Pearce, 1978; Whittle, Boughton-Smith, Moncada & Vane, 1978). We have now investigated in more detail the characteristics of the responses to antisecretory prostaglandins during different rates of histamine stimulation in both rat and mouse whole stomach.

Whole stomachs from mice or immature rats were removed to a 20 ml organ bath as described before (Bunce & Parsons, 1976; Angus, Black & Stone, 1978). The serosal solution contained (mM) NaCl 119, KCl 4.7, $MgSO_4$ 1.2, glucose 5.6, $NaHCO_3$ 30, KH_2PO_4 0.5 and $CaCl_2$ 1.0 (pH 7.6) and was gassed with 95% O_2, 5% CO_2. The mucosal solution, with buffer salts omitted and gassed with O_2, was perfused (1 ml/min) through the gastric lumen and the acid output was detected by changes in pH via a microelectrode system. In most experiments, prostaglandins were added to the serosal bathing solution and the preparation incubated for 12 min prior to addition of the secretagogue, histamine, which was also added to the serosal solution.

In the rat stomach, histamine (1.25–20 μg/ml; 0.4–7 × 10^{-5}M) caused a dose-dependent rise in the resting acid secretion (13.2 ± 0.6 μmol × 10^{-2}/min, mean ± s.e. mean, n = 106) reaching a maximal response of 22.1 ± 1.6 μmol × 10^{-2}/min (n = 37) over basal with the dose of histamine (20 μg/ml). Pre-incubation with PGE_2 (0.1–1 μg/ml; 0.3–3 × 10^{-6}M) caused a dose-related parallel shift to the right of the dose-response relationship for histamine. At maximally-stimulated acid-output with histamine (20 μg/ml), the inhibition by PGE_2 (1 μg/ml) was 53.5 ± 7.1% (n = 27; P<0.001). This inhibition was surmountable; with supra-maximal concentrations of histamine (40–80 μg/ml) there was no longer any significant (P>0.05) inhibition of acid output by PGE_2 (1 μg/ml). A parallel shift of the dose-response curve to histamine was also observed with the prostacyclin analogue, 6β-PGI, as will be demonstrated.

In the mouse whole stomach, histamine (1.25–20 μg/ml) likewise caused a dose-dependent rise in acid output with the maximal response being obtained with comparable doses to those in the rat. The mouse stomach had a resting acid output of 11.9 ± 0.8 μmol 10^{-2}/min; n = 84 and a maximal acid output of 29.2 ± 4.8 μmol × 10^{-2}/min over basal; n = 10. In contrast to the rat, no significant inhibition of acid output could be obtained by pre-incubation with PGE_2 (1–5 μg/ml) even at low rates of histamine (1.25 μg/ml)-stimulation. Whether the lack of antisecretory action with PGE_2 in the mouse stomach *in vitro*, in doses having marked antisecretory activity in the rat stomach is the consequence of rapid metabolism or failure of the prostaglandin to reach its site of action requires further evaluation. These results contrast with the potent antisecretory activity of histamine H_2-receptor antagonists in the mouse stomach (Angus, Black & Stone, 1978).

The present study reveals that in the isolated rat stomach, the degree of inhibition of acid secretion by prostaglandins in the concentrations used, is both related to the level of stimulation and is surmountable. Care must therefore be taken when comparing the antisecretory actions of prostaglandins against different secretagogues *in vitro* especially if different rates of acid secretion are obtained. The mechanisms underlying these characteristics of inhibition are as yet obscure. However, since PGE_2 and prostacyclin analogues may act by reducing parietal-cell cyclic AMP concentrations (Soll & Whittle, 1979), the nature of the interaction at the level of the adenylate cyclase may warrant analysis.

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The action of salmon calcitonin on indomethacin-induced gastric ulceration in the mouse

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Many of the non-steroidal antiinflammatory drugs, such as indomethacin and aspirin, may induce gastric ulceration. In contrast the hormone calcitonin has an antiinflammatory action in several animal models (Abdullahi, De Bastiani, Nogarin & Velo, 1975) but inhibits gastric acid secretion (Becker, Konturek, Reeder & Thompson, 1973) and gastric ulceration induced by stress (Barlet, 1974) or histamine (Barlet & Bates, 1974). These latter inhibitory effects of

calcitonin have been demonstrated after parenteral or intragastral administration (Barlet, 1974).

In an attempt to resolve this apparent paradox we have investigated the effect of salmon calcitonin on indomethacin-induced gastric ulceration in the mouse.

Gastric ulceration was induced over a 5 h period in starved (24 h) albino mice, by the i.p. administration of indomethacin (40 mg/kg) (Djahanguiri, 1969). The ulcers were stained by a modification of the method of Robert & Nezamis (1964). The excised stomachs were washed through with 1 ml of distilled water and the pH measured. Plasma calcium levels were determined using a Corning 940 calcium analyser.

Salmon calcitonin administered intragastrally as a single dose over the range from 0.1 MRC units/kg to 100 MRC units/kg did not affect gastric pH, ulceration or plasma calcium levels. Doses of 100 MRC units/kg and 400 MRC units/kg calcitonin given hourly throughout the experimental period also did not significantly affect these parameters. Subcutaneously administered salmon calcitonin (0.1 MRC units/kg–100 MRC units/kg), however, produced a marked dose dependent effect on ulceration, intragastric pH and plasma calcium levels (Figure 1). The effect on ulceration showed a correlation (Kendall's rank correlation coefficient) with changes in both pH ($P<0.01$) and plasma calcium levels ($P<0.05$).

Thus although the dose of salmon calcitonin administered intragastrally was greater than 400 times that dose required to inhibit ulceration when calcitonin was administered subcutaneously, no effect was observed.

In the pig, Barlet (1974) demonstrated an effect on stress-induced gastric ulceration using an intragastric dose of 10 times the intramuscular dose. Other workers have shown similar or lower ratios of effective doses for calcitonin when administered to rat (Bates & Barlet, 1974) and man (Ziegler, Minne Hotz & Goebel,, 1974; Hotz, Goebell, Minne & Ziegler, 1974), by these two routes of administration.

Therefore it would appear that the effects of salmon calcitonin on the indomethacin-induced gastric ulceration in the mouse, may be different from the effects observed on other models of gastric ulceration.

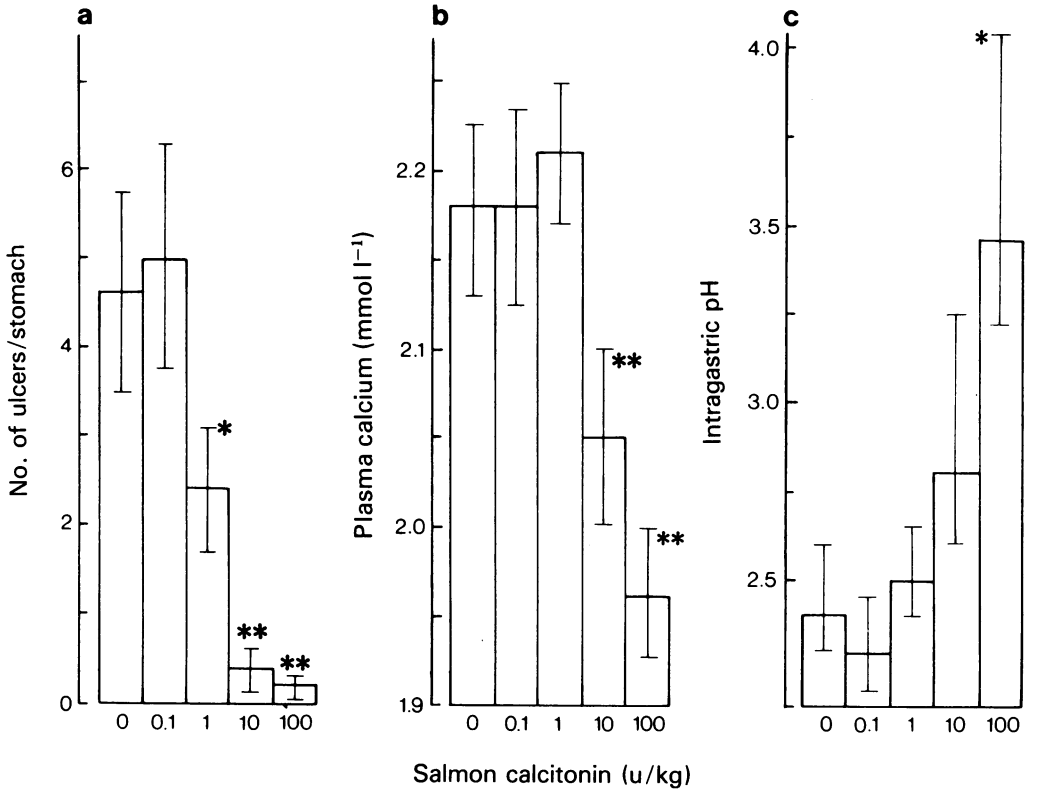

Figure 1 Effect of salmon calcitonin (SCT 0.1 MRC units/kg–100 MRC units/kg) administered s.c. on (A) gastric ulceration, (B) plasma calcium levels, and (C) intragastric pH, in indomethacin (40 mg/kg) treated mice. Salmon calcitonin was administered in a vehicle of 154 mM saline and 1 mg cm^{-3} bovine serum albumin. Controls (0 MRC units/kg) received the vehicle only. Results are expressed as mean and s.e. of mean. Each value is the mean of 8 to 10 determinations. Statistically significant differences are expressed at $P<0.05$ (*) and $P<0.01$ (**) levels (Mann-Whitney U test).

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Monkeys as metabolic models for man – the fate of amphetamine in the vervet and patas monkey

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If animal investigations are to have relevance to the human situation, the species chosen should resemble man both in response to and disposition of the drug in question. Inter-species variations in drug metabolism frequently emerge as a major factor influencing species differences in drug effect, and it has been shown that non-human primates generally exhibit metabolic patterns closer to man than those of other laboratory animals (Smith & Caldwell, 1976). Only 12 of the 214 primate species have been investigated from the viewpoint of drug metabolism. There are presently difficulties in ensuring adequate supplies of commonly used primates for these purposes, and thus evaluation of other species is desirable. We now report on the fate of the habit forming drug amphetamine in two species of Old World monkey, the vervet, or African green monkey (*Cercopithecus aethiops*) and the patas monkey (*Erythrocebus patas patas*).

The monkeys (2 adult females of each species; vervets, wt. 2.5 kg, patas, wt. 4 kg) were housed in the Primate Colony of the Department of Biochemistry, University of Ibadan, and received (±)-[^{14}C]-amphetamine sulphate (5 mg/kg i.m.; 10 μCi/animal) dissolved in sterile isotonic saline. They were placed in strong metabolic cages and their urine collected for 24 h into trays containing 5 ml of 2% $HgCl_2$ as preservative. The urines were frozen and transported by air to London for analysis. The [^{14}C] content of the urines was determined by liquid scintillation spectrometry and urinary metabolites assayed by radiochromatography and reverse isotope dilution as described by Caldwell, Dring & Williams (1972).

The quantitative and qualitative results are shown in Table 1. The recovery of administered [^{14}C] was low (ca. 25% of dose), probably due to difficulties in obtaining a complete urine collection under these conditions. In addition to unchanged amphetamine, the urine of both species contained four metabolites, free and conjugated 4′-hydroxyamphetamine, benzoic acid and hippuric acid. Table 1 also presents data obtained previously in human volunteers and other animal species (Caldwell, 1976; Caldwell, Dring, Franklin, Köster, Smith & Williams, 1977). It is clear that there occur considerable inter-primate variations in metabolism, and it is of interest to examine the vervet and patas monkey as potential metabolic models for man. Both these monkeys produce more 4′-hydroxyamphetamine than does man, and excrete correspondingly less unchanged amphetamine. The metabolic profile of amphetamine in the vervet is similar to that of man, although there is more 4′-hydroxyamphetamine formed, but in the patas monkey the pattern is different with both metabolic routes being more important than elimination of unchanged drug. Table 1 shows clearly that the metabolism of amphetamine in the marmoset, a New World monkey, and the rat has no similarity to the human situation. These studies thus show the importance of considering inter-primate variations in drug metabolism, and neither of the species considered here offers an animal model of human amphetamine metabolism as good as the rhesus monkey.

In certain studies of drug dependence, the use of