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Prevention by Stress and Cortisol of Gastric Ulcers Normally Produced by 48 80.* (25552)

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48/80, a product obtained by condensation of p-methoxyphenyl-methylamine with formaldehyde, is a particularly potent histamine liberator(1). Its most conspicuous toxic actions in the rat are anaphylactoid inflammation (with edema and cyanosis of the paws, snout, ears, and genitals) and acute hemorrhagic stomach ulcers with intense gastric edema(2). It is known that stress and glucocorticoids can also produce acute gastric ulcers, although they actually prevent anaphylactoid inflammation(3). The experiments reported here indicate that various stressors and cortisol inhibit all the just-mentioned toxic actions of 48/80, including the gastric lesions.

Methods. Eighty female Sprague-Dawley rats, with a mean initial body weight of 145 g (range: 140-154 g), were subdivided into 8 equal groups and treated as indicated in Table I. 48/80 was given intraperitoneally at the dose of 300 μg in 0.2 ml of water at 10 a.m. and 5 p.m. on one day only (Groups 1-7). The stressors employed were: Groups 3 and 8, *restraint* (animals strapped to board by adhesive tape in prone position 24 hours); Group 4, *cold* (rats were shaved and kept at 2°C for 3 hours in morning and 2 hours in evening); and Group 5, *motor denervation of extremities* (both cervical plexuses, as well as femoral and sciatic nerves, were severed under ether anesthesia). All these stressors were applied on day of 48/80 treatment, but one additional group (Group 2) was restrained on preceding day only, to show the effects of *pretreatment with stress.* In Group 6, *cortisol* was administered as suspension of microcrys-

TABLE I. Prevention by Stress and Cortisol of 48/80 Intoxication.

Group	Treatment	Shock + anaphylactoid inflammation	Gastric Ulcers	Gastric Edema
1	48/80	4+	4+	4+
2	48/80 + restraint (pretreatment)	0	Trace	Trace
3	48/80 + restraint	0	2+	0
4	48/80 + cold	0	Trace	0
5	48/80 + denervation of extremities	0	0	0
6	48/80 + cortisol (10 mg once)	0	Trace	0
7	48/80 + cortisol (1 mg/day, 10 days)	Trace	1+	Trace
8	Restraint	0	2+	0

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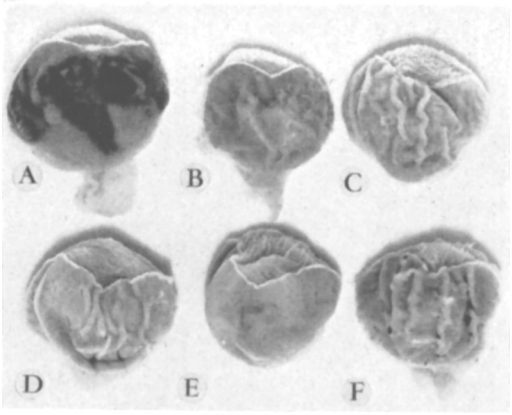

FIG. 1. Macroscopic appearance of gastric mucosa. A. 48/80; B. 48/80 + pretreatment with restraint; C. 48/80 + concurrent exposure to cold; D. 48/80 + concurrent denervation of extremities; E. 48/80 + pretreatment with single dose of cortisol; F. Restraint. Compare extensive hemorrhagic ulcerations and pronounced edema in A with virtually complete suppression of lesions in B, C, D, and E. In F, the ulcers are of the alarm-reaction type, unaccompanied by edema.

tals of its acetate, at dose of 10 mg in 0.2 ml of water, subcutaneously, once on day preceding 48/80 treatment, to produce intense but brief glucocorticoid overdosage. In Group 7, 1 mg/day of cortisol was administered in same manner during 10 preceding days, to establish the effect of a more chronic hormone pretreatment. All rats were killed with chloroform 24 hours after first 48/80 injection.

Results. In all control rats of Group 1, signs of shock and marked anaphylactoid inflammation, with edema and cyanosis of paws, snout, ears, and genitals, were seen after the first, and even more markedly after second, 48/80 injection, but none of these signs characteristic of histamine-liberator intoxication could be detected in the remaining groups, except for a trace of cyanosis and a slightly diminished spontaneous motor activity in rats of Group 7.

All control animals exhibited pronounced hemorrhagic gastric ulcers and intense edema of the gastric mucosa and submucosa. These changes were completely, or partially, prevented by various stressors (Groups 2-5) and by cortisol (Groups 6 and 7). Twenty-four hours of restraint (Group 8) is a particularly severe stressor, which elicits hemorrhagic gastric ulcers typical of the alarm reaction; these are essentially different from those induced by 48/80 (Group 1) for they are unaccompanied by gastric edema. Accordingly, when 48/80 and restraint were applied concurrently the gastric erosions of the alarm reaction developed, but were unaccompanied by edema. In rats restrained the day before treatment with 48/80, the erosions had disappeared by time of autopsy, yet the protection against the gastric lesion induced by 48/80 was still evident. Cortisol proved to be much more effective in inhibiting 48/80 intoxication when given as a single heavy dose on day preceding treatment with the histamine liberator than when the same total dose was injected during the 10 preceding days. These findings are summarized in Table I (which lists mean findings in terms of an arbitrary scale of 0-4+) and illustrated in Figs. 1 and 2.

Discussion. Gastric ulcers produced by the histamine liberator 48/80 differ qualitatively from those characteristic of the alarm reaction in that only the former are accompanied by marked gastric edema. Pretreatment with various stressors inhibits both production of anaphylactoid inflammation and

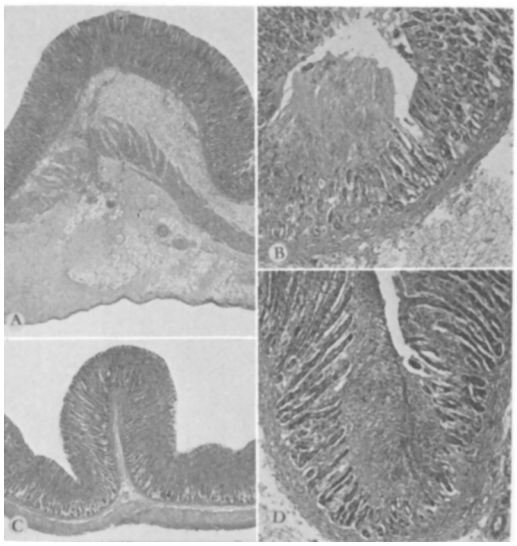

FIG. 2. Microscopic appearance of gastric mucosa. A and B, 48/80; C, 48/80 + pretreatment with restraint; D, restraint. Gigantic edema of submucosa and serosa (A) and necrosis with exulceration of mucosa (B) induced by 48/80 alone. Following 48/80 + restraint (C), gastric wall is normal; after restraint (D), necrosis with ulceration of mucosa but no edema.

induction of hemorrhagic edematous gastric lesions by 48/80. This effect of stress is presumably mediated through endogenous glucocorticoids, since it can be reproduced by pretreatment with cortisol. It had been noted that following pretreatment with 48/80 subsequent production of anaphylactoid inflammation by this same agent or other similarly acting substances is prevented. This had been ascribed to depletion of histamine reserve(4). Our observations do not invalidate this interpretation, but it must be kept in mind that the effect of such pretreatment may also be due to depletion of serotonin or of other metabolites necessary for development of an anaphylactoid inflammation and, indeed, may be the result of an alarm reaction produced by any stressor. The fact that histamine liberators greatly increase corticoid secretion(5) is consonant with the concept that even resistance induced by pretreatment with 48/80 and cognate compounds depends, at least in part, upon an increase in corticoid secretion.

Summary. Experiments on rats indicate that gastric ulcers produced by various stressors (as part of alarm reaction) differ qualitatively from those induced by histamine liberator 48/80. The latter lesions as well as the anaphylactoid inflammation and shock produced by 48/80 can actually be prevented by stressors or cortisol, although these same agents are, in themselves, capable of producing the alarm-reaction type of gastric erosion.

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