5. Acetylsalicylic acid affects the course of pregnancy in rats but it has not been established whether the foetuses are directly damaged or whether the drug acts on the placenta; as foetuses of many sizes were found in some of the rats (Fig. 2), it is probable that the haemorrhagic effect of the drug on the foetuses predominates.

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Mechanism of action of monoamine oxidase inhibitors in enhancing amphetamine toxicity

SIR,—The occurrence of toxic effects in man due to the simultaneous or successive administration of monoamine oxidase (MAO) inhibitors and either amphetamine or methylamphetamine has been reported by several workers (Mason, 1962; Dally, 1962; Hay, 1962). Since these reports Brownlee & Williams (1963a, b) have shown that there is a marked potentiation of amphetamine toxicity in mice after pretreatment with the MAO inhibitor phenelzine.

Amphetamine is known to possess central and peripheral sympathomimetic activities typified by its central nervous system stimulant activity and pressor activity on the cardiovascular system respectively. Fencamfamin (*N*-ethyl-3-phenylbicyclo[2,2,1]hept-2-ylamine hydrochloride,) is also a central sympathomimetic drug which is a chemical analogue of amphetamine and, so far as can be determined, acts on the central nervous system by a similar mechanism to that of amphetamine (Hotovy & others, 1961). By contrast, however, fencamfamin does not possess peripheral sympathomimetic activity. For example, it has no pressor effect even when given in high intravenous doses to anaesthetised cats.

The reason for the increased toxicity of amphetamine in animals previously treated with MAO inhibitors is not known with certainty, but it may be due to an enhancement of the drug's central or peripheral effects or both. If the main effect was central, the previous administration of MAO inhibitors would also be expected to increase the toxicity of fencamfamin, but for a peripheral effect, the toxicity of fencamfamin should not be greatly affected by previous administration of MAO inhibitors. Accordingly it seemed to us that it was desirable to determine:

1) the relative central stimulant activities of amphetamine and fencamfamin, and

2) the acute toxicities of these compounds in normal animals and in animals treated with effective MAO inhibitors.

We report here our findings.

Reserpine-reversal activities of amphetamine and fencamfamin. A severe depressive state, characterised by ptosis, locomotor inactivity, piloerection and hypothermia, was produced in mice by the intravenous injection of reserpine, 1·0 mg/kg. Four hr later, amphetamine (0·5 or 5·0 mg/kg) or fencamfamin (2 or 20 mg/kg) was administered orally to reverse this depression. This reversal was measured quantitatively by determining the rise in body temperature 1 hr

later (maximum antihypothermic effect) using an oesophageal thermocouple and electric thermometer (Brittain & Spencer, 1964) to determine body temperatures. The mean residual hypothermia was calculated for each group by comparison with a group of untreated control mice (Table 1). By plotting the mean residual hypothermia against log dose, it was found that fencamfamin had 34% of the activity of amphetamine.

TABLE 1. ANTIHYPOTHERMIC ACTIVITIES OF AMPHETAMINE AND FENCAMFAMIN IN RESERPINE-TREATED MICE

Treatment	Body temp., °C, 5 hr after reserpine mean ± s.e.*	Hypothermia °C	Relative antihypothermic activity
Untreated control mice	36·86 ± 0·37	—	—
Reserpine only, 1·0 mg/kg i.v.	31·64 ± 0·75	5·22	—
Reserpine i.v. followed 4 hr later with amphetamine orally			
0·5 mg/kg	34·10 ± 0·41	2·76	1·0
or			
5·0 mg/kg	35·48 ± 0·55	1·38	
Reserpine i.v. followed 4 hr later with fencamfamin orally			
2·0 mg/kg	34·34 ± 0·52	2·52	0·34
or			
20 mg/kg	35·62 ± 0·38	1·24	

* Male albino mice, 18–22 g, were used in groups of 5 for each determination.

2. *Effect of* MAO *inhibition on the acute toxicities of amphetamine and fencamfamin.* The oral LD50 values of amphetamine and fencamfamin were determined under non-crowded conditions in untreated mice and in mice pretreated orally 4 or 16 hr previously with an MAO inhibitor. Two dose levels of both a hydrazine (phenelzine) and a non-hydrazine (tranylcypromine) MAO inhibitor were investigated. The results are set out in Table 2. In untreated

TABLE 2. ACUTE ORAL TOXICITIES OF AMPHETAMINE AND FENCAMFAMIN IN MICE PRETREATED WITH MAO INHIBITORS

MAO inhibitor	Pretreatment time hr	Oral dose mg/kg	Oral LD50* amphetamine (95% limits) mg/kg	Oral LD50* fencamfamin (95% limits) mg/kg
Phenelzine	4	none	126 (97·7–163)	55·0 (45·8–66·0)
		20	7·52 (4·50–12·6)	47·5 (39·7–56·8)
		50	5·00 (3·09–8·10)	29·2 (22·5–37·9)
	16	none	89·0 (61·3–129)	58·3 (48·6–70·0)
		20	7·00 (5·47–8·96)	54·8 (43·8–68·6)
		50	9·88 (7·22–13·5)	45·4 (36·6–56·3)
Tranylcypromine	4	none	95·0 (76·6–118)	71·0 (55·9–88·9)
		2	13·7 (10·1–18·6)	68·0 (48·6–95·2)
		5	5·52 (4·18–7·29)	38·2 (30·3–48·1)
	16	none	145 (120–176)	63·5 (49·2–81·9)
		2	20·7 (14·6–29·4)	65·3 (48·3–88·2)
		5	19·3 (14·4–25·9)	56·0 (47·1–66·7)

* Male albino mice, 18–22 g were used in totals of 40–50 for each determination. LD50's (95% fiducial limits) were calculated by the method of Litchfield & Wilcoxon (1949).

mice, fencamfamin is between 1½ and 2 times as toxic as amphetamine. However, the toxicity of amphetamine is markedly increased by both phenelzine and tranylcypromine. In contrast, the toxicity of fencamfamin is unaffected except 4 hr after the larger dose of phenelzine or tranylcypromine, when an approximately 2 fold increase was produced. Under identical conditions, the toxicity of amphetamine was increased some 15 to 25 times. Simultaneously

with these LD50 determinations, mice from the same source and of similar weight range were used in biochemical determinations of brain and liver MAO activity. Both phenelzine and tranylcypromine, at each dose level and after 4 and 16 hr pretreatment produced 85 to 100% inhibition of liver MAO activity, and 90 to 100% inhibition of brain MAO activity.

Conclusions. Both fencamfamin and amphetamine antagonise reserpine-induced depression in mice, fencamfamin having about one-third the potency of amphetamine in this test. However, the toxicity of fencamfamin, unlike that of amphetamine, is not markedly enhanced by previous administration of MAO inhibitors. It seems probable, therefore, that the main cause of the increased toxicity of amphetamine in animals previously treated with MAO inhibitors is due to an enhancement of its peripheral sympathomimetic effects. The toxicity of fencamfamin was increased only by high doses of phenelzine or tranylcypromine. It is difficult to attribute this increase to a specific drug effect and it is probably due to summation of the central and peripheral toxic effects of the two drugs.

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Effect of adrenalectomy on the response of rat skin to an intradermal injection of histamine and 5-hydroxytryptamine

SIR,—The immediate oedema produced in the ears of haematoporphyrine-treated rats by illumination with a small dose of visible light is greater in adrenalectomised rats maintained on saline than in intact animals and is mediated by 5-hydroxytryptamine (5-HT) to a greater extent than by histamine (Ashford, 1963). This fact prompted an investigation into the effect of histamine and 5-HT on capillary permeability in the skin of adrenalectomised and intact rats.

Female albino Wistar rats (140 and 180 g) were bilaterally adrenalectomised through a dorsal incision under ether anaesthesia. Sham-operated and non-operated control animals were included. The room temperature was 27° and adrenalectomised animals drank saline instead of tap water. Histamine acid phosphate and 5-hydroxytryptamine creatinine sulphate were made up in isotonic saline and were injected intradermally into the dorsal, and in some instances abdominal, skin in a volume of 0·1 ml immediately after an intravenous injection of pontamine sky blue (0·1 ml 2%/100 g). Intradermal injections were made on either side, and well clear of the mid-line. The rats were killed 15 min later, and the diameter of the wheals was measured on the underside of the skin by means of calipers. The results (Table 1) show that neither saline nor histamine were more effective whealing agents in adrenalectomised than in intact rats with