LETTERS TO THE EDITOR

Drugs and Rat Pregnancy

SIR,—Whilst investigating the role of histamine in rat pregnancy, it became necessary to study the action of certain drugs in animals which had been mated. The results however may be of interest clinically as some of the drugs which are used in human pregnancy produced abortion in rats. No foetal abnormalities like those seen after thalidomide in humans and rabbits have so far been produced but this may only be because conditions for such malformations have not been achieved. Besides, experimental work on laboratory animals during the past 10 years has revealed that many chemical substances have the power when administered to the pregnant female of producing congenital malformations in the young (see Millen, 1962).

We tried to discover why the rat foetus forms much histamine during the last third of gestation and why the maternal urinary excretion of free histamine increases more than 10-fold during this period. The uterine and placental histaminase activity increases to about the same extent at this time yet the maternal uterus becomes relatively insensitive to histamine. Thus, the hypothesis was made that the function of histamine formed by the rat foetus is to help control the blood flow through the placenta (Kameswaran, Pennefather and West, 1962).

TABLE I

SUBSTANCES INFLUENCING RAT PREGNANCY (DOSES IN MG./KG. GIVEN DAILY SHOWN IN PARENTHESIS)

Drugs without effect	Substances with toxic actions
Histamine (100)	5-Hydroxytryptamine (10)
Lysergic acid diethylamide (1)	Mepyramine (50)
2-Bromolysergic acid diethylamide (4)	Promethazine (25)
1-Methyllysergic acid butanolamide (4)	Cyproheptadine (25)
Bretylium (15)	Aprobit (2)
Guanethidine (10)	Reserpine (0·5)
Aminoguanidine (20)	Chlorpromazine (30)
α-Methyl-dihydroxyphenylalanine (75)	Compound 48/80 (2)
Semicarbazide (20)	Polymyxin B (5)
	Compound L1935 (2)

In our first series of experiments, 24 pregnant rats were used. Daily subcutaneous doses of α-methyldihydroxyphenylalanine (75 mg./kg.) or of semicarbazide (20 mg./kg.) were given throughout pregnancy in an attempt to inhibit the histidine decarboxylase activity in the foetal liver. To inhibit uterine and placental histaminase in other rats, daily subcutaneous doses of aminoguanidine (20 mg./kg.) were given. However, neither treatment had any effect on the life-history of the litters although there was a slight reduction in the capacity of all the foetal livers to form histamine when foetuses from each group were examined about the 20th day of pregnancy.

In the second series 81 pregnant rats were used. Daily subcutaneous doses of histamine (100 mg./kg.) and daily intraperitoneal doses of specific anti-5-hydroxytryptamine drugs such as the three lysergic acid derivatives shown in Table I were found to be non-toxic to rat foetuses, and they too slightly reduced the enzyme activity in the foetal liver. In sharp contrast, both 5-hydroxytryptamine (10 mg./kg.) and the specific antihistamine drug mepyramine (50 mg./kg.) were toxic to foetuses although the histamine-forming

capacity of the foetal liver and the histaminase activity of the placenta were unchanged. Two other antihistamine drugs, cyproheptadine and promethazine, produced death of some of the foetuses when given intraperitoneally in high dosage (25 mg./kg.). The most toxic antihistamine drug tested was Aprobit, 2-hydroxyethyldimethyl-1-(10-phenothiazinylmethyl) ethylammoniumch loride; this quaternary drug fails to pass the placenta barrier and readily accumulates in the placenta where it may antagonise the vasodilator action of histamine which has been formed by the foetus. Aprobit is more than 10 times as toxic as promethazine in rat pregnancy, and at least 100 times more toxic to the foetus than to the mother. Although promethazine and Aprobit are toxic when injected into pregnant rats, they are both used orally in human pregnancy to alleviate nausea and vomiting; a warning note should therefore be sounded.

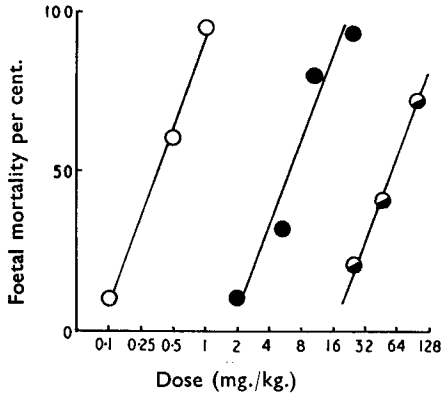

FIG. 1. The relation between log dose of reserpine (○), Aprobit (●) and promethazine (◔) and foetal mortality in rats.

In the third series 56 pregnant rats were used. The antihypertensive drugs, guanethidine (10 mg./kg.) and bretylium (15 mg./kg.), were given daily but no observable effects on the course of pregnancy or on the offspring were noted. In sharp contrast, daily doses of both reserpine (0·5 mg./kg.) and chlorpromazine (30 mg./kg.) were toxic, many foetuses being resorbed by the 20th day of gestation. These four drugs are now widely used in human pregnancy and care also seems necessary in their use. Various synthetic histamine liberators (for example, compounds 48/80 and L1935, and polymyxin B) produced abortion and death of some of the rat foetuses, but these drugs are not used routinely in man. Experiments upon animals such as these reported here may thus be valuable in determining which drugs are most likely to exhibit teratogenic activity in man.

Woollam (1962) has suggested that any drug which will kill the foetus will also deform it if given in a lower dose, and it may be that one of the most practicable methods of detecting teratogenicity is to relate the foetal toxicity to the toxic dose for the mother. Dr. G. F. Somers (in a personal communication) has suggested that it may be better to determine the foetal resorptions in relation to the dose administered to the mother (that is, not to the toxic dose for the mother). If this relationship is traced, say, for reserpine, Aprobit and promethazine (see Fig. 1), the lines are quite steep and there is only a narrow band of doses where teratogenicity is possible. The corresponding lines for

other drugs which have been shown to produce congenital malformations in the young may be flat so that a 10- to 20-fold increase in dose may produce only a moderate increase in toxicity.

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Anti-inflammatory Activity of Musk

SIR,—Musk is a dried secretion obtained from the prepucial follicles of *Moschus moschiferus* linn. (Fam. Cervidae.) (Chopra, 1958.) Practitioners of the indigenous system of medicine claim to obtain beneficial results with musk in arthritis, and we have now examined its anti-inflammatory properties.

Male albino rats weighing between 150–175 g. were subdivided into 5 groups. The hair of the back was removed with depilatory and the area washed and sterilised with ethanol. Three sealed musk pod samples of authentic musk obtained from the Institute of History of Medicine and Medical Research, India, were examined. Each was made into an emulsion in Tween 80, itself inactive, and injected subcutaneously in 10 rats for each dose of 1·0, 1·5 and 2·0 mg. for each of the 3 samples. Hydrocortisone suspension (Glaxo), 1 mg. in 0·1 ml., was injected subcutaneously to a group of 10 rats and another group of 10 rats kept as control. Granuloma pouches were made 24 hr. later in all the animals, under light ether anaesthesia, by injecting 25 ml. of air deep into loose subcutaneous tissue in the interscapular region using a No. 27 needle followed by the injection through the same needle of 1 ml. of one per cent croton oil solution in olive oil, into the resulting pneumodermal space. During the first 2 to 3 days, the pouches were essentially similar in all the groups. The changes began from the fourth day onwards. In the control group, the wall of the pouch began to thicken and haemorrhagic fluid started filling the cavity. In the musk- and hydrocortisone-treated animals, the wall of the pouch was very thin, transillumination revealing no haemorrhagic fluid and the gradual collapse of the pouch as the air was absorbed.

The experiment was terminated on the fourteenth day after the croton oil injection. The granuloma pouch was dissected, the amount of haemorrhagic fluid present was measured and the pouch wall weighed after careful washing. In the control animals, the pouch was filled by a large amount of haemorrhagic exudate and the pouch wall was extremely hard. In the musk- and hydrocortisone-treated animals only a slight elevation of the skin remained, which indicated that a small amount of the air remained.

The results are given in Table I. The "*t*" test was done to determine the mean values and Snedecor's "F"-test to find out the significance of the difference between the three samples of musk. Since, at the same dose level, the samples gave statistically homogeneous results, they were pooled. The difference