more reliable than arterial samples at the end of infusion. Since the blood level required to induce sleep increases with infusion time this was standardized to 4-6 min.

In Table 1 the findings with different doses of some drugs are pooled, since these were similar within the range used. After chlordiazepoxide, more ethanol was needed to produce sleep ($P<0.01$). This increase was associated with increased concentrations of ethanol in the venous blood ($P<0.005$). After pentobarbitone, although less ethanol was needed to produce sleep, the difference was not significant. Blood alcohol concentration was significantly less ($P<0.05$). The decline of ethanol concentration in the blood following 0·8 g/kg was not affected by chlordiazepoxide.

TABLE 1. *Average amount of alcohol required to produce sleep after rapid infusion of 8% w/v and venous blood levels taken 3–4 min after loss of consciousness*

Premedication: atropine (0·6 mg) plus:	Average dose of alcohol required to produce sleep		Blood ethanol concentration (mg/100 ml)		
	No. of observations	mg/kg per $\sqrt{\text{min}}$	No. of observations	Average	Range
—	31	274±13	14	186±12	111–270
Chlordiazepoxide 100–140 mg	43	393±11	14	291±16	207–459
Diazepam 10–30 mg	44	295±16	12	187±11	147–282
Pentobarbitone 100–120 mg	28	256±14	11	150±14	97–194
Promethazine 50 mg	32	301±5	17	186±10	124–305
Cyclizine 50 mg			12	176±18	90–286

Thus, this drug appears to induce true cerebral tolerance to alcohol while clinical doses of pentobarbitone have the opposite effect.

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The promotion of phenolic alcohol formation in man by reserpine and ethanol

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Reserpine (Sandler & Youdim, 1968) and ethanol (Smith & Gitlow, 1966; Davis, Brown, Huff & Cashaw, 1967a) administration in man promote the formation of 4-hydroxy-3-methoxyphenylglycol (HMPG) at the expense of 4-hydroxy-3-methoxy-

mandelic acid (VMA), and ethanol similarly increases 5-hydroxytryptophol formation and decreases that of 5-hydroxyindoleacetic acid (Davis, Brown, Huff & Cashaw, 1967b). The present study was carried out to establish whether such a pathway alteration is a general finding for the further metabolism of all aldehydes deriving from the oxidative deamination of biologically active monoamines.

Six male volunteers were injected intravenously with saline and, after one week, with reserpine (1·25 mg). Urine collections were made at 1, 3, 6, 9, 12 and 24 h after injection of test and control. For the ethanol studies the same volunteers consumed 300 ml vodka diluted with 500 ml orange juice over a period of 1 h. The same branch of orange juice was later drunk by the same subjects as control. Urine collections were made at similar collection intervals after the start of drug administration as before.

All samples were analysed for phenolic acids and alcohols gas chromatographically (Karoum, Ruthven & Sandler, 1968; Karoum, Anah, Ruthven & Sandler, 1969). Total metadrenaline output was measured by the method of Ruthven & Sandler (1965).

Both drugs caused a significant shift of intermediate aldehyde metabolism from an oxidative to a reductive route, an increase in phenolic alcohol output being noted in the following pairs up to the 6–9 h collection: HMPG and VMA; 4-hydroxy-3-methoxyphenylethanol and homovanillic acid; tyrosol and *p*-hydroxyphenylacetic acid; 4-hydroxy-3-methoxybenzyl alcohol and vanillic acid. With the exception of HMPE, which showed a greater increase after reserpine, the effect of ethanol was more striking, with a proportionately larger alcohol peak at the expense of the acid. The reserpine effect was accompanied by a marginal decrease only in acid output. The endogenous production of *p*-hydroxyphenylglycol and *p*-hydroxymandelic acid could not be quantified accurately; orange juice administered during the ethanol experiment and not excluded from the dietary during the urine collection period following reserpine or control injection, contains large amounts of synephrine (Stewart, Newhall & Edwards, 1964) which is degraded to these end-products.

In common with reserpine, ethanol appears to bring about some degree of amine release, for a significant increase in total metadrenaline output was detected up till the 1–3 h urine collections.

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The effect of tyramine on phenolic acid and alcohol excretion in man

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Against a background of extensive animal experimentation (Kopin, 1966), the ability of tyramine to liberate noradrenaline from its binding sites has recently been investigated in man (Engelman & Sjoerdsma, 1964; Sandler & Youdim, 1968). The metabolism of tyramine itself has been well documented in the rabbit (Lemberger, Klutch & Kuntzman, 1966), but has not been studied systematically in the human. It would appear that tyramine administration gives rise to two series of metabolites, those deriving from its own degradation and those from the metabolism of other amines liberated by it. The possible implication of tyramine in the pathogenesis of a migraine variant has aroused considerable interest in this area of investigation (Sandler, Youdim, Southgate & Hanington, 1970). The availability of quantitative gas chromatographic procedures (Karoum, Ruthven & Sandler, 1968; Karoum, Anah, Ruthven & Sandler, 1969) has now enabled us to obtain further information about both series of metabolites.

Urine samples were collected at intervals of 1, 3, 6, 9, 12 and 24 h after administration on different days of 5 mg tyramine intravenously and 125 mg tyramine orally, with appropriate placebo experiments, to six healthy adult male volunteers.

No significant increase in 4-hydroxy-3-methoxymandelic acid or 4-hydroxy-3-methoxyphenylglycol output was detected after either route of administration, in general agreement with previous observations in the same volunteers (Sandler & Youdim, 1968) that released noradrenaline is predominantly O-methylated. A significantly increased output of homovanillic acid, probably too large to be accounted for by any direct conversion of tyramine to dopamine (Lemberger, Klutch & Kuntzman, 1966), was observed, however, during the first 9 h after intravenous tyramine, with a peak at 3–6 h. This increase in output of homovanillic acid presumably derives from dopamine release and is in accordance with *in vitro* evidence (Collins & West, 1968); it may have significance in human Parkinsonism.

Of the metabolites deriving directly from tyramine metabolism, the excretion of *p*-hydroxyphenylacetic acid closely paralleled the administered dose of amine; but despite this high output, there was no evidence of the corresponding alcohol, tyrosol. Whether the enhanced excretion of *p*-hydroxymandelic acid during the first hour after intravenous tyramine stemmed directly from its conversion to octopamine (Kopin, 1966) or indirectly from the release of endogenous octopamine stores (Molinoff, Landsberg & Axelrod, 1969) can only be decided by the use of radioisotopically labelled tyramine. Such studies would also be helpful in pinpointing the origin of the increased homovanillic acid output observed after tyramine injection.

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