Mucosal Susceptibility in Peptic Ulceration; a Method for Testing (34885)

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Gastric hypersecretion in excess of the neutralizing power of the duodenum is a major determinant in the pathogenesis of peptic ulcer (1). Experimental peptic ulcer produced by histamine injection (2), the Mann-Williamson preparation (3), or the administration of gastrin (4), and clinical peptic ulcer of the Zollinger-Ellison syndrome (5) or adjacent to gastric mucosa in a Meckel's diverticulum (6), support this hypothesis.

Gastric ulcers, and ulcers resulting from indomethacin (7), steroid (8), or salicylate therapy (9) do not fit this neat hypothesis. It becomes necessary to evoke other factors such as decreased mucosal resistance to digestion. Menguy and Masters (8) suggested that cortisone diminished gastric mucin secretion and altered its steric configuration to predispose it to enzymatic destruction, leaving the relatively fragile mucosa to physical trauma and acid peptic digestion.

In intact animals, cortisone produces superficial hemorrhagic erosions scarecely resembling peptic ulcers. In the rat (10, 11), these are small hemorrhagic and ulcerated areas in an island of normal glandular tissue whose mucosal height is only slightly diminished. In the presence of starvation, steroids produce true mucosal ulcerations (12). By contrast, histamine in beeswax produces punched out ulcerations of the duodenum and stomach, whose perforation is the usual cause of death of the animal (13).

Acute gastroduodenal ulcers, stress and steroid ulcers in humans are similar to the experimental histamine–beeswax ulcers. Though mucosal resistance may be reduced, peptic digestion is still responsible for the ulceration. It is the purpose of this study to present an experimental model which would take into account both of these ulcerogenic factors so that the role of each could be evaluated. In the presence of induced gastric hypersecretion of a magnitude insufficient to produce an ulcer, factors which lower mucosal resistance to peptic digestion and their antagonists, can be tested. Among the antagonists to steroid induced gluconegenesis might be the androgenic nitrogen retaining anabolic agents.

Materials and Methods. Hartley strain white female albino guinea pigs weighing 300-400 g, fed Purina lab chow *ad libitum*, were utilized throughout. Hay *et al.* (13) found that a dose of 5 mg of histamine base daily in a histamine in beeswax preparation, uniformly produced gastric hypersecretion and perforated gastroduodenal ulcers in guinea pigs. This was confirmed in a nonexperimental group. Experience indicated to us that a dose of 1 mg of histamine base in beeswax, seldom produced ulcers. Six experimental groups were studied.

1. Steroid alone: 15 animals were given 12.5 mg of hydrocortisone succinate intramuscularly twice daily.

2. Histamine alone: 31 animals were injected with 1 mg of histamine base in beeswax (0.05 ml) daily.

3. A group of 12 guinea pigs given 5 mg daily served as simultaneous controls for histamine and beeswax base.

4. Histamine and steroid: 22 animals received both histamine and steroid (1 mg of histamine in beeswax daily and 12.5 mg of hydrocortisone succinate twice daily).

5. Histamine, steroid, and nandrolone propionate: 32 animals received histamine and cortisone in the same doses as above. In addition, they received a parenteral anabolic agent, nandrolone phenpropionate, 25 mg intramuscularly 1 day before and 4 days after

initiating histamine–hydrocortisone therapy.

6. Histamine, steroid, nandrolone propionate, and stanozolol: 28 animals received histamine and hydrocortisone in the doses above. Nandrolone propionate was administered in the above dose 1 day before initiating histamine–steroid therapy and repeated every third day. Stanozolol was administered daily as a 4 mg/oz suspension in the drinking water, on each day of histamine–cortisone therapy.

Results. The results are summarized in Table I. All animals treated with hydrocortisone alone survived to the conclusion of the study (2 weeks) and none had ulcers at autopsy after sacrifice. Eight of 31 animals treated with histamine alone, survived and were without ulcers. Only 5 of the dead animals had ulcers at autopsy; death occurred after an average of 8.4 days of histamine therapy.

Addition of hydrocortisone to the histamine regimen raised the mortality due to duodenal ulcer performation from 16 to 59%; 13 of 22 guinea pigs died of this cause in an average of just under 6 days. Two animals survived 2 weeks (and had no ulcers at autopsy).

Disruption of the stomach wall caused the deaths of 6 histamine and 6 histamine–hydrocortisone treated animals. This lesion was not a distinct area of gastric perforation, but rather involved a ragged linear rupture of a long segment (usually more than half) of the gastric wall.

Coincidental deaths were all due to bronchospasm occurring within minutes of the histamine injection.

Addition of an anabolic injectable agent to the regimen had an unfavofable effect on survival (100% died, 53% of perforated duodenal ulcer in an average time of 6.3 days). Increasing the frequency of administration of the anabolic agent and addition of a second oral agent, had little effect on overall survival (3 of 28) or the incidence of death due to duodenal ulcer perforation (50%). The mean time to death was slightly prolonged (to 7.1 days).

Statistical analysis of these results by X^2 confirms the significance of the reduced ulcer formation ($p < .01$) and the increased survival ($p = .05$) of guinea pigs given 1 mg of histamine compared to the 5-mg control group (Table II). There was no significant difference between ulcer formation, fundic disruption or survival between the histamine–hydrocortisone group and the 5-mg histamine controls, but the added steroids made a significant difference in ulcer formation ($p = .001$) when compared to the animals receiving the 1 mg daily "subulcerogenic" histamine dosage.

Addition of anabolic agents to the histamine–hydrocortisone mixture made no signifi-

TABLE I. Genesis of Peptic Ulcer.
Results of histamine hypersecretion and steroid induced mucosal sensitivity.

Group	No. in group	Perforated ulcer (%)	Perforated ulcer: Mean time of death (days)	Fundic disruption[a] (%)	Bronchospasm (%)	Survival[b] (%)
1. Histamine, 5 mg	12	58	5.9	42	18	0
2. Histamine, 1 mg	31	16	8.0	19	39	26
3. Hydrocortisone, 25 mg	15	0		0	0	100
4. Histamine, hydrocortisone	22	59	5.9	27	15	9
5. Histamine, hydrocortisone, nandrolone	32	53	6.0	13	12	0
6. Histamine, hydrocortisone, nandrolone, stanozolol	28	50	7.1	7	19	11

[a] Some animals had both perforated ulcers and fundic disruption.

[b] Totals do not equal 100%: some animals had gastroduodenal erosions at autopsy but no perforation.

TABLE II. Tests of Significance (X^2) and Probability Values of Compared Groups of Induced Ulcerogenesis.

Groups	Peptic ulcer		Fundic disruption		Survival	
	X^2	p	X^2	p	X^2	p
1. Histamine, 5 mg vs histamine, 1 mg	7.7	<.01	2.3	NS	3.8	.05
2. Histamine–hydrocortisone vs histamine, 1 mg	10.6	.001	1	NS	2.3	NS
vs histamine, 5 mg	1	NS	1.2	NS	1.2	NS
3. Histamine–hydrocortisone–nandrolone vs histamine–hydrocortisone	1	NS	1.3	NS	3.0	NS
4. Histamine–hydrocortisone–nandrolone–stanozolol vs histamine–hydrocortisone	1	NS	3.7	.05	1	NS
3 and 4 Combined vs histamine–hydrocortisone	—	—	6.2	.02	—	—

cant differences in ulcer formation or survival. Of the 60 animals treated with anabolic agents, there were only 6 deaths due to fundic disruption, whereas four of 17 guinea pigs treated with histamine–cortisone without anabolic agents died of this cause. This finding is significant at the $p < .02$ level.

Discussion. Both acid hypersecretion and mucosal susceptibility play significant roles in experimental histamine–hydrocortisone ulcers and in clinical stress ulcers. As indicated by documented antecedent ulcer history, a significant proportion of patients developing stress ulcers (at least 38%) are acid hypersecretors (14). This incidence of antecedent ulcer is more than four times the 8.6% frequency of ulcer history elicited from all hospital admissions. That the incidence of ulceration rises in proportion to the severity of surgical stress can be likened to the addition of steroid administration to the hypersecreting animal (15). Thus thoracic and vascular patients, who compose less than 4% of our hospital population, contribute nearly 30% of the stress ulcer patients to this and other series (16). A related finding is the increased frequency of ulceration in burned hypersecreting dogs (17).

The experimental model of the histamine–hydrocortisone ulcer facilitates determinations of the relative roles of hypersecretion and mucosal susceptibility. In this series, anabolic agents were added in an attempt to block the increased mucosal susceptibility of steroid administration. Although the incidence of perforated peptic ulcer was not reduced by two of these agents, a significant reduction in the incidence of fundic disruption was observed. Whether the resistance of the gastric wall to acid destruction is increased by the anabolic agents is questionable since localized perforations, particularly in the duodenum, still occur. Another factor, such as local vascular changes in the bowel wall (18), induced by the circulating histamine or other gastric secretogogue, may explain not why the perforations occur, but rather where. That this "other factor" is probably secondary is elicited by the clinical observation and Dragstedt's experimental demonstration (19) of improved healing of established ulcers in the presence of exogenously administered alkali. This is one of the building blocks on which the prophylaxis of clinical stress ulcers can be built.

Most important, medical therapy directed toward stress ulcers cannot be developed unless a satisfactory animal model is available. The preparation herein described is suitable for testing the efficacy of drug therapy. Although anabolic steroids did not prevent the occurrence of acute ulcers, the development of other potent antagonists of glucocorticoid activity may prove more effective. Substances which influence the secretion of mucous should be investigated in this animal screen. If a successful therapy for stress ulcers were to be developed, the demonstration of its

value in clinical experience would be difficult because of the infrequency of this clinical problem. Before adequate statistics could be accumulated, many years might elapse. Therapy directed toward this problem must be investigated with an appropriate experimental model. This is the first publication of a prepreparation which evokes both secretion and mucosal resistance in peptic digestion.

Summary and Conclusions. An experimental model was designed to test the relative roles of histamine-induced gastric hypersecretion and steroid-induced reduced mucosal resistance, in acute gastroduodenal ulceration. Reduction of dosage of histamine reduces the frequency of deaths due to perforated duodenal ulcer. Addition of hydrocortisone eliminates this change in mortality. Clinical correlation is discussed.

The results provide further evidence for the hypothesis that, in the presence of reduced mucosal resistance, peptic digestion is still necessary for ulceration.

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