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Influence of Intestinal Content on Radiation Lesions of the Small Intestine.* (31890)

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It was observed in this laboratory that the content of the small intestine seems to influence nitrogen mustard enteritis. In dogs with a Thiry-Vella fistula of a segment of jejunum, the intestinal lesions resulting from intravenous injection of an LD_{80} dose of nitrogen mustard (1.5 mg per kilo) are less intense in the isolated segment than in the small intestine in continuity (Fig. 1). A T-V fistula is a loop of small intestine with intact blood vessels and nerves, through which the intestinal content does not pass.

This communication reports the pathological changes observed in an isolated, fistulous loop as compared with the small intestine in continuity, when external radiation instead of a radiomimetic drug is used.

Methods and materials. Five dogs were prepared with T-V fistulas, each consisting of a 15-cm segment of mid-jejunum. One to two weeks post-operatively, when the animals appeared completely recovered, each was lightly anesthetized with sodium pentobarbital. Two dogs were radiated with 1,000r to the abdomen: 3 with 1,500r. These doses are in the lethal range(1). Following radiation, the dogs were maintained on the routine kennel care until the animals succumbed or until gross blood appeared in the stool. These occurred on the third and fourth days in the dogs given 1,500r and the third day in the 2 given 1,000r. The animals with blood in the stools seemed terminal. In these the experiment was ended with intravenous sodium pentobarbital. All the animals were autopsied.

Results. The fistulous segments appeared grossly intact, with glistening, pale pink mucosa covered in part by a little pale yellow mucus. In contrast, the rest of the small intestine was dilated throughout, with a diffusedly injected, edematous mucosa having dark red, elevated, linear, longitudinal streaks; the lumen contained copious, turbid, thick, pink, feculent fluid. The colon also was slightly dilated, with pale pink mucosa having similar red streaks.

In hematoxylin-eosin sections, the mucosa in the fistulous segments was relatively well-preserved. In contrast, the rest of the small intestine had changes that follow exposure to radiation(2). These include mucosal erosions with hemorrhage, reduction in over-all thickness of mucosa, attenuated or absent villi, an inflamed, congested lamina propria, and greater distention of mucosal glands, with stasis of mucus (Fig. 2). In both the fistulous and the non-fistulous small intestine, the usual post-radiation atypias and abnormalities of intestinal epithelial cells were observed, of comparable degree in each location(1).

Discussion. This experiment suggests that the intestinal content exacerbates radiation injury of the small intestine, just as it ag-

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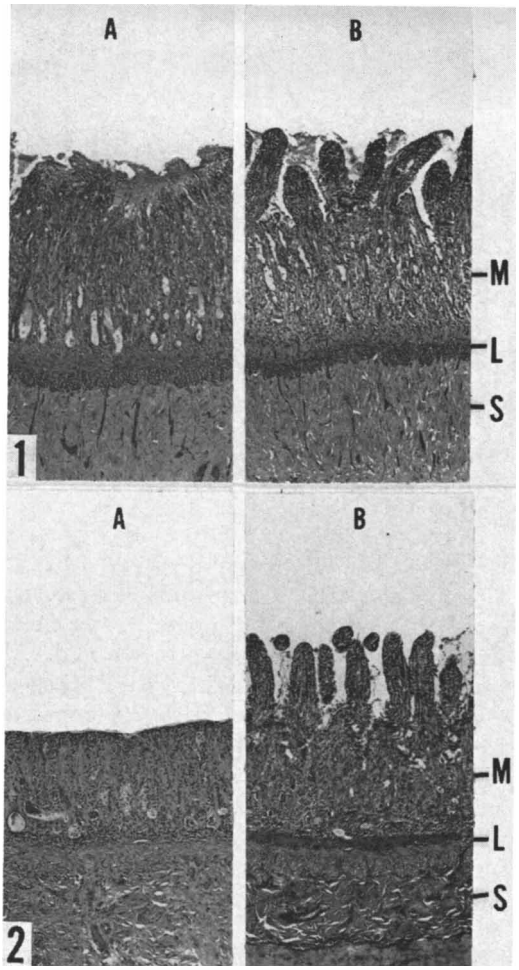

M = mucosa; L = muscularis mucosae; S = submucosa.

Fig. 1. Small intestine after injection of nitrogen mustard into dog with T-V fistula: (A) Intestine in continuity. (B) Isolated loop (x40).

Fig. 2. Small intestine after abdominal radiation (1,500r) of dog with T-V fistula: (A) Intestine in continuity. (B) Isolated loop (x40).

gravates the lesions induced by a radiomimetic drug. After radiation only the epithelial changes are the same in the isolated loop and in the small intestine in continuity. The mucosal erosions, the bleeding, the flattening of the villi and the infiltration with inflammatory cells are much less conspicuous in the isolated loop, which at the time of radiation, contains nothing but a small amount of mucoid cellular debris and possibly some succus entericus. The small intestine in continuity, which contains all the elements of the intestinal content, shows the typical changes that follow exposure of the abdomen to a lethal dose of radiation(3). It is unlikely that mechanical factors or intestinal bacteria are involved in the differences observed(1). It is more likely that bile or the proteolytic enzymes of the pancreas are involved. The matter is being investigated.

It has been observed that conversion of an irradiated loop of small intestine into a T-V fistula distinctly improves post-radiation survival in rats. However, on microscopic examination the isolated loops do not differ from control irradiated loops(4,5). In the quoted experiments, the segments of intestine were irradiated several hours to 2 days *before* they were isolated; intestinal content was present during the irradiation. This may account for the similarity of the microscopic appearances in the isolated and control segments. As for the present experiment, it is possible that the mucosa in a segment of jejunum isolated for 1-2 weeks undergoes changes that render it less sensitive to radiation. However, preradiation biopsies of the fistulas show on microscopic examination what appears to be normal jejunum (Fig. 3).

Many observers feel that the "intestinal death" that quickly follows exposure to a lethal dose of irradiation is due to the loss of fluid, proteins and electrolytes into the tissues and lumen of the small intestine(6). The present experiment suggests that the loss into

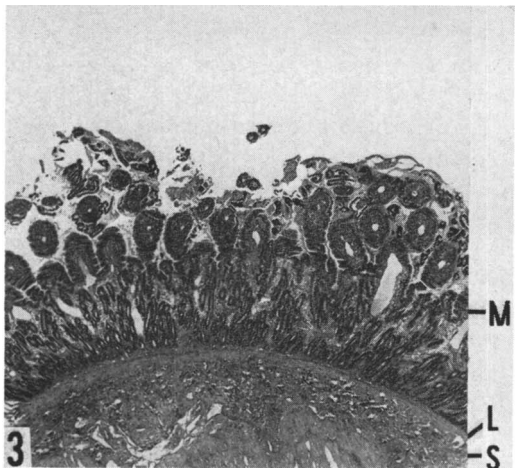

Fig. 3. T-V fistula before abdominal radiation (x40).

the tissues and lumen of irradiated intestine is considerably magnified in the presence of intestinal content. Consequently, lengthening of the isolated segment and shortening of the intestine in continuity should significantly improve post-irradiation survival. This is being investigated.

Summary. The abdomens of dogs with T-V fistulas of the jejunum were irradiated with 1,000 and 1,500r. The post-irradiation lesions in the small intestine in continuity were typical. Those in the fistulas, where intestinal content was absent, were considerably less intense.

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Antitumor Effects of Kethoxal-Bis(Thiosemicarbazone) and 6-Mercaptopurine in Neonatally Thymectomized Mice.* (31891)

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Although Sarcoma 180 (S-180) is not histocompatible with the random-bred HaICR Swiss mice, implants grow in 100% of these animals and regress in only 0 to 20% of the cases. This incidence of rejection is not increased even after the initial growth of the tumor is retarded by treatments with effective chemotherapeutic agents(1). Therefore, the complete regression of this tumor seen in Swiss mice fed a vitamin B_6 deficient diet(2), or treated with either 6-mercaptopurine (6 MP)(3) or kethoxal-bis (thiosemicarbazone) (KTS)(4), acquires particular significance.

It is not known whether the regression of S-180 induced by certain treatments is due to the action of host defenses directed against the chemotherapeutically impaired tumor. This idea is inconsistent with the fact that some of the treatments which induce complete regression of S-180 are also capable of depressing immunological defenses. For instance, both dietary depletion of vit. B_6 and treatment with 6 MP have been shown to impair certain immunological responses(5,6). Yet recent evidence indicated that in vit. B_6 deficient Swiss mice the regressions of S-180 are dependent upon the immunological competence of the host(7).

In this study it is shown that the incidence of tumor regressions elicited by KTS and 6 MP is greatly reduced in neonatally thymectomized mice. Although the initial growth inhibition of S-180 caused by these drugs was similar regardless of neonatal surgery, the delayed retardation of tumor growth appeared to be dependent upon the presence of the thymus. In intact mice, only a slight retardation of skin allograft rejection was caused by 6 MP and KTS at doses effective against S-180.

Materials and methods. The solid form of S-180 was implanted subcutaneously in HaICR Swiss mice. Standard procedures were followed for implantation of the tumor and evaluation of its growth(1). The purified diets used were described in detail elsewhere (5). Aqueous solutions of 6 MP were prepared immediately before use and were injected intraperitoneally once daily; KTS was fed mixed in the purified diets. Thymectomy

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