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

following hypophysectomy and found that the histological changes in the stomach as well as the reduction in pepsin secretion were already maximal after a week. Only Jacobson and Magnani(4) reported in dogs a progressive decrease in volume of secretion, in acid and in pepsin during the 5 months that followed hypophysectomy. They did not, however, find any histological changes in the gastric mucosa.

In the present experiment, the influence of the duration of the post-hypophysectomy interval on formation of steroid-induced ulcers was studied.

Methods. Female, Sprague-Dawley rats (180-200 g) were hypophysectomized by the transauricular technique, modified(3) after Koyama(12,13) and Falconi and Rossi(14). At various times following the operation (1, 2, 3, 4, 6, 12 and 17 weeks), the animals were injected subcutaneously daily for 4 days with 5 mg of prednisolone (a glucocorticoid known to produce gastric ulcers in intact rats)(15, 16). They were fed Purina Laboratory Chow, drank water *ad libitum* and were killed with chloroform at the end of the 4-day treatment. Hypophysectomies were scheduled at such times that treatment with prednisolone was started on the same day for all the animals. For each post-hypophysectomy time interval, 2 groups of rats were used, one receiving prednisolone and the other the vehicle. Two groups of non-hypophysectomized rats, one receiving prednisolone and the other the vehicle, were added for comparative purposes. At autopsy, completeness of hypophysectomy was verified by examination of the sella turcica with a 2× magnifier. The stomachs were first mixed and coded to prevent immediate identification. They were then opened along the greater curvature, rinsed with lukewarm water and examined with a 2× magnifier for the presence of ulcerations. For each group, the ulcers were expressed in terms of "ulcer index"(15) which is the sum of a) per cent incidence (divided by 10) of animals with ulcers; b) average severity of the ulcers from a scale of 0 to 3+. For each stomach, the severity was rated as that of the most severe ulcer for that stomach; c) average number of ulcers per stomach. The spleens were also removed and weighed as an index of another peripheral action of prednisolone.

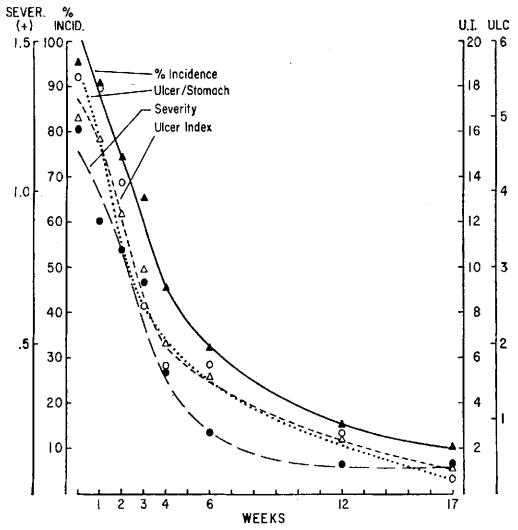

FIG. 1. Effect of hypophysectomy on steroid-induced ulcers. Abscissa: intervals since hypophysectomy. Severity: severity of ulcers from scale 0 to 3+. Incid.: % incidence of animals with ulcers. U.I.: ulcer index. ULC.: no. of ulcers per stomach.

Results. Steroid-induced ulcers were decreased after hypophysectomy (Fig. 1) by comparison with unoperated animals. The longer the interval since hypophysectomy, the greater was the protection. After 17 weeks, there was almost complete inhibition of ulcer formation ("ulcer index" decreased by 98%). Actually, at this time, the stomachs of 2 rats out of 20 were ulcerated and they showed only one small ulcer per stomach. On the other hand, the catabolic effect of prednisolone (shown by loss of body weight after 4 days of treatment) (Table I) was about the same in all groups, including the non-hypophysectomized animals. Similarly, atrophy of the spleen in prednisolone-treated animals, another characteristic effect of glucocorticoids, was already maximal one week after hypophysectomy (Fig. 2).

Discussion. Atrophy of adrenals, thyroid and testes was previously reported to be complete 28 days after hypophysectomy; when these same organs were weighed at various intervals up to 400 days after the operation, there was no further decrease. Since structures controlled by the pituitary involute so

TABLE I. Effect of Prednisolone on Body Weight in Hypophysectomized Animals.

	Intact		Hypophysectomized													
			1 week		2 weeks		3 weeks		4 weeks		6 weeks		12 weeks		17 weeks	
	Con	Pred	Con	Pred	Con	Pred	Con	Pred	Con	Pred	Con	Pred	Con	Pred	Con	Pred
No. of animals	10	20	12	30	7	19	7	20	7	20	7	19	7	20	7	20
Initial body* weight, g	191	191	182	183	171	173	192	189	185	185	187	185	188	189	191	192
Final body weight, g	195	162	182	155	176	156	193	162	189	161	188	158	192	164	187	162
Body weight difference, g	+4	-29	0	-28	+5	-17	+1	-27	+4	-24	+1	-27	-6	-25	-4	-30

* Initial body weight: on the day prednisolone was started. Final body weight: 4 days later, when animals were killed. Con: control group, receiving vehicle for prednisolone. Pred: prednisolone, 5 mg daily for 4 days.

rapidly, the *progressive* resistance of hypophysectomized rats to steroid-induced ulcers, found in the present study, was unexpected and is indeed difficult to interpret. The following hypotheses are considered.

a) The progressive resistance to ulcer formation does not seem to be due to a parallel inhibition of gastric secretion because, as demonstrated by several authors, reduction in such secretion is already maximal a few days following hypophysectomy(2,1,3).

b) It is unlikely that some pituitary-dependent glands would take up to 17 weeks to stop functioning, since as mentioned above, atrophy of adrenals, thyroid and testes is maximal within a month after hypophysectomy(17,18). Rat corpora lutea, however, were reported to be still persisting several months after hypophysectomy(17,19). Whether these were still functioning, however, was not established. In this connection, it may be recalled that the incidence of peptic ulcer is lower in women than in men (ratio 1 to 4), although this has not always been the case. Available statistics indicate that prior to 1900-1910, peptic ulcer was predominantly a disease of women(20). On the other hand, intact female rats were found to be more sensitive than males to ulcers produced by restraint(21). Whether a very slow involution of the corpus luteum accounts for the progressive insensitivity to steroid ulcer formation after hypophysectomy is open to question and could be decided by repeating the present experiment in hypophysectomized and ovariectomized animals.

c) Even if pituitary-dependent glands stop functioning within a few days post-hypophysectomy, the peripheral effects of some of their secretions (*e.g.*, thyroid hormone) may linger for prolonged periods. Such an effect may be the maintenance of sensitivity of the stomach to develop steroid-induced ulcers.

d) Since the animals were hypophysectomized from 1 to 17 weeks before receiving prednisolone, they were not of same age at the time of treatment, although approximately of same body weight. This age difference, however, does not appear to have influenced the results because we previously found that glucocorticoids are equally ulcerogenic in intact rats of various ages provided the dose is

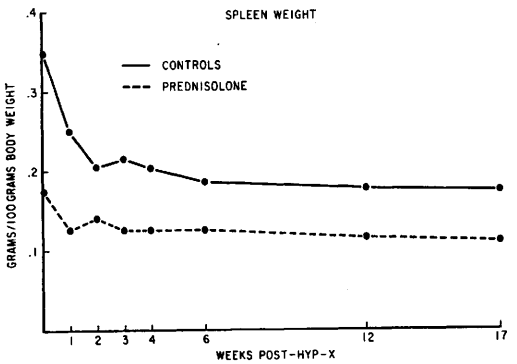

FIG. 2. Weight of spleen after hypophysectomy and prednisolone. Abscissa: intervals since hypophysectomy.

adjusted on a body weight basis (unpublished).

e) Hypophysectomy may result in elaboration, in progressively greater quantities, of factor(s) endowed with antiulcer properties. The source of these hypothetical substances is unknown; in view of the close relationship between the pituitary and the hypothalamus, the latter may be suspected. Such substances, unlike hypothalamic "releasing factors," would not require the pituitary for exerting their anti-ulcer action; on the contrary, according to this hypothesis, they would act optimally in the absence of the pituitary.

f) Finally, it is not known whether resistance would also develop against other types of ulcers (*e.g.*, restraint, histamine, reserpine) by waiting long enough after hypophysectomy.

Summary. Hypophysectomy in the rat reduced gastric ulcers induced by administration of prednisolone for 4 days. Ulcer inhibition became more marked as the interval between hypophysectomy and treatment with prednisolone increased. Seventeen weeks after hypophysectomy, the animals were almost completely resistant to ulcerations. This slowly developing refractoriness was not accompanied by resistance to other properties of prednisolone; thus, body weight loss and spleen atrophy produced by the corticoid were maximal already one week after hypophysectomy and remained so throughout the 17 weeks of the experiment. Pituitary-dependent structures (adrenals, thyroid, testes) were previously reported to be maximally involuted within a month following hypophysectomy. To interpret this unique effect of hypophysectomy, it is suggested that either a humoral factor, of unknown origin, endowed with anti-ulcer activity, may be formed in progressively increasing amounts after removal of the pituitary or that the peripheral effects of the secretion of some pituitary-dependent gland(s) persist for variable intervals after hypophysectomy. The possible protective role of corpora lutea, persisting after hypophysectomy, is also considered.

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