In Vivo Effect of Potassium on Small Bowel

RICHARD N. MYERS, M.D., CLARK E. BROWN, M.D.,
J. MONTGOMERY DEAVER, M.D.

From the Department of Surgery and the Division of Research, Lankenau Hospital, Philadelphia, Pennsylvania 19151

IN THE PAST 3 years an increasing number of patients with circumferential, stenosing, ulcerated lesions of the small bowel has been reported.[2, 5, 6] Although the pathogenesis of these lesions remains controversial, early evidence implicated the thiazide or enteric-coated thiazide-potassium drugs as possible etiologic agents. More recent investigations exonerate both thiazide drugs and enteric coating, but postulate a high local concentration of potassium as the precipitating factor.[1, 3, 4] In some of these later studies, lesions similar to those seen in patients were produced experimentally in animals by a rapid release of a high concentration of potassium chloride within the small bowel lumen and its absorption over a short segment. To date, however, there have been no clinical reports of the *in vivo* effect of intraluminal potassium. We have recently studied the local effects of hypertonic potassium chloride within an isolated segment of bowel with an intact blood supply in patients undergoing elective bowel resection. In addition, in some cases, hypertonic sodium chloride was instilled for comparison, while others received isotonic sodium chloride as controls. Although the time of exposure of the bowel to potassium in this study was necessarily relatively short, some insight has been obtained into the mechanism of the initial action of potassium chloride on human bowel mucosa. The lesions produced in this study parallel those produced experimentally in animals and are consistent histologically with what could be anticipated in the early stages of circumferential stenosing small bowel ulcerations in humans.

Material and Methods

Twenty patients undergoing elective small or large bowel resection for neoplastic disease were selected. Studies were made of the small bowel in 16 and of the large bowel in four. In all, segments of bowel 2 to 3 inches in length, which ordinarily would be included in the resected specimen, were isolated between tapes at the onset of the resection. Care was taken to keep the blood supply of these segments intact (Fig. 1). Using a syringe and a #25 needle, solutions of hypertonic 7% potassium chloride, hypertonic 5% sodium chloride, and isotonic 0.9% sodium chloride

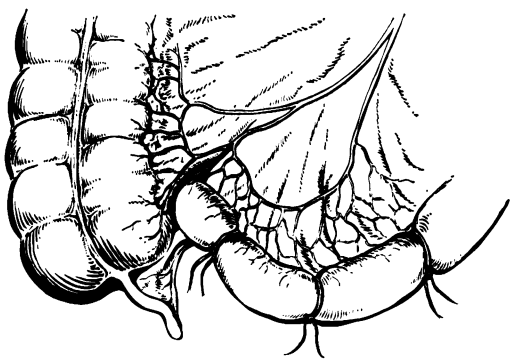

FIG. 1. Isolated, taped segments of terminal ileum with intact blood supply.

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TABLE 1.

Case No.	Salt	Mucosa			Submucosa		Muscularis			Serosa	
		Excess Mucus	Cellular Fragmentation	Cytolysis	Capillary Dilatation	Edema	Nuclear Pyknosis	Fiber Shrinkage	Nerve Shrinkage	Capillary Dilatation	Edema
1	7% KCl	+3	+3	+3	+3	+3	+2	+2	+3	+3	+3
2	7% KCl	+3	+2	+2	+3	+3	+3	+2	+2	+3	+3
3	7% KCl	+2	+1	0	+1	+1	+2	+2	+1	+2	+2
4	7% KCl	+3	+3	+3	+3	+3	+3	+3	+2	+3	+3
5	7% KCl	+2	+1	0	+3	+2	0	+3	0	+3	+3
6	7% KCl	+3	+3	+2	+3	+3	+3	+3	+2	+3	0
7	7% KCl	+3	+2	+2	+2	+2	+3	+3	+2	+3	+3
8	7% KCl	+3	+3	+2	+3	+3	+3	+3	+3	+3	+3
	5% NaCl	+2	+1	+1	+3	+3	+3	+3	+3	+3	+3
9	7% KCl	+3	0	+1	+3	+3	+3	+2	+2	+3	+3
	5% NaCl	+3	+1	+2	+1	+1	+1	+1	+1	+3	+2
10	7% KCl	+3	0	0	+3	+3	+2	+2	+2	+3	+2
	5% NaCl	+3	0	0	+3	+3	+2	0	+1	+3	+2
11	7% KCl	+3	0	0	+3	+3	+2	+3	+2	+3	+2
	5% NaCl	+3	0	0	+3	+3	+2	0	+1	+3	+2
	Iso NaCl	0	0	0	+1	0	0	0	0	+1	+1
12	7% KCl	+2	+3	+3	+3	+2	+3	+2	+1	+3	+3
	5% NaCl	+1	+2	+2	+3	0	+2	+1	0	+3	+3
13	7% KCl	+3	+2	0	+2	+2	+3	+2	+2	+3	+3
	5% NaCl	+1	+1	0	+2	0	0	0	0	+2	+2
	Iso NaCl	0	0	0	+1	0	0	0	0	+1	+1
14	7% KCl	+2	+3	+3	+3	+3	+3	+3	+3	+3	+3

TABLE I. (*Continued*)

Case No.	Salt	Mucosa			Submucosa		Muscularis			Serosa	
		Excess Mucus	Cellular Fragmentation	Cytolysis	Capillary Dilatation	Edema	Nuclear Pyknosis	Fiber Shrinkage	Nerve Shrinkage	Capillary Dilatation	Edema
	Iso NaCl	0	0	0	0	0	0	0	0	0	0
15	7% KCl	+3	+3	+1	+1	+2	+3	+3	+2	+3	+2
	Iso NaCl	0	0	0	+2	0	0	+2	0	0	0
16	7% KCl	+3	+3	+2	+3	+3	+3	+3	+3	+3	+3
	Iso NaCl	+1	0	0	+1	+1	0	+1	+1	+3	+3
(Colon) 17	7% KCl	+3	+1	+1	+3	+3	+3	+1	+2	+3	+1
18	7% KCl	+3	+3	+2	+2	+2	+3	+3	+3	+2	+3
19	7% KCl	+3	+3	+2	+3	+3	+3	+3	+2	+2	+2
	Iso NaCl	0	0	0	+1	0	+1	0	0	+3	+2
20	7% KCl	+1	+3	+1	+3	+3	+3	+2	+1	+3	+3
	Iso NaCl	0	0	0	+1	0	+1	+1	+1	+3	+3

were then injected intraluminally into the isolated loops of bowel. Care was taken not to distend the isolated loop. Exposure time of the mucosa to the various solutions ranged between 30 and 85 minutes. All patients received potassium chloride, while seven had physiologic saline injected as a

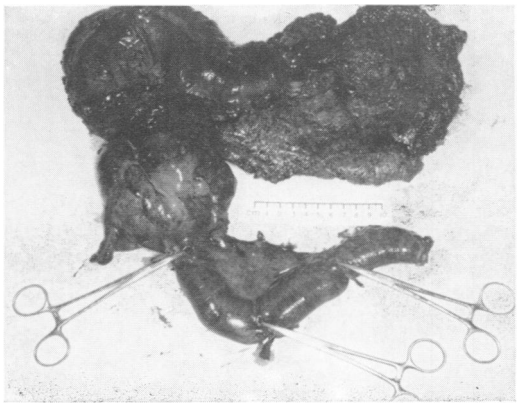

FIG. 2a. Specimen following a right colectomy. Isolated, taped segment of small bowel with potassium injected distally, and isotonic saline proximally.

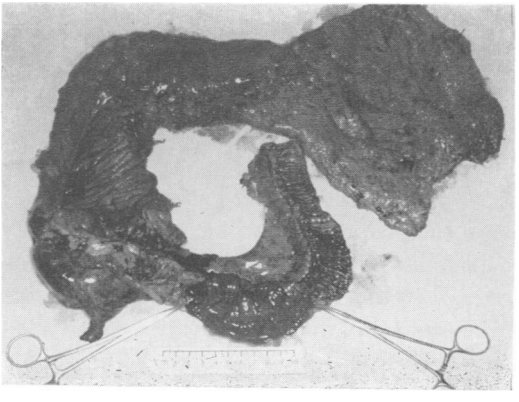

FIG. 2b. Opened specimen showing edematous, thickened, congested bowel at site of potassium application.

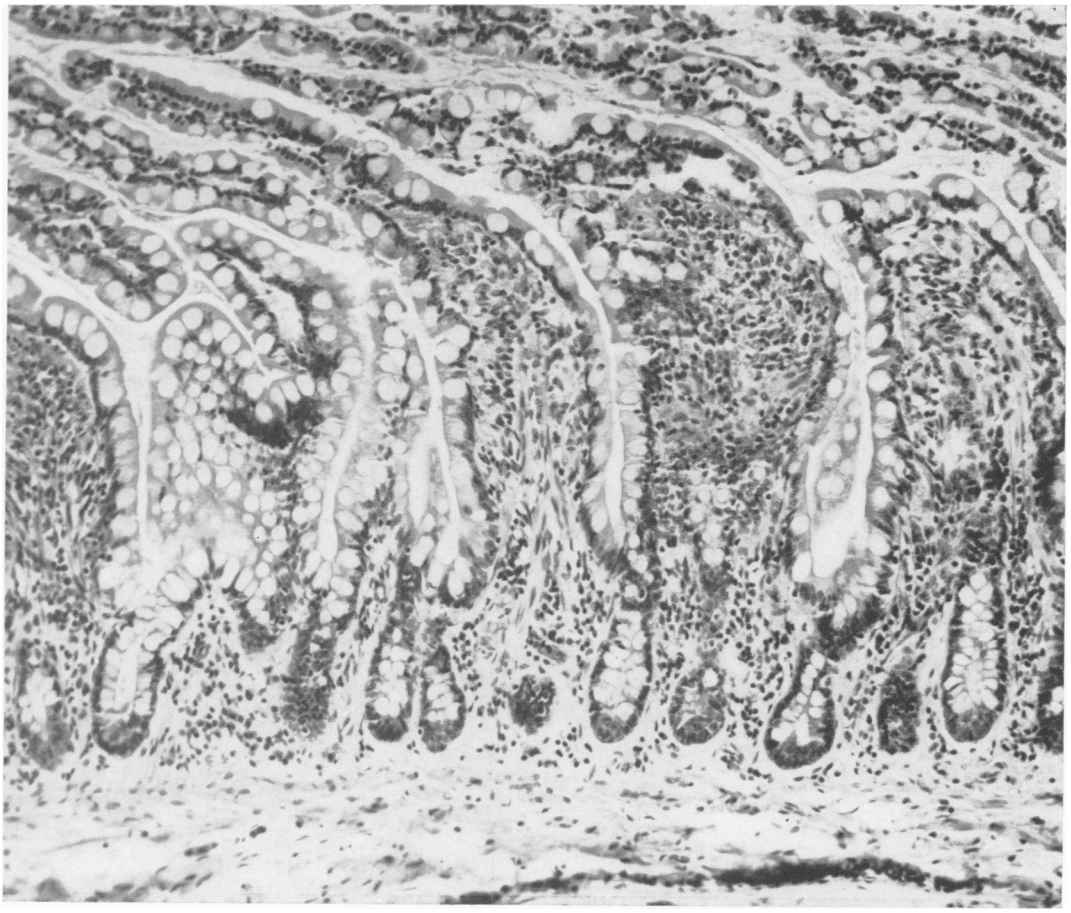

FIG. 3. Small intestine. Normal mucosa. Note intact epithelium.

control, and six received hypertonic saline. Resection of the diseased bowel in continuity with the isolated loops was then carried out in the usual manner, with the time interval noted between the injection of solutions and the division of the isolated segments' blood supplies. After resection, the surgical specimen was opened and sections of the isolated perfused bowel were taken for microscopic examination.

To maintain as high a degree of histologic objectivity as possible, a series of criteria was tabulated to indicate acute cellular injury in the four layers of the bowel. The changes were classified as follows:

1) *Mucosa:* a) Mucous hypersecretion, a prompt sign of irritation; b) mucosal cell fragmentation; c) cellular cytolysis, characterized by a smeary blurred staining quality of mucosal epithelium, lymphocytes, and connective tissue. 2) *Submucosa:* a) Capillary dilatation; b) edema. 3) *Muscularis:* a) Muscle cell nuclear pyknosis or swelling; b) muscle fiber shrinkage; c) nerve ganglion shrinkage or vacuolation. 4) *Serosa:* a) Capillary dilatation; b) edema. The changes were graded from 0 to +3 according to the degree of severity of injury (Table 1).

Results

Grossly, the effects of potassium chloride were striking. The exposed segments of bowel became thickened, edematous,

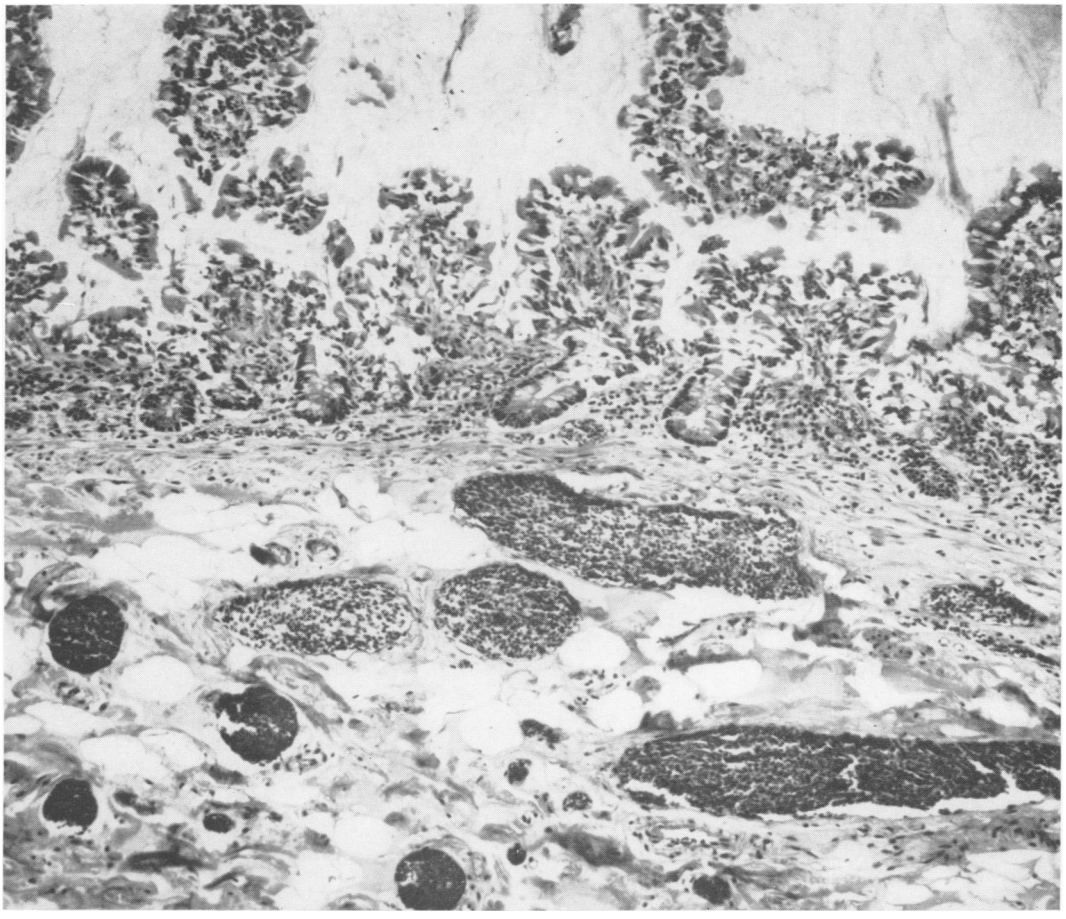

FIG. 4. Small intestine. Exposure to potassium produces hypersecretion of mucus, fragmentation of epithelium, and shrinkage of mucosal cells. The submucosal vessels are dilated and the adjacent loose fibrous tissue is edematous.

and took on a dark purple hue. The mucous membrane became covered with thick stringy mucus. There were similar changes, but to a lesser degree, in segments of bowel exposed to hypertonic sodium chloride. All loops injected with isotonic saline appeared normal grossly (Fig. 2a, 2b). In no case was there any gross change in the mesentery. All noted effects were more striking in the small than in the large bowel. There was a general, but not consistent, relationship between the time of exposure and quantity of potassium chloride to the severity of injury.

On microscopic examination, rather consistent changes of advanced degree occurred in all bowel segments exposed to hypertonic potassium chloride. The most severe changes were in the mucosa and diminished in the outer coats. Practically all changes in this group were graded plus 2 or 3. Hypersecretion of mucus in the mucosa, dilatation and congestion of capillaries and veins in all layers, and shrinkage of muscle nuclei and nerve plexus ganglion cells, were reliable indications of an early irritative effect. Red cells within the submucosal capillaries often appeared shrunken and pyknotic, suggesting diffusion of the salt through the vessel wall. Microscopic changes in the intestinal wall following exposure to potassium chloride

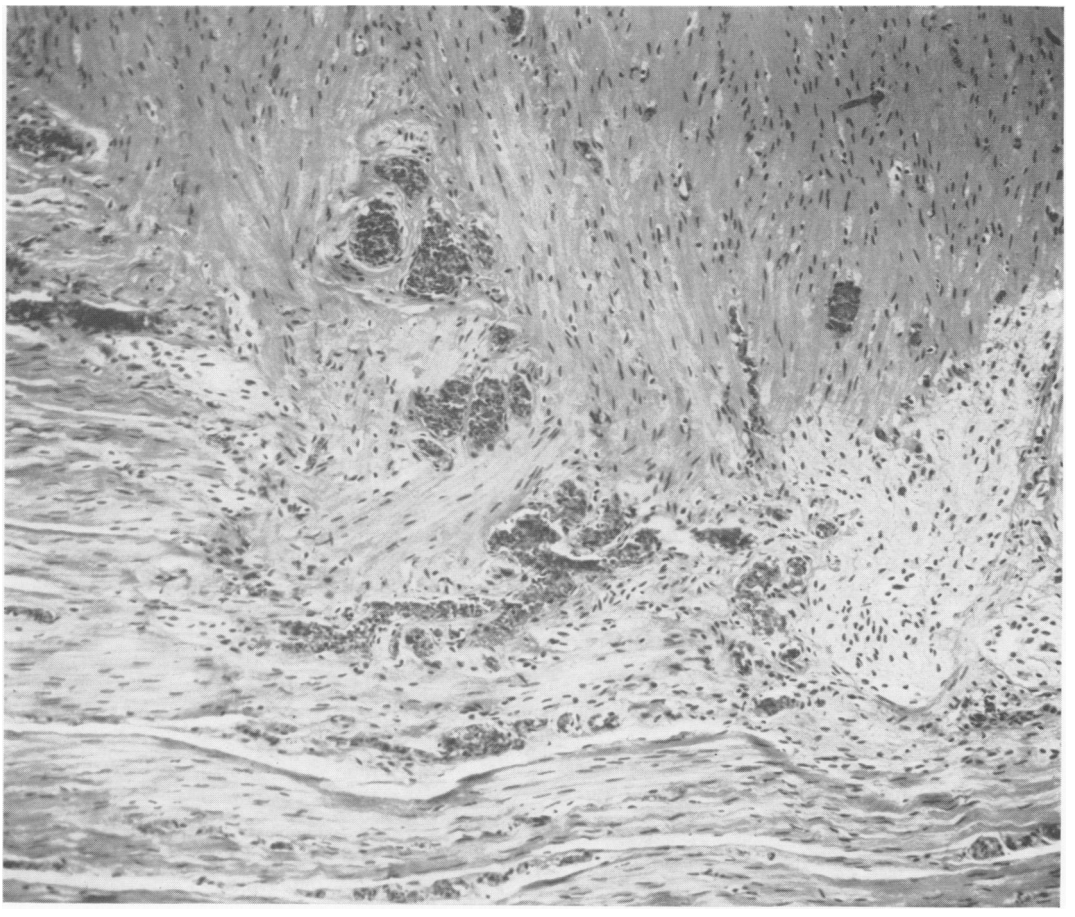

FIG. 5. Small intestine. After potassium, in the muscularis layer the capillaries are distended, smooth muscle cells and intramural nerve fibers swollen.

are illustrated in Figures 3 to 7. Also noted in some cases were early exudative phenomena such as margination of polymorphonuclear leukocytes in distended serosal capillaries. Because these occasionally occurred in some of the isotonic saline control loops as well as in the potassium injected loops, these changes could be attributed to operative manipulation or other factors related to the condition for which the patient was operated.

In the colonic specimens there were similar changes but to a lesser degree. Less active absorption by the colonic mucosa and generally less richness of the capillary bed were thought to explain this difference.

Although advanced degrees of the above changes were noted consistently in the potassium chloride-treated bowel, it was of interest that similar but slightly less intense changes were also noted when hypertonic sodium chloride was used (Fig. 8). Little or no change, except for the serosal one described above, was noted with the isotonic sodium chloride controls. The results of exposure of the bowel to the three salt solutions are shown in Table 1 and Figures 9–12.

Discussion

It has recently been postulated that the so-called "primary nonspecific stenosing ul-

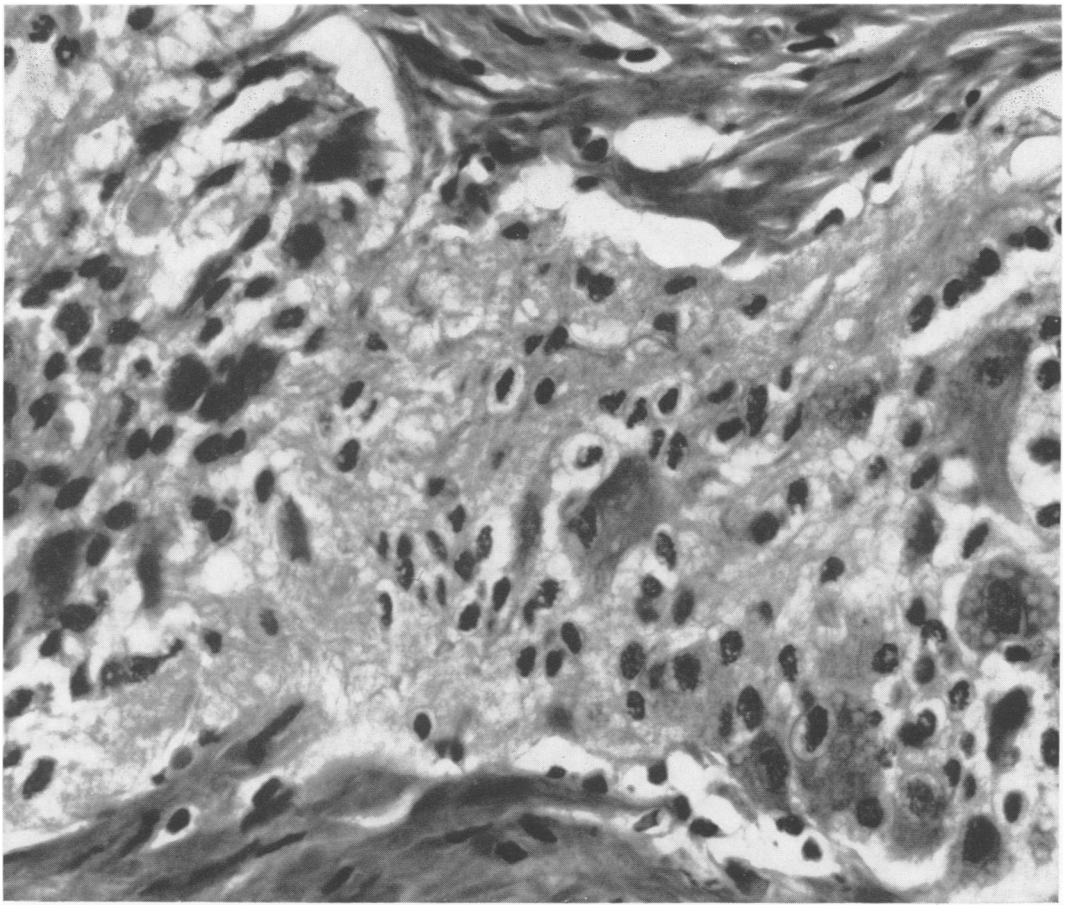

FIG. 6. Small intestine. Higher power illustrating swelling and vacuolization of ganglion cells and pyknotic nuclei.

ceration" of the small bowel is actually the end results of exposure or repeated exposures of a given segment of intestine to local high concentrations of potassium chloride. This is indicated not only from clinical analyses of reported cases, but by reproduction of similar lesions in the experimental animal. The exact pathogenesis of the lesion remains controversial. It has been stated that the lesion is basically a segmental venous infarction, since the same entity can be produced in the experimental animal by either the local action of potassium chloride or by the intravascular mesenteric injection of microspheres. It is hypothesized that resulting intense local spasm of the intramural and mesenteric capillaries and veins causes congestion and infarction, with subsequent ulceration and later fibrosis and stenosis.

This study corroborates the results of animal studies to the extent that similar lesions could be reproduced consistently in patients by the *in vivo* intraluminal injection of hypertonic potassium chloride. The fact that there was not a consistent relationship between time of exposure and dosage to severity of injury not only parallels what is seen in the experimental animal but also further supports the clinical impression that there is an additional factor of individual susceptibility to the drug. It is well known that many patients have taken large doses of enteric-coated potas-

FIG. 7. Small intestine. There is dilatation of several capillaries and serosal edema.

sium chloride over long periods of time without developing any bowel lesion, while the dosage and duration of ingestion has varied widely in those patients in whom lesions have developed.

Another observation was that although potassium chloride produced cellular changes in all layers of the intestinal wall, the most severe changes were greatest in the mucosa and diminished in the outer coats. A vascular effect was also noteworthy as evidenced by a high degree of capillary and venous distension in all layers. This suggests prompt absorption of the instilled drug. Also consistently observed was cellular damage in the muscularis layer, which readily explains later chronicity and subsequent stenosis. In addition, intramucosal nerves and ganglia showed evidence of injury.

However, this study raises the question of whether these changes are due primarily to a specific toxic effect of the potassium ion or rather simply to a hyperosmolar effect. When comparing the potassium chloride-treated loops with the hypertonic sodium chloride-treated loops, histological alterations appeared much the same. Perhaps in some instances the degree of change was greater with potassium chloride, but usually hypersecretion of mucus, shrinkage of muscle nuclei and fibers, and vessel dilatation of the internal and medial coats were the same in both. This, of course, sug-

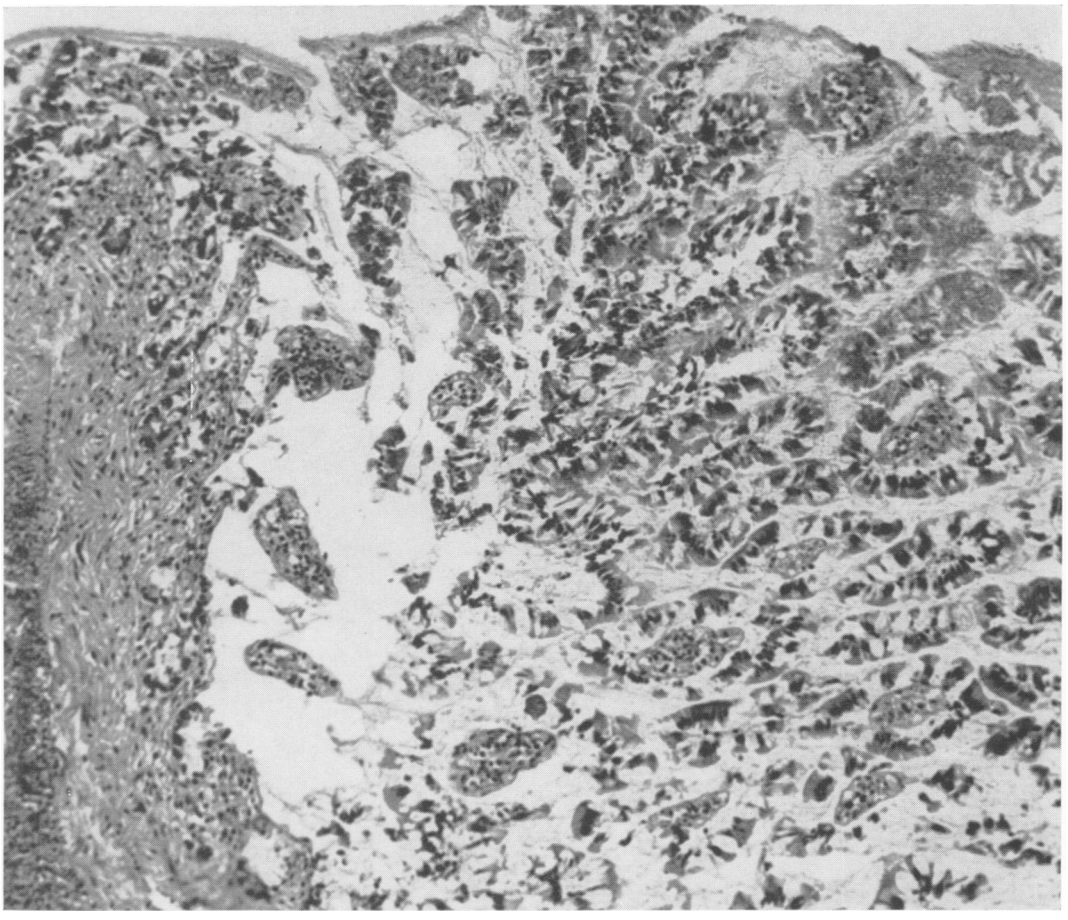

FIG. 8. Small intestine. Mucosa after exposure to hypertonic sodium chloride. The changes are similar to the potassium effect, although to a lesser degree.

gests that solution hypertonicity may be a significant factor.

The problem of relating acute changes resulting from short-term exposure to various agents as described above to ultimate stenosing ulceration is not easy. The technic of directly instilling solutions into isolated loops of bowel, however, produces obvious immediate effects on the mucosa, vascular system, musculature, and nerve elements in the bowel wall. With such changes, it is plausible to assume that venous infarcts would result, with subsequent irreversible muscle and nerve damage. Ulceration and stenosis would follow. However, it is not conclusive from this study whether the nature of this damage in its early phase is one of direct ionic toxicity, hyperosmolarity, or both. Further investigation designed to clarify these parameters more precisely is currently in progress.

Summary

The acute local effects of hypertonic potassium chloride, hypertonic sodium chloride, and isotonic sodium chloride on isolated segments of bowel in 20 patients undergoing elective resection have been studied.

Both hypertonic solutions produced gross and microscopic evidence of acute cellular injury in all layers of the bowel wall. These changes are consistent with what is seen in

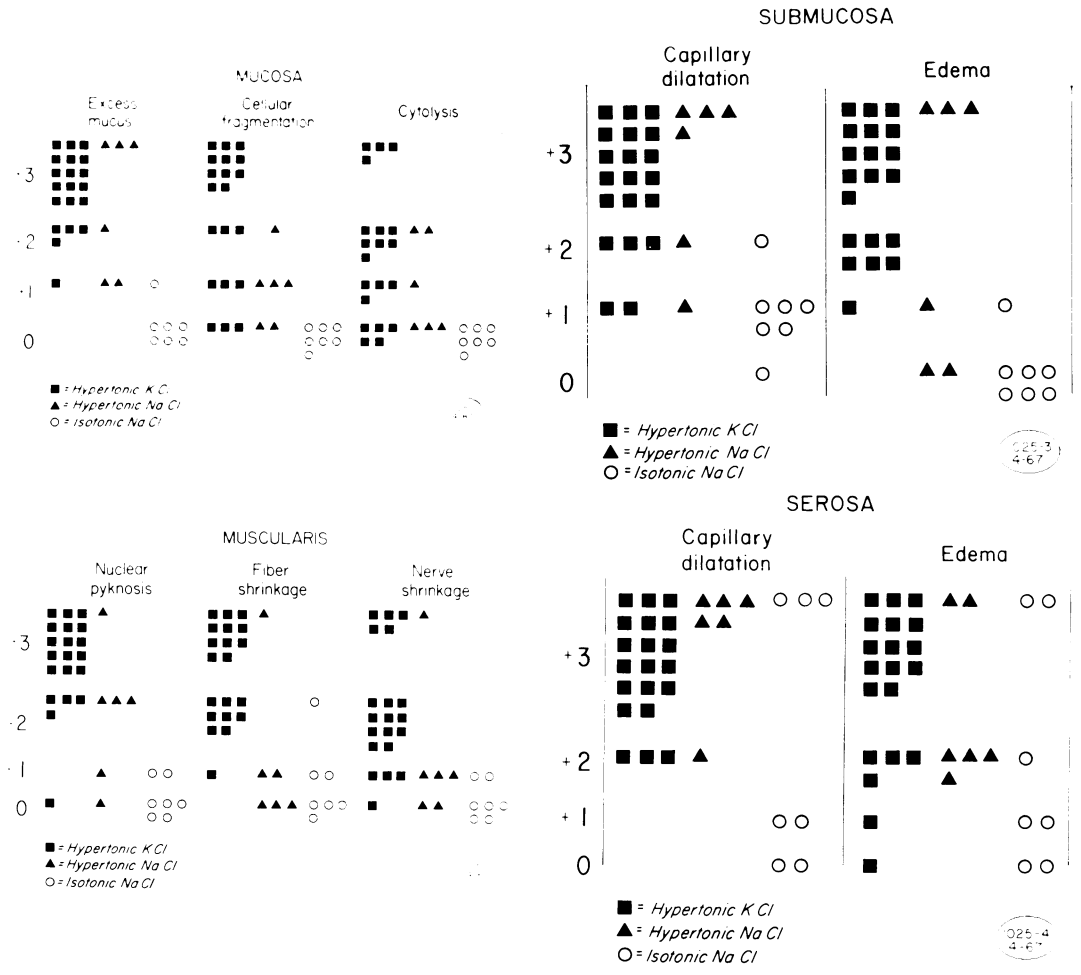

FIG. 9–12. Tabulation of effects of various solutions in the four layers of the bowel wall.

the early stages of primary nonspecific ulceration of the small bowel. The pathogenesis of this lesion is discussed.

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Discussion

DR. JONATHAN E. RHOADS (Philadelphia): Dr. Bricker, Members of the Association and Guests: Drs. Myers, Brown, Haupt and Deaver have seized an important opportunity to study the reaction of the human small bowel to chemicals. The fact that the mucosal reaction to hypertonic sodium chloride was only moderately less than the reaction to hypertonic potassium chloride is rather striking.