WILLIAMS. (*Department of Biochemistry, St Mary's Hospital Medical School, London W.2, U.K.*)

Homosulphanilamide (4-aminomethylbenzenesulphonamide) is a valuable antibacterial drug when used topically for burns (Lindberg, Moncrief, Switzer, Order & Mills, 1965). Systemically it is ineffective because it is rapidly converted into the inactive 4-carboxybenzenesulphonamide (Hartles & Williams, 1947). The renewed therapeutic interest in this drug caused us to reconsider its metabolism, in particular the possibility of its deamination by the intestinal tissues.

[^{35}S]Homosulphanilamide was administered orally (50 mg/kg) to the rhesus monkey, rat, guinea pig and rabbit, and two metabolites apart from the unchanged drug were found in the urine. These were 4-carboxybenzenesulphonamide and 4-acetamidomethylbenzenesulphonamide, the latter being shown to be a metabolite for the first time. In the monkey, guinea pig and rabbit the major product was 4-carboxybenzenesulphonamide (70–90% of the 24 h excretion) with smaller amounts of the free and the acetylated drug. In the rat, however, the outputs of total homosulphanilamide and 4-carboxybenzenesulphonamide were approximately the same. The drug was thus less readily deaminated in the rat than the other species.

Homosulphanilamide is a substrate for monoamine oxidase (Beyer & Govier, 1945; Blaschko & Duthie, 1945), which is present in both liver and intestine. Therefore the effect of route of administration on the deamination of the drug was examined. The amount of 4-carboxybenzenesulphonamide excreted in the 24 h urine in the rabbit (50% of dose) and rat (30% of dose) was the same whether [^{35}S]homosulphanilamide (500 mg/kg) was administered orally or intravenously. This suggests that the intestine may not play a major role in deaminizing the drug.

The metabolism of the ^{35}S -labelled drug was studied in rabbits and rats pretreated with the monoamine oxidase inhibitor iproniazid (1-is-

nicotiny-2-isopropylhydrazine; Marsilid). In the rabbit the rate of excretion of ^{35}S was increased by about 25% by pretreatment, but in the rat it decreased by 25%. In both species the excretion of 4-carboxybenzenesulphonamide was markedly depressed and there was a corresponding increase in the excretion of total homosulphanilamide. Various combinations of oral and intravenous administration of homosulphanilamide and iproniazid were tried in an attempt to obtain information about the role of the gut compared with the other tissues in deaminating the drug, but no definite conclusions could be drawn from the results. It appeared that the drug was deaminated mainly by the liver rather than by the intestine.

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Protection by Zinc Ions against the Toxicity of Cadmium Ions

By M. WEBB. (*Strangeways Research Laboratory, Wort's Causeway, Cambridge CB1 4RN, U.K.*)

Although Zn^{2+} is known to protect against the selective injurious effect of Cd^{2+} on the rat testis (Pařizek, 1960; Kar, Das & Mukerji, 1960; Gunn, Gould & Anderson 1961; Mason & Young, 1967), the mechanism of this protection has not been established. It seems unlikely that this is due to inhibition of the displacement by Cd^{2+} of Zn^{2+} from metalloenzymes, a possibility considered by Pařizek (1960), since the primary action of Cd^{2+} appears to be on the vascular system (e.g. Clegg, Carr & Niemi, 1969). The amount of Cd^{2+} accumulated by the rat testis is small (e.g. Pařizek, 1960) and does not lead to displacement of Zn^{2+} . Indeed, the testicular content of Zn^{2+} remains unaltered for 48 h after injection of Cd^{2+} (2.2 $\mu\text{mol}/100\text{g}$ body wt.) and then increases to a value 9–10-fold greater than normal at 30 weeks.

In contrast with the testes, appreciable amounts of the injected Cd^{2+} accumulate in the livers and kidneys, this accumulation being accompanied by increases in the contents of Zn^{2+} . In both tissues most of the bound Cd^{2+} is found as a single fraction in the cell sap, which also contains Zn^{2+} . These proteins, in which the cations are bound at thiol groups, are not identical, but have properties in

* Present address: Department of Pharmacology and Toxicology, Bionetics Research Laboratories, 5510 Nicholson Land, Kensington, Md. 20795, U.S.A.