Gastric Ulceration in Rats with Experimentally-Induced Polycythemia. (25038)

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Increased incidence of peptic ulcer in patients with polycythemia rubra vera has never been explained satisfactorily. First reported by Friedman(1) it has been confirmed by many clinical investigators. These include Wilbur and Ochsner(2) and Lawrence(3) who observed peptic ulcer in 8 and 13%, respectively, of their large series of patients with polycythemia rubra vera, as compared with 2 to 3% in control groups of patients with other primary disorders. Boyd(4) suggested that the mechanism of ulcer formation is related to the well-documented(5) tendency to thrombosis also present in patients with polycythemia rubra vera. He postulates that local thrombosis within the vasculature supplying gastric and duodenal mucosa, leads to tissue necrosis and subsequent digestion by the gastric juice. Microscopic studies of ulcers in these patients, however, have failed to demonstrate consistent evidence of the postulated local thromboses(4). As our first step an attempt has been made to determine whether a similar relationship between polycythemia and ulceration could be demonstrated in the experimental animal.

Methods. Male rats of Sprague-Dawley and Holtzman strains, weighing 250 to 300 g, were utilized. Included were adrenalectomized, hypophysectomized, and sham-adrenalectomized and sham-hypophysectomized animals in addition to normal rats. They were rendered polycythemic by intravenous administration of washed and packed homologous rat erythrocytes. The erythrocytes were administered in 3 doses, at 2-day intervals, to a total dosage of 8% of body weight. In 2 control groups, normal rat plasma and isotonic saline, in equal amounts and administered in identical fashion, were substituted for the packed erythrocytes. By the sixth day, hematocrit levels greater than 75% were observed in all animals that received erythrocytes, whereas hematocrit levels of other groups showed no consistent change from preinjection values. All animals were autopsied 3 days following final infusion.

Results. Apart from generalized hyperemia, abnormalities in polycythemic animals were confined to the stomach (Table I). The stomachs of 26 of the 29 animals, including all 14 adrenalectomized, hypophysectomized, and sham-operated animals, showed ulceration that resembled human peptic ulcers both

TABLE I. Gastric Findings at Autopsy.

Type of infusion	Type of rats used	No. of animals: Total	Ulcer	Gastritis	Normal animals
Packed erythrocytes	Normal	15	12	3	0
Idem	Adrenalectomized	5	5	0	0
"	Hypophysectomized	5	5	0	0
"	Sham-adrenalectomized	2	2	0	0
"	Sham-hypophysectomized	2	2	0	0
	Totals	29	26 (90%)	3 (10%)	0 (0%)
Normal rat plasma	Normal	6	0	0	6
Isotonic saline	"	6	0	0	6
No infusion	"	10	0	0	10
Idem	Adrenalectomized	2	0	0	2
"	Hypophysectomized	2	0	0	2
"	Sham-adrenalectomized	2	0	0	2
"	Sham-hypophysectomized	2	0	0	2
	Totals	30	0	0	30 (100%)

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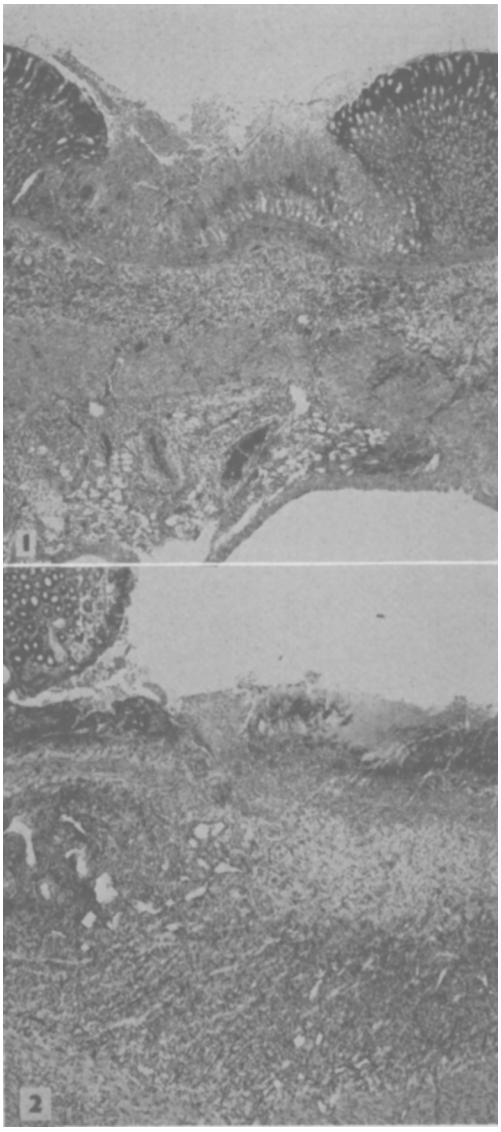

FIG. 1. Microscopic appearance of section of ulcer observed in polycythemic rat. Hematoxylin, eosin, and azure II stain (× 34).

FIG. 2. A more chronic-appearing lesion demonstrating granulation tissue and fibroblastic proliferation. Hematoxylin, eosin, and azure II stain (× 42).

grossly and microscopically. The ulcers were located in the body and antral regions of stomach, and were single in 22 and multiple in 4 animals. They were round or oval and ranged from a mm to over a cm in diameter. The craters were sharply circumscribed, with dark bases. Stomachs of the 3 remaining rats of this group, although not exhibiting discrete ulceration, were nevertheless abnormal, demonstrating multiple small areas of superficial hemorrhagic erosion along the tops of the rugal ridges. No lesions were present in any animal of either of control groups.

Microscopic study of ulcerations revealed typical fibrino-necrotic crater base demarcated sharply from surrounding normal-appearing mucosa. The more acute-appearing lesions were characterized by intact muscularis mucosae (Fig. 1). The associated leucocytic infiltration extended in some instances entirely through the serosa to peritoneal surface, and was accompanied by moderate to marked intercellular edema. The more chronic-appearing ulcers extended through the muscularis mucosae and demonstrated crater bases composed of granulation tissue with underlying fibroblastic proliferation (Fig. 2). This type of ulcer showed a tendency to bleed massively into the bowel, resulting in hematocrit reductions to 45% overnight.

Thrombosed blood vessels were present in only 1 specimen. This showed a small vein and a small artery thrombosed, both located at base of crater, within the necrotic layer. In this location, the etiologic significance is questionable, for, as observed by Anderson(6) in his description of human peptic ulcer, these may have occurred secondary to ulceration. Stomachs of the 27 remaining animals of the polycythemic group showed no evidence of thrombosis in regions studied microscopically.

Discussion. These experiments demonstrate, therefore, that gastric ulceration in the rat can be produced by transfusion-induced polycythemia. Absence of demonstrable vascular thrombosis in all but one of the lesions suggests that additional factors may be involved in their pathogenesis.

Gastric ulceration was reported by Highman and Altland(7) in a small percentage (5 of 79) of rats exposed to simulated high-altitude and thereby rendered secondarily polycythemic. However, it is not clear whether the ulceration observed was related to the non-specific stress induced by hypoxia or to the polycythemia. Indeed, the stress of hypoxia may have been the important factor since Reynolds and Phillips(8) reported gastric ulceration in rats subjected to simulated

high-altitude which did not become frankly polycythemic.

Since adrenalectomy and hypophysectomy did not abolish the ulcerogenic effect of transfusion observed in our study, it seems unlikely that a non-specific stress reaction, usually thought to be mediated through the pituitary-adrenal axis(9,10), accounts for the results we observed.

It is possible that the relative circulatory stasis present in the distended vasculature of the polycythemic animals, similar to that discussed by Brooks(11) in studies on circulatory adjustments in human polycythemia rubra vera, may diminish tissue resistance sufficiently to allow ulceration even in the absence of frank thrombosis and mucosal infarction. Alternatively, by allowing CO_2 to accumulate in the gastric mucosa as a product of cellular metabolism, stasis may predispose to ulceration by increasing hydrochloric acid secretion via the carbonic anhydrase-dependent equilibrium: $CO_2 + H_2O \leftrightarrows H^+ + HCO_3^-$, which may be the basic mechanism of gastric acid secretion as recently demonstrated and emphasized by Davies(12) and Janowitz(13). The attractiveness of this latter speculation is enhanced by the observation that ulcers in patients with polycythemia rubra vera are largely (90%) duodenal(2,3), a location that has been most often associated with gastric hypersecretion of acid(14).

These findings suggest an interesting parallel between our experimental system and the patient with polycythemia rubra vera and its associated increased incidence of peptic ulcer. Additional studies are in progress to determine whether gastric hypersecretion of acid occurs secondary to the induced polycythemia, as we have postulated, or whether, in its absence, vascular factors alone may initiate ulcer formation.

Summary. Induction of polycythemia by repeated intravenous injections of homologous erythrocytes produced gastric ulceration in 26 of 29 rats, including normal, adrenalectomized, hypophysectomized, and sham-operated animals. An experimental system has therefore been developed for the study of etiologic factors which may parallel those leading to development of peptic ulcers in patients with polycythemia rubra vera.

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Effect of Norepinephrine and Epinephrine on Nonesterified Fatty Acid Concentration in Plasma. (25039)

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It has been suggested that the sympathetic nervous system has a role in regulation of fat transport(1). Fatty acids are transported in plasma, partially in nonesterified form(2,3). Their source in a fasting animal appears to be adipose tissue(4-6). Injection of epinephrine increases plasma nonesterified fatty acid (NEFA) concentration(2,3,7) by enhancing