

Experimental Burns Accompanied by Histamine Administration Abets the Ulcer Diathesis.*

STANLEY R. FRIESEN AND OWEN H. WANGENSTEEN.

From the Department of Surgery, University of Minnesota, Minneapolis, Minn.

The spontaneous occurrence of ulceration in the duodenum or stomach of man following burns has been recognized for more than 100 years. In an extensive review of the literature, Harkins¹ noted among 680 patients dying of burns submitted to necropsy 26 ulcers, an incidence of 3.8%, with a ratio of duodenal to gastric ulcer of 4.5 to 1.

The explanation of the occurrence of ulcer following burns is as yet unknown. The pathological changes which occur most commonly in the gastrointestinal tract following burns consist of hyperemia and congestion.^{2,3} Necheles and Olson⁴ studied gastric secretion in dogs with isolated gastrotomized stomachs following torch burns to the hind leg of the animal. They noted that such burns augmented gastric secretion, if infusions of fluid were given at the time of study. Hartman⁵ was unable to confirm these findings, and found that both the free hydrochloric acid and the total acid were reduced following burns. Hartman, employing live steam and a 50 to 60% burn in dogs in a period of observation extending up to 13 days, observed ulceration in the duodenum and stomach in 63.3% of the animals. In another series in which tanning agents were employed as a lenitive to infection, the incidence of spontaneous ulcer was 6.6%.

It is the purpose of this study to determine whether experimental burns accelerate the occurrence of the histamine-in-beeswax provoked ulcer. In rabbits bona fide ulcers cannot be produced with histamine alone.⁶ In dogs, Hay and his associates⁶ noted that 40 days were necessary to produce ulcer with regularity in all dogs injected. In Hay's series of 12 dogs, 23 days was the average time for ulcer production employing the histamine-in-beeswax technic. In another series of 14 control dogs to which 30 mg of histamine-in-beeswax was administered daily, killed from 4 to 14 days after commencement of administration of histamine, ulcer was observed in one dog, after 7 daily doses of histamine. Over a 6-year interval during which time histamine-in-beeswax has been given to a large number of dogs, ulcer has been observed twice at 4 days following the daily administration of 30 mg of histamine implanted in beeswax.

Methods. These experiments were carried out on dogs and rabbits in 3 series. The method of burn used in each series consisted of immersion in water at 100°C, the body surface area and period of exposure varying in the 3 series. Immersion was found to be a satisfactory method of producing burns in that accurate standardization is possible, the tissue is not broken at the time of burn, and no added factor of pressure is present. All animals were anesthetized with sodium pentobarbital, 15 mg per pound body weight intravenously. In almost all instances, the anesthesia was adequate to obviate pain or any suggestion of discomfort on the part of the animal during the burning process; occasionally, Demerol, 50 mg IM was used. The hair was closely clipped prior to scalding. No postoperative treatment of the burn

* The researches upon which this presentation is based were supported by the Augustus L. Searle Fund for Experimental Surgical Research, the Citizens' Aid Society, the Dr. and Mrs. Harry B. Zimmermann Fund for Experimental Surgical Research, and by grants of the Graduate School of the University of Minnesota.

¹ Harkins, Henry N., *Surgery*, 1938, **3**, 608.

² Paek, George T., *Arch. of Path. and Lab. Med.*, 1926, **1**, 767.

³ Harkins, Henry N., *Arch. Path.*, 1944, **38**, 147.

⁴ Necheles, H., and Olson, Wm. H., *Surgery*, 1942, **11**, 751.

⁵ Hartman, F. W., *Ann. Surg.*, 1945, **121**, 54.

⁶ Hay, L. J., Vareo, R. L., Code, C. F., and Wangenstein, O. H., *Surg., Gyn., and Obst.*, 1942, **75**, 170.

TABLE I.
Dogs Subjected to 40% Burn Accompanied by Administration of Histamine-in-Beeswax Mixture.

Dog No.	Wt in lb	Daily dose, histamine base mg	No. of injections	Results	Remarks
6	20	30	1	Petechial bleeding Gastric ulcers	Sacrificed 24 hr, melena
7	22	30	1	Bleeding gastric ulcer	Died 2nd day, exsanguination
8	40	30	1	Bleeding duodenal ulcers; hemorrhagic gastritis	Died within 24 hr; exsanguination
9	33	30	1	Bleeding duodenal ulcers	Same
10	30	30	1	" " "	" "
24	32	30	5	Duodenal ulcers; one perforated	Died 5th day; peritonitis
25	22	30	3	Pyloric and duodenal ulcers	Died 3rd day
31	30	30	1	Two duodenal ulcers	Sacrificed in 24 hr
Controls (40% burn but no histamine)					
5	20	0	0	Antral erosion	Sacrificed in 24 hr
11	37	0	0	No ulcers or erosions	Same
26	26	0	0	Minute bleeding; ulcers	Died on 6th day
27	31	0	0	Marked congestion; no ulcers	" " 2nd "
28	15	0	0	No ulcers or erosions	" " 4th "
29	24	0	0	" " " "	" " 5th "
30	30	0	0	" " " "	" " 5th "
Controls					
1	33	30	2	No ulcers or erosions	Sacrificed after 2 inj.
2	24	30	3	Same	" " 3 "
3	20	30	4	" "	" " 4 "
4	38	30	5	" "	" " 5 "

TABLE II.
Dogs Subjected to 15% Burn Accompanied by Administration of Histamine-in-Beeswax.

Dog No.	Wt in lb	Daily dose, histamine base mg	No. of injections	Results	Remarks
12	34	30	2	Antral erosions	Died 2nd day
13	22	30	5	Bleeding duodenal ulcers	Died exsanguination 5th day
17	23	30	5	Bleeding duodenal ulcers; one perforated	Died 5th day, peritonitis
18	33	30	2	Bleeding pyloric ulcers	" 2nd day
19	32	30	5	Pyloric ulcers	" 5th "
22	27	30	1	Bleeding antral erosion	" 1st "
Controls (15% burn, but no histamine)					
14	29	0	0	No ulcers or erosions	Sacrificed 5th day
15	41	0	0	Bleeding duodenal ulcers; gastric petechiae	Died 9th day
20	25	0	0	Antral petechiae; no ulcers	" 14th "
21	32	0	0	No ulcers or erosions	" 14th "

was instituted. Histamine-in-beeswax mixture prepared after the method of Code and Varco⁷ was injected intramuscularly (30 mg base in the dog and 15 mg base in the rabbit) each evening, the first injection being

⁷ Code, C. F., and Varco, R. L., *Am. J. Physiol.*, 1942, **137**, 225.

given 2 hours prior to the burn. The dogs' feed pans were removed and no more food given until the following morning. No restriction of food intake was exercised in the instance of the rabbits. The time of sacrifice in the dogs was determined by the occurrence of spontaneous hematemesis or

TABLE III.
Rabbits Subjected to 40% Burn Accompanied by Administration of Histamine-in-Beeswax Mixture.

Rabbit No.	Size	Daily dose of histamine base	No. of inj.	Results
1	Adult	15	1	Fundic ulcer, bleeding petechiae
5	"	"	2	Bleeding fundic ulcer with bleeding petechiae
6	"	"	2	(Same)
7	"	"	2	Few petechiae
8	"	"	2	Bleeding fundic ulcer
9	"	"	1	Numerous antral ulcers
11	"	"	2	Petechiae fundus and duodenum
12	"	"	2	Small bleeding antral ulcer
16	"	"	3	Few petechial bleeding points
Controls (40% burn but no histamine)				
2	"	0	0	No petechiae, erosion or ulcers
3	"	0	0	Bleeding petechiae fundus
4	"	0	0	(Same)
10	"	0	0	No petechiae, erosions or ulcers
13	"	0	0	" " " " "
14	"	0	0	(Same)
15	"	0	0	"

melena or extreme weakness. The rabbits were sacrificed at varying periods of time. In all animals sections of stomach, duodenum, the burned area, brain, liver, kidney, lung and adrenal were obtained for microscopic observations and further study.

Experiments. Series I. Fifteen dogs were used in this series. Each dog received a 40%, 3rd degree burn by immersion in 100°C water for 10 seconds. Eight of these dogs received daily injections of histamine-in-beeswax mixture.

Series II. Ten dogs were used in this series. Each dog received a 15%, 3rd degree burn by immersion in 100°C water for 20 seconds. Six of these dogs received daily injections of histamine-in-beeswax mixture.

Series III. Sixteen rabbits were used in this series. Each rabbit received a 40%, 3rd degree burn by immersion in 100°C water for 5 seconds. Nine of these rabbits received daily injections of histamine-in-beeswax mixture.

Results. Series I. (Table I) All of the 8 dogs receiving a 40%, 10-second burn accompanied by histamine-in-beeswax administration developed ulcers within 5 days. Six of the 8 dogs died of exsanguination or were sacrificed within 24 hours, all showing ulceration, 5 actively bleeding. One of the 7 dogs not receiving histamine-in-beeswax in-

jections developed minute-gastric-bleeding ulcers in 6 days.

Series II. (Table II) All of the 6 dogs receiving a 15%, 20-second burn accompanied by histamine-in-beeswax administration showed erosion or ulcer within 5 days. Four of the 6 showed bleeding ulcers within 5 days. One of the 4 dogs not receiving histamine-in-beeswax injections showed bleeding duodenal ulcers with gastric petechiae at 9 days. Another with burn alone showed antral petechiae in 14 days; the other 2 dogs showed no significant gastrointestinal pathologic change, other than congestion, in 5 and 14 days.

Series III. (Table III) Seven of the 9 rabbits receiving a 40%, 5-second burn accompanied by histamine-in-beeswax administration showed erosion, ulcer, or petechial bleeding points within 2 days. Two of the 7 rabbits subjected to burn alone showed only petechial bleeding points of the fundus within 2 days.

Four control dogs receiving daily injections of histamine-in-beeswax mixture alone failed to develop ulceration when sacrificed in 2 to 5 days. All the animals subjected to burns displayed gastrointestinal hyperemia and congestion, especially of the duodenum and stomach at necropsy.

Discussion. It is apparent from these ex-

periments that burns abet the ulcer diathesis; that is, ulcers are provoked more readily and quickly with histamine in the presence of gastrointestinal congestion resulting from experimental burns. The evidence of gastric and/or duodenal ulceration in animals subjected to experimental burns depends upon the type, degree, extent, therapy, and period of observation of the burn. The incidence of ulcers in untreated dogs subjected to burns alone in this study was 2 of 11 dogs, or 18.2%; 7 of the 11 dogs died or were sacrificed within 5 days; the 2 dogs developing ulcers died on the 6th and 9th day. It is possible that, if the survival time

in these animals were prolonged, the incidence of spontaneous ulceration in dogs with burn alone would be greater. Of the 14 dogs subjected to burning in addition to histamine administration, all showed erosion or ulcer within 5 days. Twelve of the 14 presented definitive ulcers, 8 of which were actively bleeding.

Conclusions. 1. Experimental burns, when accompanied by administration of histamine-in-beeswax mixture, produce gastric and/or duodenal ulceration in which the incidence of hemorrhage is high. 2. Experimental burns abet the ulcer diathesis.

15565

Morphologic Effect of Desoxycorticosterone Acetate on the Thymus.*

P. DONTIGNY (Introduced by H. Selye.)

From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montréal, Canada.

A reciprocal relationship between adrenal and thymus size has been discussed by several investigators.¹⁻⁶ Adrenal enlargement caused by nonspecific damage,³ by adrenocorticotrophin⁷⁻¹¹ or treatment with corticoids¹²⁻¹⁵ is accompanied by thymus atrophy. In the absence of the adrenals, however, neither damage nor adrenocorticotrophin produce this effect.¹²

Wells and Kendall¹⁵ claimed that though several glucocorticoids, such as dehydrocorticosterone, corticosterone and Kendall's compound "E," produce this response, desoxycorticosterone and its acetate (D.C.A.) do not at the doses of 10 mg every 3rd day for 9 days. This latter finding is in disagreement with that of Selye¹⁶ and Selye

* This investigation was subsidized by a grant of the Commonwealth Fund. The author is also greatly indebted to Dr. E. Schwenk of the Schering Corporation, of Bloomfield, N.J., who supplied the D.C.A.

¹ Hammett, F. S., *J. Metabolic Res.*, 1925, **78**, 91.

² Anderson, D. H., *J. Physiol.*, 1935, **85**, 162.

³ Selye, H., *Endocrinology*, 1937, **21**, 169.

⁴ Dohán, F. C., *PROC. SOC. EXP. BIOL. AND MED.*, 1942, **49**, 404.

⁵ Ingle, D. J., *PROC. SOC. EXP. BIOL. AND MED.*, 1938, **38**, 443; 1940, **44**, 174.

⁶ Kendall, E. C., *Ann. Rev. Biochem.*, 1941, **10**, 285.

⁷ Cramer, W., and Horning, E. S., *Lancet*, 1939, **1**, 192.

⁸ Moon, H. D., *PROC. SOC. EXP. BIOL. AND MED.*, 1940, **43**, 42.

⁹ Noble, R. L., and Collip, J. B., *Endocrinology*, 1941, **29**, 234.

¹⁰ Houssay, B. A., *J. Am. Med. Assn.*, 1942, **118**, 833.

¹¹ Dougherty, T. F., and White, A., *PROC. SOC. EXP. BIOL. AND MED.*, 1943, **53**, 132.

¹² Selye, H., *Brit. J. Exp. Path.*, 1936, **17**, 234.

¹³ Carrière, G., Morel, J., and Ginesti, P. J., *C. R. Biol. Paris*, 1937, **126**, 46.

¹⁴ Ingle, D. J., *Endocrinology*, 1939, **24**, 194.

¹⁵ Wells, B. B., and Kendall, E. C., *Proc. Staff Meet. Mayo Clinic*, 1940, **15**, 133.

¹⁶ Selye, H., *Canad. Med. Assn. J.*, 1940, **42**, 113.

¹⁷ Selye, H., and Albert, S., *Am. J. Med. Sci.*, 1942, **204**, 876.