The inhibitory effect of subcutaneously administered degraded carrageenan on gastric secretion

SIR,— We have shown that subcutaneously administered degraded carrageenan has a pronounced inhibitory action on the acid secretory response of the intact guinea-pig stomach (Watt, Eagleton & Marcus, 1966b). This inhibitory action was observed in relation to histamine-stimulated secretion but not to the secretion stimulated by 3-(2-aminoethyl)pyrazole dihydrochloride (ametazole hydrochloride; Histalog) an analogue of histamine. We have now investigated the time course relative to this inhibitory action and, in addition, the effect of degraded carrageenan on fasting secretion.

Adult male albino guinea-pigs (550–750 g) were prepared for secretory studies by a preliminary fast of 15 hr, during which time they wore loosely-fitting Perspex collars to prevent coprophagy. Gastric secretion was then stimulated by the intramuscular injection of histamine acid phosphate (1 mg/kg) in aqueous solution (1 mg/ml). One hr later, the gastric juices were collected by intubation of the unanaesthetized animal. Total acid concentration was measured by titration using phenolphthalein as indicator.

Freshly prepared degraded carrageenan (5% aqueous solution) derived from the red seaweed *Eucheuma spinosum*, was administered as a single subcutaneous injection in a dose of 400 mg/kg. In the time course study, secretory tests were made on separate groups of animals at 2 hr intervals over the first 24 hr and at 2, 3, 9 and 14 days after the administration of carrageenan. Groups varied in size from 2 to 10 animals; the control group (at zero hr) comprised 20 animals. The effect of degraded carrageenan on the fasting secretion was studied in animals which had received the drug subcutaneously (400 mg/kg) 18 hr previously.

The time course study (Fig. 1) indicates a significant reduction (2 standard deviations below the mean of the control values) in both volume and total acid concentration of the histamine-stimulated juice from about 6 to 24 hr following a single injection of degraded carrageenan. By 3 days all values are within the normal range.

The effects of degraded carrageenan on the fasting gastric secretion are shown in Table 1. Degraded carrageenan lowers the volume significantly and tends to reduce the total acid concentration of fasting secretion.

It has been known for some time that orally administered degraded carrageenan, apart from possessing antipeptic activity, also causes a temporary reduction of gastric acidity in response to histamine (Anderson, Marcus & Watt, 1962). The results of the present investigation show that degraded carrageenan administered parenterally has a pronounced inhibitory effect on histamine-stimulated gastric secretion and that this effect is a prolonged one

TABLE 1. EFFECT OF 18 HR PRETREATMENT WITH SUBCUTANEOUSLY ADMINISTERED DEGRADED CARRAGEENAN ON FASTING GASTRIC SECRETION (MEANS ± ONE S.D.). NUMBER OF ANIMALS IN PARENTHESES

Treatment	Gastric secretion			
	Volume (ml)		Total acid (m-equiv/litre)	
Fasting (10)	3·3 ± 2·5	$P < 0.05$	98·5 ± 27·1	$P > 0.20$
Degraded carrageenan and fasting (10)	1·0 ± 1·0		85·8 ± 32·1	

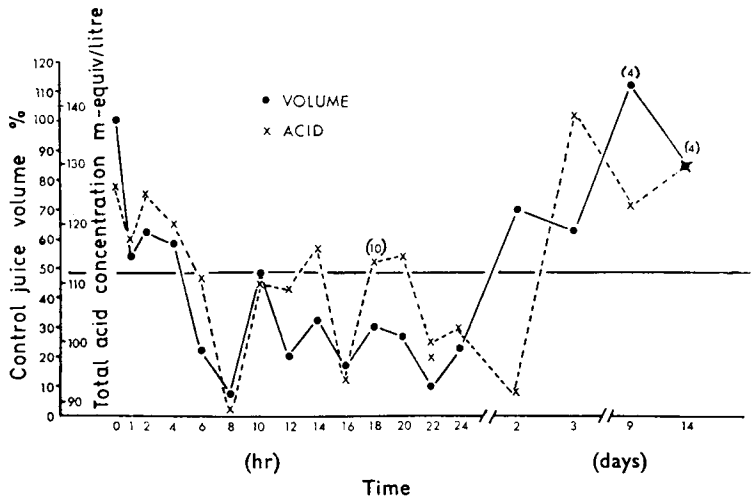

FIG. 1. Time course study. Effect on histamine-stimulated gastric secretion of degraded carrageenan administered subcutaneously. Two animals used at each point except as indicated at 18 hr, 9 and 14 days. The horizontal dark line represents two standard deviations below the means of the control values for both volume and total acid concentration.

lasting from about 6 to 24 hr. By the third day, the inhibition is no longer apparent. The results also suggest that degraded carrageenan suppresses the fasting gastric secretion.

We have previously suggested that the inhibitory effect of degraded carrageenan on histamine-stimulated gastric secretion in the guinea-pig may be due to complexing of the sulphated polysaccharide with histamine (Watt & others, 1966b). Another possible mechanism is the release of diamine oxidase from the intestine into the plasma, as occurs in the rat in response to heparin (Maudsley & Kobayashi, 1968). A prompt rise in plasma diamine oxidase also occurs in man after the injection of heparin (Dahlbäck, Hansson, & others, 1968).

Recently, the sulphated polysaccharide heparin has been shown to exert inhibitory effects on stimulated gastric secretion in experimental animals (Thompson, Lerner & others, 1966; Watt & others, 1966a). It has also been demonstrated that intravenous heparin inhibits both stimulated and basal gastric secretion in man (Thompson, Lerner & Musicant, 1966). Its use in the treatment of peptic ulceration, however, is inadvisable because of its anticoagulant properties. Such objection may not be applicable to degraded carrageenan. Anderson & Duncan (1965) have made a comparison of the anticoagulant properties of a variety of carrageenans and have shown that degraded carrageenan has only very slight anticoagulant activity. This is in accord with our own observation that no haemorrhagic diathesis was produced in any of our animals in the doses used. As with heparin, there is no granulomatous reaction in the subcutaneous tissues at the site of injection. It is possible that degraded carrageenan, or some other sulphated polysaccharide, administered parenterally may prove to be of therapeutic value in the management of peptic ulceration.

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Effect of some psychotropic drugs on mice from a spontaneously aggressive strain

SIR,—The spontaneous or provoked aggressiveness of different animal species has often been used to study the antagonistic action of psychotropic drugs (Valzelli, 1967). In the mouse, a typical aggressiveness is manifested only after prolonged isolation of 3 to 4 weeks, which is technically difficult, or after painful stimulation.

A spontaneous aggressiveness is found in the male mice of the strain CF 1 (IFFA-CARWORTH) more than one month old, which is exhibited by tail wounds in mice grouped in a cage, only one animal, the "boss", remaining unwounded.

Preliminary tests were made to utilize this particular behaviour using the presentation of another animal to an aggressive mouse alone in his cage or in a new cage. However, in these conditions, prompt onset of fighting did not regularly occur.

To suppress the effect of a recent change of territory, we used the following conditions: preliminary isolation for 24 to 48 hr; the presentation of non-aggressive mice (male, Swiss strain, identical weight) according to the following protocol: every 30 min, two mice were successively presented, each animal being withdrawn after the first attack and being left, at the maximum, 5 min in the cage.

Under these conditions, 90% of mice behaved regularly in an aggressive manner, the others being easily eliminated. For the study of psychotropic drugs, we used groups of 8 aggressive mice for each dose. A repetition of the test every 30 min permitted the establishment of the kinetics of any anti-aggressive effect. In the control tests, we regularly obtained 16 aggressions for each animal; the effect of drugs was expressed as a percentage of the diminution of this aggressiveness.

The results are shown in Table 1. Efficacious doses are similar to those found by other experimenters using different methods (see Valzelli, 1967). This method seems to be better from two points of view: utilization of a natural aggressiveness and the technical facility of the test.