Radiation Inhibition of Peritoneal Adhesions: An Experimental Study (34515)

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This paper is concerned with the evaluation of abdominal irradiation on operative or chemically induced peritoneal adhesions. Postoperative abdominal irradiation is being used with increasing frequency. The effect of postoperative abdominal irradiation on peritoneal adhesion formation is unknown.

The peritoneum consists of a single layer of flattened mesothelium having perietal and visceral reflections (20). It secretes and absorbs a lubricating serous fluid. Peritoneal adhesions have been induced in experimental animals by a variety of surgical procedures and chemical irritants. These include bile, pancreatic enzyme, blood, sclerosing agents, bacteria, talc, and silica dioxide (1, 2, 8, 9, 11, 13, 14, 15, 20). Following injury, fibrin is produced in various amounts. This fibrin is usually absorbed, or if organized by fibroblasts, peritoneal adhesions form (3). Peritoneal adhesions are often responsible for intestinal obstruction. Therefore, investigators have tried to prevent peritoneal adhesions. Numerous agents have been studied. These agents include sodium citrate, heparin, liquid paraffin, olive oil, ACTH, cortisone, 5FU pepsin, fibrinolysin, amniotic fluid, papain, low molecular weight dextran, DMSO, hyaluronidase. Although some agents can diminish the amount of adhesions, none have prevented adhesions (1, 5, 6, 7, 16, 17, 19). No procedure has been shown to be as worthwhile as careful attention to the details of surgical technique (4).

There has been no laboratory or animal study to evaluate the effects of irradiation on surgical or chemical induced peritoneal adhesions (12, 18, 21). We have investigated this effect and noted some interesting differences in peritoneum response related to the site and type of trauma.

Materials and Methods. Experimental animals used were adult, male Sprague-Dawley rats, weighing 400–500 g. A two-part experiment was designed.

Experiment I. All animals were subject to intraabdominal surgery. Following intraperitoneal nembutal anesthesia, the abdomen was shaved and prepared with Betadine. A midline incision was made. The cecum and ileum were delivered. The antimesenteric cecal serosa was split. A 7-cm length of antimesenteric ileal serosa from the cecum was stripped. One surface of the mesentery between the ileum and cecum was denuded. A 2- by 2-cm segment of parietal peritoneum extending from the suture line was excised. There was a 20% immediate mortality from either the surgery or anesthesia. The surviving animals were then divided into three subgroups:

Group A: Eight rats that served as controls

Group B: Six rats that had total abdominal irradiation, 350 rads, 30 min after surgery

Group C: Five rats that had total abdominal irradiation, 350 rads, per day for 3 successive days.

The initial irradiation was given 30 min after surgery. The 6-MeV Linear Accelerator was used with a 7- by 7- cm abdominal port and bolus.

Experiment II. Following intraperitoneal nembutal anesthesia, all rats were injected

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TABLE I. Experiment I. Surgical Induced Adhesions (Gross Anatomic Findings).

Group	Cecum-ileum adhesions	Abdominal wall adhesions	Abdominal suture line adhesions	Liver adhesions
A (control)	8/8[a]	2/8	1/8	0/8
B (350 rads, day 1)	5/6	1/6	1/6	0/6
C (350 rads per day × 3)	5/5	1/5	1/6	0/6

[a] Number of rats showing change/total no. of rats per group.

intraperitoneally with 0.2% colloidal silica dioxide pH 7.4, 2.5 cc/100 g body wt. 10% of all rats died from the anesthesia or the toxic effects of silica dioxide. The surviving rats were divided into three subgroups:

Group A: Seven rats that served as controls

Group B: Five rats that were irradiated with 350 rads 10 hours after silica injection

Group C: Six rats that were irradiated with 350 rads per day for 3 successive days, the initial irradiation given 10 hr after injection.

The 6-MeV Linear Accelerator was used as described in Experiment I.

All animals were sacrificed at 5 weeks and autopsied. Histologic sections were stained with hematoxylin and eosin. Microscopic sections of the skin, parietal peritoneum, liver capsule, and intestinal adhesions were graded from 0–4, according to the thickness of the collagen scar. Grading was done without foreknowledge of the experimental animal group. The collagen in the scar was also evaluated under polarized-light microscopy.

Results. Experiment I. Surgery induced peritoneal adhesions.

Gross autopsy. Almost all animals in all three groups had a well defined, firm area of ileocecal adhesion. The antimesenteric border of the ileum was adhered to an adjacent segment of small bowel or cecum. Few animals had adhesions to the split antimesenteric border of the cecum. Almost all animals were free of adhesions to the suture line or the denuded parietal peritoneum (Table I).

Histopathology. There was less intestinal adhesion collagen in the irradiated groups. There was no significant difference between Group B (irradiated 350 rads), and Group C (irradiated 350 rads per day for 3 days). The irradiated and control-group skin and parietal peritoneum healed with mature eosinophilic collagen that was birefringent to polarized light. The intestine adhesion healed with basophilic collagen that was weakly birefringent to polarized light (Table I, II) (Figs. 1, 2, 3).

Experiment II. Silica dioxide induced liver adhesions.

Gross autopsy. Approximately half of all livers in each group were engorged and fused. There were random adhesions of omentum, intestine, and parietal peritoneum.

Histopathology. There was little difference in liver capsule collagen thickness between the control and irradiated groups. The single irradiated group (Group B), demonstrated less liver capsule collagen than did either the control or fractionated irradiated group. The collagen in the liver adhesions did polarize and demonstrated infrequent, fine, collagen bridges between fused liver lobes. Almost all livers in each group had the same amount of

TABLE II. Experiment I. Surgical Induced Adhesion (Microscopic Findings).

Group	Skin collagen average	Parietal peritoneum collagen average	Intestine adhesion collagen average
A (control)	2.4[a]	3[a]	2.6[a]
B (350 rads, day 1)	2.6	2.4	1.6
C (350 rads per day × 3)	2.2	2.8	1.8

[a] Mean of amount graded from 0 to 4+.

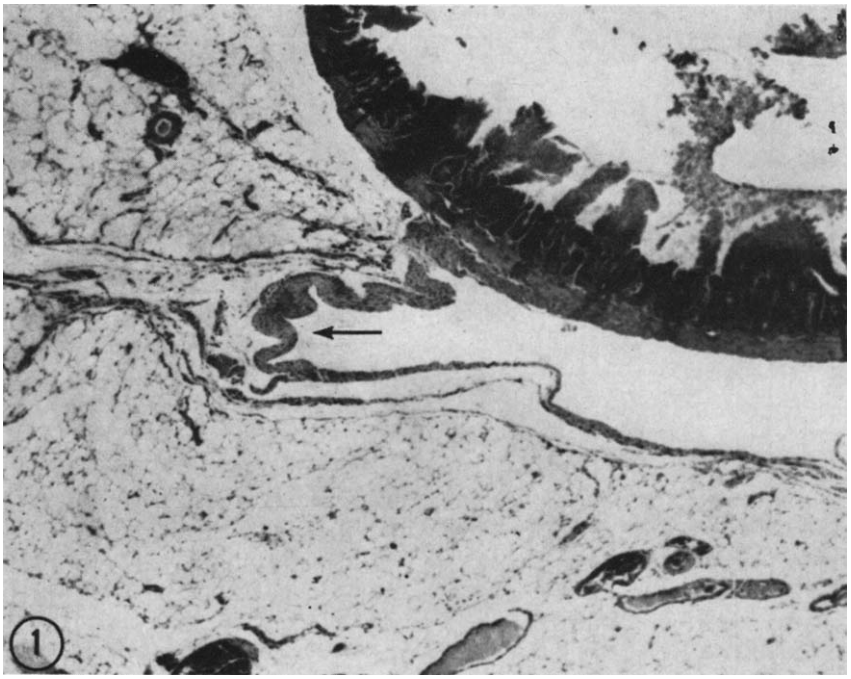

FIG. 1. Mesenteric adhesion of a nonirradiated operated rat (Group A). Note the fibrous thickening of the serosal surface; H & E, ×46.

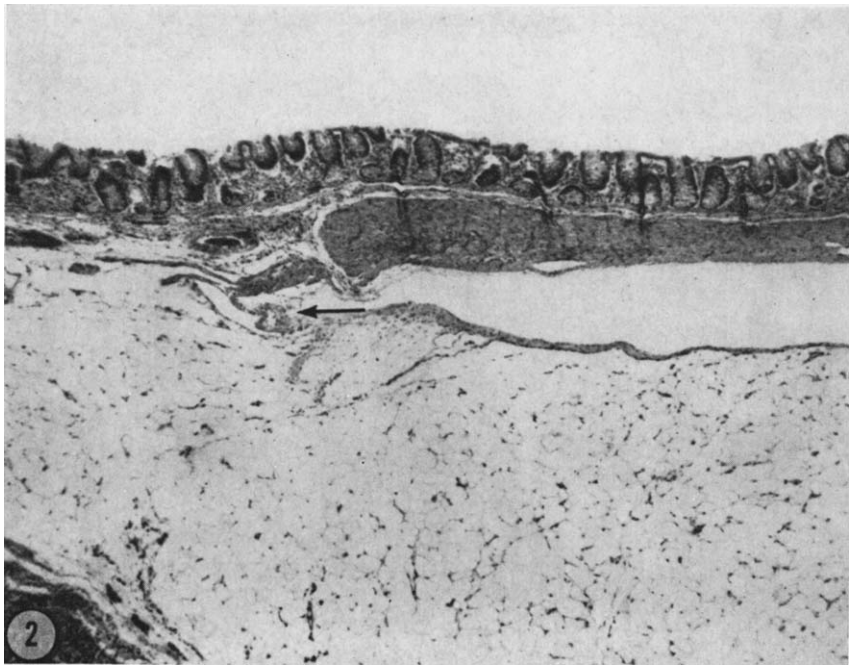

FIG. 2. Mesenteric adhesion of an irradiated operated rat (Group C). Note there is less fibrous thickening of the serosal surface compared to Fig. 1; H & E ×46.

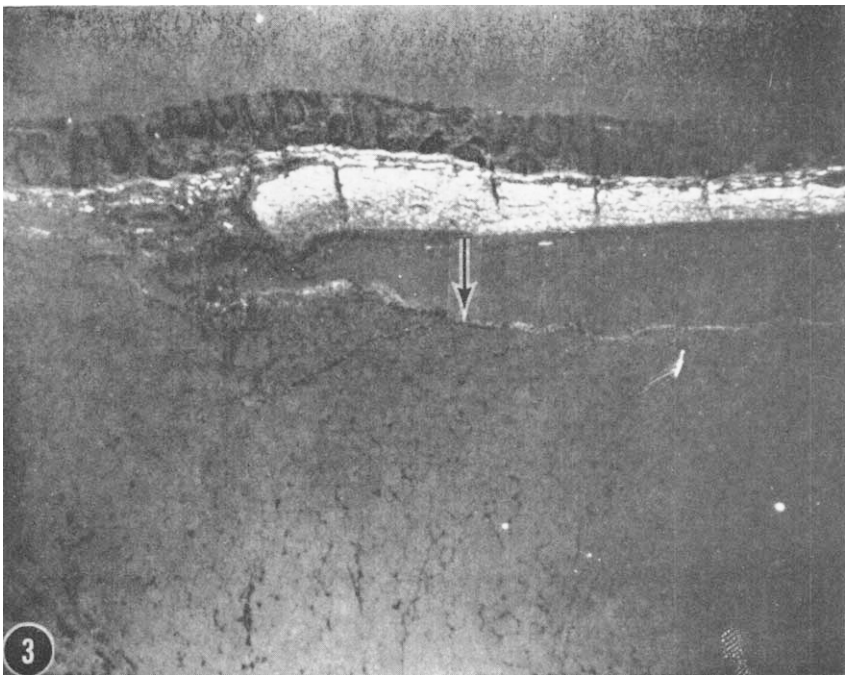

FIG. 3. Polarized light microscope of Fig. 2. Note the weakly birefringent collagen in the serosal surface scar.

silica granuloma, consisting of a mixture of histocytes and lymphocytes. The silica granuloma did not contain material which polarized. There was extensive liver-plasma cell infiltration in all groups (Table III) (Figs. 4, 5).

Discussion. Adhesions are a normal response to peritoneal injury. Clinical and experimental studies have shown that extensive peritoneal injury heals rapidly and smoothly, frequently without adhesions. If the irritant is mild, fibrin is usually absorbed and no adhesions are produced. However, if the irritant is severe, there is increased fibrin production which may be organized by fibroblasts and form adhesions. Following denuding of the peritoneal surface, a new serosa forms within 3 days by three processes:

1. An ingrowth from adjacent margins
2. Transformation of fibroblasts migrating upward
3. Grafting of free floating peritoneal cells onto the raw surface (3, 14).

Any process that denudes the visceral peritoneum has been shown to reliably produce adhesions. In this experiment, almost all animals formed adhesions by serosal stripping of the antimesenteric border of the ileum. 70% of animals formed adhesions following intraperitoneal injection of silica dioxide. Few animals formed adhesions to denuded parietal peritoneum.

We have investigated the effects of irradiation on denuded visceral and parietal peritoneum. Other investigators have shown that total abdominal irradiation of rats above 500 rads reduced their life expectancy. A small percentage sustained acute intestinal deaths; most sustained a delayed but premature

TABLE III. Experiment II. Silica Dioxide Induced Adhesions.

Group	Gross liver adhesions	Microscopic liver adhesions average
A (silica control)	5/7	1.7[a]
B (silica X-ray, 350 rads, day 1)	2/5	1.2
C (silica X-ray, 350 rads per day × 3)	4/6	1.6

[a] Mean of amount graded from 0 to 4+.

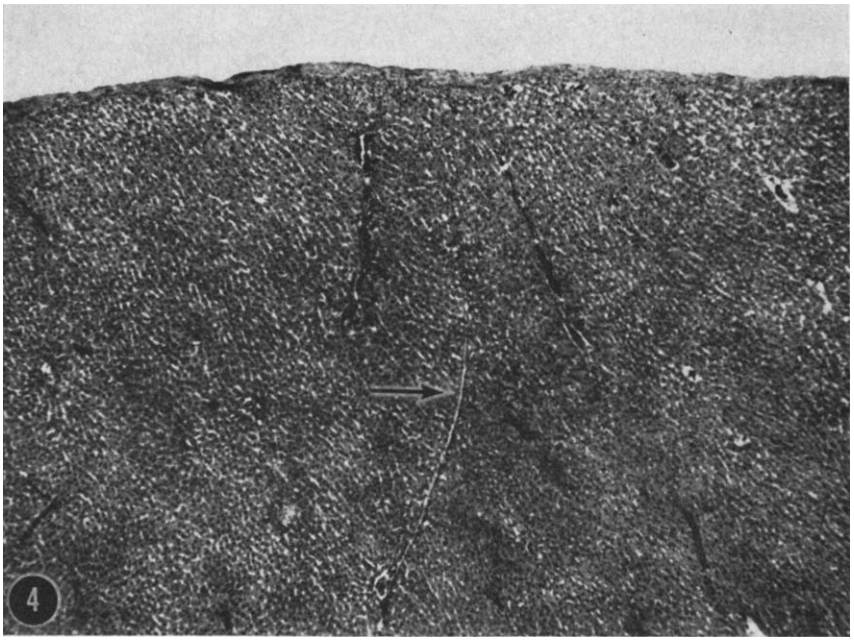

FIG. 4. Liver from a rat given ip colloidial silica dioxide. Note the two liver lobes have become fused by adhesions.

unexplained death between 250–420 days (10). When Venablis irradiated a 2- by 2-cm segment of denuded parietal peritoneum, all irradiated rats had wound surfaces covered with a continuous layer of cells within 3 days (12). Therefore, we elected to use total abdominal irradiation limited to 350 rads for 3 days.

Abdominal irradiation administered promptly after surgery in either a single dose of 350 rads or fractionated doses of 350 rads per day for 3 days did not prevent intestine adhesions, but did diminish the amount of intestine adhesion collagen. Irradiation did not prevent silica dioxide induced liver adhesions. Single dose irradiation administered 10 hr after the introduction of silica dioxide did reduce the thickness of the liver capsule collagen scar, but fractionated irradiation of 350 rads per day for 3 days did not. Irradiation did not affect the degree of silica dioxide induced liver granuloma.

It was of interest to note the variation in response to injury of the parietal and visceral peritoneum. Parietal peritoneal adhesions rarely formed after denuding the serosa, usually healed with the production of mature collagen, and did not diminsh in thickness after fractionated postoperative irradiation. Liver adhesions and liver fibrosis formed in 70% of the animals given intraperitoneal silica dioxide, healed with the production of mature collagen, and did not diminish in thickness after fractionated postinjection irradiation. Intestinal adhesions formed in almost all animals after denuding the serosa and healed with the production of amorphous collagen, which on hematoxylin and eosin stain was basophilic and weakly birefringent to polarized light. Intestinal adhesions diminished in amount after post-operative abdominal irradiation. Adhesion formation may be different in the intestine, liver, and parietal peritoneum. This may account for the clinical observation that reperitonealization does not favorably influence the incidence of adhesions, whereas careful avoidance of intestinal tissue trauma does favorably influence the incidence of adhesion.

Conclusion. Postoperative abdominal irradiation is being used with increasing frequency for many intraabdominal neoplasms. A common complication of intraabdominal surgery is the formation of adhesions. The effect

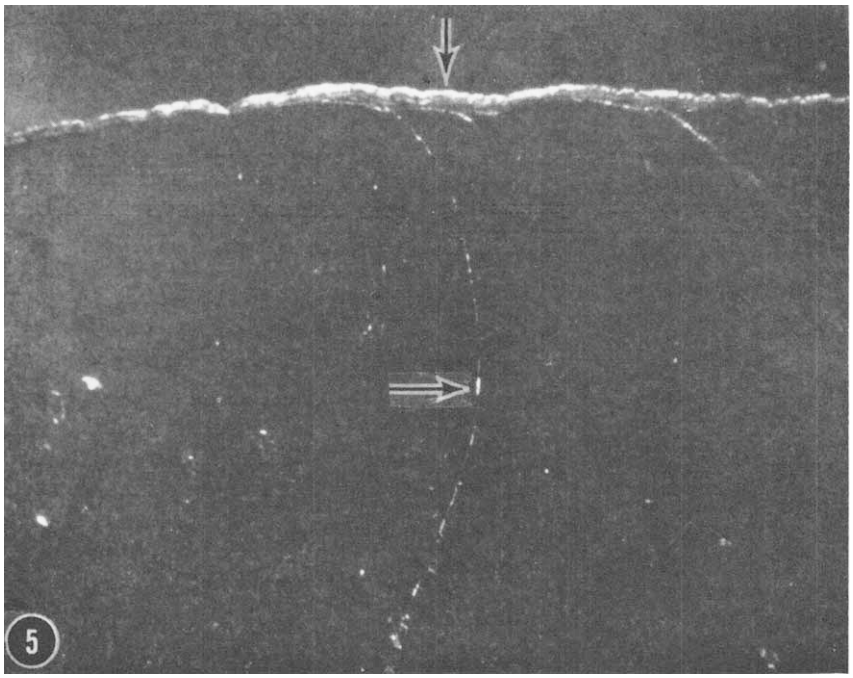

FIG. 5. Polarized light microscopy of Fig. 4. Note the strongly birefringent collagen in the liver surface scar and the curvilinear birefringent collagen in the adhesion.

of postoperative irradiation on adhesion formation in the rat was investigated. Radiation administered immediately postoperatively and fractionated over 3 days in the rats inhibited the amount of adhesion scar; however, it neither prevented nor enhanced the extent of intraabdominal adhesions.

By comparing the response to irradiation of denuded intestine, liver, and parietal peritoneum, significant differences in response to injury are noted: Adhesions are infrequently seen to the parietal peritoneum, are frequently seen to the interlobar surfaces of the liver, and are almost always seen to the intestine at the site of denuded peritoneum. Parietal peritoneum and liver capsule adhesion collagen is mature and strongly birefringent to polarized light. Intestine adhesion collagen is basophilic, resembling mature collagen on hematoxylin and eosin stain, and weakly birefringent to polarized light. Liver capsule adhesion does not diminish in amount with irradiation. Intestinal adhesion does diminish in amount with postoperative irradiation. Therefore, there appears to be substantial differences in the response of parietal, liver, and intestine peritoneum to injury and to irradiation.

Summary. The effect of total abdominal irradiation on the development of intraabdominal adhesions in the rat was investigated. Intraabdominal adhesions were induced by surgically stripping the serosa of the antimesenteric border of the ileum, or by intraperitoneal injection of colloidal silica dioxide. The groups were subdivided. Total abdominal irradiation was given to one subgroup, 350 rads on day 1. The second subgroup received 350 rads per day for 3 days. The third group was not irradiated and served as the control. Postoperative irradiation did diminish the amount of intestine adhesions; however, it did not prevent or enhance the extent of intestine adhesion.

The parietal, liver, and intestine peritoneum responded differently to injury and irradiation. Adhesions rarely formed to the parietal peritoneum, frequently formed to the interlobar liver surface, and uniformly formed to the intestine. Liver capsule adhesions and skin union formed with the development of mature collagen that was

strongly birefringent to polarized light. Intestine adhesions formed with amorphous basophilic collagen that was weakly birefringent to polarized light. Irradiation diminished the amount of adhesion scar to the intestine but not to the liver or the parietal peritoneum.

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