hPTH 1–34) (Tregear, Reitschoten, Greene, Keutmann, Niall, Reit, Parsons & Potts, 1973; Niall, Sauer, Jacobs, Keutmann, Segre, O'Riordan, Aurbach & Potts, 1974) in the subcutaneous version of a bioassay depending on measurements of hypercalcaemia in chicks (Parsons, Reit & Robinson, 1973). Both Trasylol and ϵ-amino caproic acid (EACA) substantially enhanced the hypercalcaemia measured 2 h after injection. It was confirmed by radioimmunoassay that this enhancement reflected an increase in circulating blood levels of hPTH 1–34, the greatest increase being seen 1 h after injection. Similar enhancement in circulating blood levels of another peptide hormone was observed when EACA and Trasylol were added to porcine calcitonin, injected subcutaneously to chicks. Large doses of calcitonin can be given to these birds and the resulting blood levels were followed directly by injecting their plasma intravenously to rats and measuring the hypocalcaemic response as described by Kumar, Slack, Edwards, Soliman, Baghdiantz, Foster and MacIntyre (1965).

A quite independent approach to the evaluation of subcutaneous losses appears to be possible by using controlled intravenous infusion to imitate the changing blood levels measured after s.c. injection. The intravenous technique allows certainty that all hormone administered enters the bloodstream and comparisons of s.c. and i.v. administration in freely mobile dogs with indwelling venous cannulae have yielded preliminary evidence to confirm that substantial local destruction must occur when hPTH 1–34 is injected subcutaneously.

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Drug clearance in the rabbit twenty-four hours after an intoxicating dose of ethanol

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Acute ethanol intoxication is known to inhibit the *in vivo* metabolism of a variety of drugs, including barbiturates, in animals and in man (Rubin, Gang, Misrad & Lieber, 1970), although it is not so clear whether this is a direct inhibitory effect of the ethanol itself. The levels of ethanol required to inhibit the metabolism of most drugs by the hepatic microsomal fraction, around 100 mM (Rubin *et al.,* 1970; Cinti, Grundin & Orrenius, 1973), are in general higher than those encountered except under cases of severe intoxication. It was of interest therefore to examine *in vivo* drug clearances several hours after a single dose of ethanol, when the ethanol had been completely removed from the blood.

Rabbits were fed ethanol (4.25 g/kg) as a 50% solution (v/v) by stomach tube. A peak blood ethanol concentration (mean $\pm$ s.e. mean, $n = 3$) of 397 ± 7 mg/100 ml was achieved within 2 h and had fallen to 1.3 ± 0.9 mg/100 ml by 24 hours. Blood acetaldehyde levels after 24 h, 0.11 ± 0.01 mg/100 ml, were no different from control values 0.09 ± 0.01 mg/100 ml ($P > 0.05$). Hexobarbitone sodium (50 mg/kg) administered intravenously, was removed from the blood with a half life (mean $\pm$ s.e. mean, $n = 7$) of 22.9 ± 1.3 min in control animals and 41.0 ± 5.8 min ($n = 4$, $P < 0.01$) in animals pretreated with ethanol 24 h previously. There appeared to be no significant difference in the half life for the removal of intravenously administered aniline hydrochloride (50 mg/kg) between control 29.5 ± 1.2 min ($n = 6$) and ethanol pretreated animals 34.1 ± 2.6 min ($n = 4$, $P > 0.05$). The decrease in the rate of removal of hexobarbitone could not be accounted for by any change in the hepatic microsomal metabolism of hexobarbitone measured *in vitro,* control 2.3 ± 0.1, ethanol pretreated 2.2 ± 0.1 nmol min^{-1} mg protein^{-1} ($n = 7$, $P > 0.05$) or in the levels of microsomal cytochrome P-450, control 1.0 ± 0.1 ethanol pretreated 1.0 ± 0.1 nmol mg protein^{-1} ($n = 3$). Microsomal aniline hydroxylation was similarly unchanged,

control 0.50 ± 0.02, ethanol pretreated 0.57 ± 0.06 nmol min^{-1} mg $protein^{-1}$ ($n=7$, $P>0.05$).

One possible explanation for the decrease in the rate of hexobarbitone removal might lie in the release of adrenal cortical hormones by the ethanol. Serum cortisol levels were 4.2 ± 0.5 μg/100 ml ($n=5$) in control animals and 14.5 ± 2.4 μg/100 ml ($n=6$, $P<0.01$) in animals pretreated with ethanol 24 h previously. Corticosterone administered to rats *in vivo* is known to inhibit the hepatic microsomal metabolism of hexobarbitone (Chung & Brown, 1976).

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Influence of age and sex on the duration of action of ketamine in the rat

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In order to study the influence of age and sex on the duration of action and metabolism of ketamine, groups of six rats of both sexes, ranging in age from one to 16 weeks were injected intraperitoneally with ketamine hydrochloride (75 mg/kg). Time to loss of righting reflex (onset time) and duration of loss of the righting reflex (sleeping time) were recorded for each rat. The rats were killed by decapitation at the point of recovery, and blood samples were collected for assay of plasma concentrations of ketamine, its *n*-demethylated metabolite (I), and the subsequent oxidation product (II), as previously described (Livingston & Waterman, 1976).

There was a significant increase in onset time from 1 to 6 weeks of age in both sexes, but after this it did not alter significantly. Sleeping time decreased markedly with increasing age from 1 to 4 weeks, in both males (97.2 to 24.1 min) and females (90.1 to 30.0 min) but thereafter it did not vary significantly. The females tended to show a longer sleeping time than the males from 4 weeks old onwards but the difference was only statistically significant in the 16 week old age group.

In the male rats the concentration of ketamine in the plasma at recovery was 4.1 ± 0.39 μg/ml in the 1 week old rats, falling to 2.67 ± 0.25 μg/ml at 6 weeks, after which it remained close to this level. Metabolite I levels followed the same pattern (2.27 ± 0.26 μg/ml at 1 week to 1.27 ± 0.17 μg/ml at 6 weeks), but no metabolite II was detected in the plasma until 3 weeks, the concentration then rose steadily with age to 6 weeks when it reached 1.25 ± 0.19 μg/ml. The changes in plasma levels of ketamine and its metabolites in the female rats followed the same pattern as the males, but the concentrations of ketamine and metabolite I were always higher than in the males of corresponding age, whilst the levels of metabolite II were always lower.

The data suggest that the decreasing sensitivity to the actions of ketamine, as demonstrated by a decrease in sleeping time from 1 to 4 weeks of age, is related to the appearance of the second metabolite in the plasma. In addition, there appears to be a sex difference in the duration of action of the drug which may be related to the difference in the ability of the sexes to produce metabolite II. These results indicate that, in the rat, the second (oxidative) step may be the rate limiting one in the degradation of this drug.

A.E.W. is a Wellcome Research Training Scholar.

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