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Intestinal Propulsion in Restrained and Unrestrained Rats. (30944)

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Although the production of gastric mucosal erosions in rats by immobilization has been studied(1), the effect of this type of stress on the propulsive activity of the small intestine has received little attention. Brodie and Hanson(2) observed in rats a high incidence of defecation during early moments of immobilization and decreased gastric retention after 24 hours of restraint. They concluded that restraint increased gastrointestinal motility.

To investigate the direct effect of immobilization on the propulsive activity of the small intestine we have studied the intestinal passage of a charcoal suspension in restrained and control rats, by a modification of the technique of Macht and Barba-Gose(3). We observed a pattern of propulsion which persisted in both restrained and unrestrained animals.

Materials and methods. Male rats of the Wistar strain (weight: 70-150 g) were allowed to consume only water for 24 hours. The test meal consisted of 5 ml/kg of a 6% suspension of charcoal powder in 0.5% tragacanth. Immediately after the test meal was administered by gavage, individual rats were restrained by taping together the forelimbs and the hindlimbs and taping the tail to the body. Each rat was then wrapped in a piece of galvanized steel window screen, molded to the contour of the animal's body and stapled firmly. In this state the animal was prevented from making all but the most limited struggling movements. The unrestrained control animals were returned to their cages immediately after receiving the test meal. All animals were deprived of food and water for the remainder of the experiment.

At intervals varying from 5 to 240 minutes after administration of the meal, the animals were sacrificed with ether and the small intestines removed. Each intestine was extended with minimal stretching upon a table, and the distance from pylorus to cecum was measured. The transit of the test meal was expressed as the per cent of the small intes-

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TABLE I. Transit of the Meal at Various Times After Dosing.

Time (min)	Unrestrained Transit ± S.E.	Unrestrained No. of rats	Restrained Transit ± S.E.	Restrained No. of rats
5	34.4 ± 2.2	20	6.9 ± 3.7	13
6	37.3 ± 3.0	10		
7	38.3 ± 2.5	15		
10	45.3 ± 2.2	20	22.3 ± 2.8	23
12	50.8 ± 2.0	24		
15	49.5 ± 3.0	10		
20	57.2 ± 3.0	10	28.3 ± 4.2	10
30	63.0 ± 2.2	20	34.9 ± 2.0	47
45	68.3 ± 3.2	9		
60			33.5 ± 3.2	17
120			59.6 ± 3.4	16
240			72.2 ± 3.2	17

Transit equals the percent of small intestinal length traversed by the leading edge of the meal. Standard errors were calculated using the pooled standard deviation for either restrained on unrestrained animals.

tine traversed by the leading edge of the meal.

To study the effect of dichloroisoproterenol (DCI), a beta adrenergic blocking agent, 5 mg/kg of its hydrochloride salt (in aqueous solution, 1 ml/kg) was injected subcutaneously into 2 groups of 10 rats each. Thirty minutes later both groups were given the test meal. One group was then restrained and the other group was returned to cages. Thirty minutes after administration of the test meal, the animals were sacrificed and the transit of the meal was measured and expressed as above. Controls for each group differed only in that they were injected with 1 ml/kg of saline instead of the dose of DCI.

Results. Transit in unrestrained animals. The average transit of the test meal at various intervals between 5 and 45 minutes after administration is shown in Table I. A plot of the data suggested that the transit was proportional to the logarithm of the time after dosing, and a line was fitted to these points by the method of least squares (Fig. 1). The F test(4) was applied to these data and no significant deviation from this line was noted.

Transit in restrained animals. Transit was delayed in the restrained rats; the time required for approximately 70% transit was 240 minutes in the restrained animals as compared with 45 minutes in the unrestrained animals (Table I, Fig. 1). The data for the transit of the meal at 5, 10, 20, 30, 120 and 240 minutes were analyzed by the method of least squares and the F test as above. No significant deviation from linearity was noted for these points. Although transit at 60 minutes was below that predicted by the line, the linearity of the other data was so statistically striking as to suggest an overall pattern of propulsion temporarily disrupted between 30 and 120 minutes after dosing.

Transit in DCI-treated animals. A comparison of the transit in DCI-treated restrained animals (49.4%) with that in DCI-treated unrestrained animals (51.8%) suggests that DCI blocks at least partially the effect of restraint upon transit (Table II). The data also show that DCI slows transit in unrestrained animals.

Discussion. The concept of the regulation of the propulsive activity of the intestine by a myogenic gradient of contraction(5) has been questioned(6). In the dog, several studies have suggested that a duodenal pacemaker controls the rate of contraction of the distal intestine(6,7). The frequencies of electrical slow waves(8), and of intestinal contractions(7) have been reported to decrease as one proceeds distally from the pylorus. Furthermore, the rate of travel of a test meal has been observed to decline with distal pro-

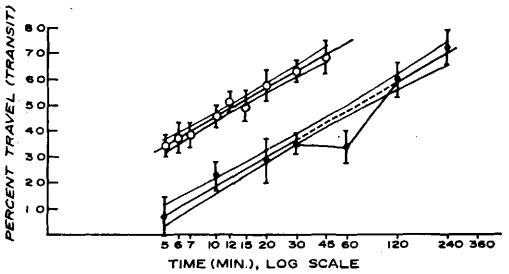

FIG. 1. Transit of the meal in unrestrained and restrained rats. ○—Mean transit in unrestrained rats. ●—Mean transit in restrained rats. Transit is defined as % of small intestinal length traversed by the leading edge of test meal. The lines fitted to the data by the method of least squares, and 95% confidence limits of these lines are shown. Brackets enclose 95% confidence limits for each experimental mean. All confidence limits were calculated using the pooled standard deviation for either the restrained or unrestrained animals. Data for the restrained group at 60 minutes were not used in computing the line (see text).

TABLE II. Effect of DCI on Transit of the Meal at 30 Minutes in Restrained and Unrestrained Rats.

Treatment	Transit ± S.E.	No. rats
Unrestrained controls	67.2 ± 3.1	9
Restrained "	38.2 ± 3.0	10
DCI-treated unrestrained	51.8 ± 3.6*	10
DCI-treated restrained	49.4 ± 3.1*	10

* The difference between these 2 groups is not significant ($p > .35$). For any other comparison, difference is significant ($p < .05$).

gression in the dog(9). A similar finding has been reported in rats(10).

We have also observed that the velocity of a test meal decreases as it passes through the small intestine of the rat. Moreover, when the transit observed in unrestrained animals was plotted against the logarithm of the time after dosing, a straight line in the interval between 5 and 45 minutes (35 to 70% transit) was obtained (Fig. 1). The line, calculated by the method of least squares, was described by the equation:

$$D = 8.8 + 36.7 \text{ Log } T \qquad (I),$$

where D is the transit of the test meal and T the time (in minutes) after dosing. The differential with respect to time described the velocity (V) of the test meal:

$$V = 36.7/T \qquad (II).$$

Thus, the velocity was inversely proportional to the time elapsed. Solving (I) for T:

$$T = 10^{(D-8.8)/36.7} \qquad (III).$$

Substituting (III) in (II):

$$V = 36.7/10^{(D-8.8)/36.7} \qquad (IV),$$

or, more simply,

$$V = 62.9 \times 10^{-D/36.7} \qquad (V).$$

Thus, the velocity of the test meal declined exponentially as the distance from the pylorus was increased. More specifically, the velocity was halved every time the meal advanced 11% of intestinal length. During this interval (5 to 45 minutes after dosing) the velocity of the meal declined from 7.4 to 0.8% per minute.

The transit in the interval 0 to 5 minutes was impossible to determine accurately because of technical problems. After 45 minutes the meal had reached the cecum in some of the animals. Since the transit could no longer be measured precisely, data for intervals in excess of 45 minutes in unrestrained rats were not used in the study. The same considerations limited the study to the 5- to 240-minute interval in the restrained rats.

For the restrained rats the equation describing the relationship between the transit and the time after dosing was $D = -18.6 + 37.5 \log T$ (excepting the interval from 30 to 120 minutes, as noted above). When the transit was plotted against the logarithm of the time after dosing, the slopes of the lines for the restrained and unrestrained rats (37.5 and 36.7, respectively) were not significantly different (Fig. 1). Therefore, as functions of *time,* the velocities in the restrained and unrestrained animals were nearly identical. In both groups the velocity was halved every time the meal advanced 11% of intestinal length. Such similarity in the patterns of intestinal propulsive activity in the restrained and unrestrained animals strongly suggests the existence of a persistent physiological mechanism which regulates the propulsive activity of the small intestine.

The expression for the velocity as a function of *transit* in the restrained animals (*i.e.,* the analogue of equation (V), above, for the unrestrained animals) was $V = 12.0 \times 10^{-D/37.5}$. Clearly, as a function of transit, the velocity of the test meal in the unrestrained animals was approximately 5.1 times that for the restrained animals. Thus, a given segment of intestine in the unrestrained animals propelled a bolus 5 times more rapidly than the corresponding segment in the restrained animals.

As noted above, the transit in the 30- to 60-minute interval was delayed in the restrained rats. This indicates that a mechanism operated selectively at this point to retard temporarily the progress of the meal. Subsequently a compensatory acceleration must have occurred to restore the basic pattern of propulsion which was preserved at later inter-

vals. The nature of this mechanism remains to be elucidated.

The observation of decreased intestinal propulsive activity in restrained rats is at variance with the conclusion of Brodie and Hanson(2). These investigators, however, did not measure small intestinal propulsion.

The means by which DCI opposed the retarding effect of restraint on the propulsive activity of the rat intestine is unknown. Perhaps the mechanism is related to this drug's demonstrated opposition to the inhibiting effects of isoproterenol on the dog's intestine (11).

Summary. The pattern of propulsion of a test meal in the small intestine of the rat has been studied. Between 5 and 45 minutes after administration of the test meal, the velocity of the meal was related inversely to the time after dosing, and declined exponentially with increasing distance from the pylorus. With every advance of 11% of intestinal length, the velocity of the meal was halved. When the rats were restrained in wire screens these relationships generally persisted despite a reduction in the over-all velocity with which the meal traversed the intestine. The persistence of this pattern strongly suggests the existence of a physiological mechanism which regulates the propulsive activity of the small intestine. DCI partially reversed the decrease in velocity in the restrained animals.

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Prevention of Ulcer Formation by Hypophysectomy. (30945)

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The pituitary gland was reported to exert a marked influence on gastric morphology and secretion as well as on ulcer formation. In general, hypophysectomy was found to inhibit gastric cellular elements(1) and gastric secretion (volume, acid(2,3,4), pepsin(1,3, 4) and mucus(3)). STH (somatotrophic hormone) administered to hypophysectomized rats restored nearly completely the acid(3), partially the volume(5,3) and the mucus(3) but not the pepsin(5,3); in the dog even pepsin secretion was normalized by STH(4). Hypophysectomy reduced ulcers produced in the rat by some techniques (Shay ulcers(6), cauterization of gastric wall(7)) but it did not influence ulcers due to excision of a portion of the mucosa(8) or to restraint(9). STH, on the other hand, inhibited ulcers obtained in rats by injection of formalin into the gastric wall(10) and by administration of prednisolone(3). STH also reduced histamine ulcers in guinea pigs(11).

In all but two of the above mentioned studies with hypophysectomized animals, the observations were made within 2 to 4 weeks following the operation. Very rarely did it extend over a period of several months. Baker and Abrams(1) studied rats up to 128 days