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Letters to the Editor

Effect of acetylsalicylic acid on foetal rats

SIR,—During the course of testing drugs for those most likely to exhibit teratogenic activity in man, a study was made of the action of orally administered acetylsalicylic acid on foetal development in rats. In the preliminary experiments, doses about ten times the maximum human therapeutic dose were used and, as other workers (e.g. Obbink & Dalderup, 1964) have reported, not one live birth was obtained. In later experiments, however, lower doses similar to those used clinically (3 × 5 grain tablets four times a day = 50 mg/kg daily) were used, and a relatively large number of dead foetuses and resorption sites were still obtained.

Acetylsalicylic acid powder was mixed with each of two diets, one which had a high sucrose content (sucrose 65%, casein 24%) and one with a high casein content (casein 89%). The remainder of each diet consisted of corn oil (5%) and the vitamin and salt mixture (6%), as used by Colby & Frye (1951). Drinking water was allowed *ad lib.* Each hooded Lister rat of approximately 200 g body-weight consumed 14–16 g food per day when this was made up into a thick paste with water. Males were left in with the females for three days, after which they were removed and the females were given the test diet in place of the standard diet (No. 41 B, London Flour Millers). With this mating regimen, 70–80% of the females were successfully mated. Animals were killed on the 20th day of gestation, the number of live and dead foetuses and resorption sites were counted, and foetal mortality was thus calculated for each dose of acetylsalicylic acid. Results are shown in Table 1 and Fig. 1.

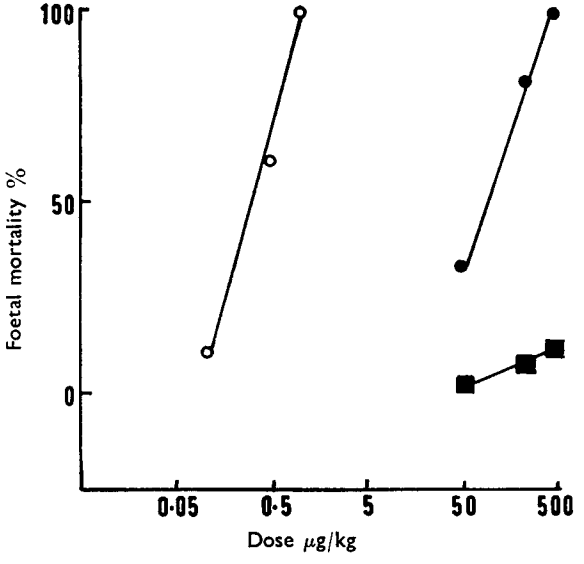

FIG. 1. The relation between foetal mortality and log dose of acetylsalicylic acid (●), thalidomide (■) and reserpine (○) in rats fed on the high sucrose diet.

TABLE 1. THE EFFECT OF ACETYLSALICYLIC ACID ON FOETAL DEVELOPMENT IN RATS FED ON DIFFERENT DIETS

Diet	Dose of acetyl-salicylic acid (mg/kg)	No. of rats	Mean weight gain (g) Day 6–Day 16	No. of implants (and per litter)	No. of foetuses			No. of resorption sites	Deaths (%)
					Total	Live	Dead		
High Sucrose	0	11	+45·3	95 (8·6)	94	94	0	1	1
	50	6	+41·9	74 (12·3)	64	49	15	10	34
	250	4	+31·0	46 (11·5)	23	10	13	23	80
	500	10	−10·0	120 (12·0)	6	0	6	114	100
High Casein	0	10	+16·6	102 (10·2)	100	100	0	2	2
	500	9	+10·0	96 (10·7)	32	0	32	64	100

The following points should be made.

1. The steep slope of the dose-response curve for acetylsalicylic acid is similar to that of reserpine but unlike that of thalidomide (West, 1963); in consequence, acetylsalicylic acid appears to be less likely to produce congenital malformations in the young since a 10-fold increase in dose produced a large increase in lethal action.

2. The smallest dose of acetylsalicylic acid used in the present experiments was equivalent to the maximal B.P. dose used clinically; as it produced a relatively large number of dead foetuses and resorption sites, the question is raised of the possibility of acetylsalicylic acid producing foetal death in humans.

3. Rats fed on the high casein diet containing the largest dose of acetylsalicylic acid continued to increase in weight during gestation whereas those on the high sucrose diet lost weight; there were also relatively more whole foetuses, suggesting that the high protein diet was beneficial and tended to reduce the toxic effects of acetylsalicylic acid, despite the fact that in the absence of acetylsalicylic acid foetuses on the high casein diet were usually smaller than those of the high sucrose diet.

4. The incidence of gastric ulceration was greater in the rats fed on the high sucrose diet (45%) than in those on the high casein diet (22%), again illustrating the beneficial effect of the high protein diet; however, rats which later proved to be non-pregnant showed no toxic effects of acetylsalicylic acid when fed on either of the diets.

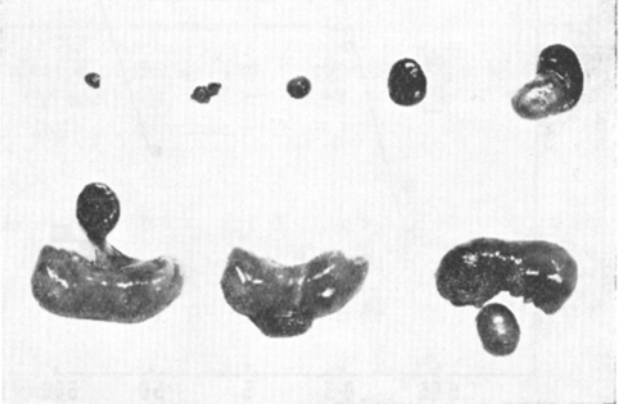

FIG. 2. Some of the contents of the uterus of a pregnant rat after receiving daily doses of acetylsalicylic acid (50 ml/kg) mixed with the high sucrose diet. Animal killed on 20th day of gestation. Note the different stages of disintegration of the foetuses.

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