The Natural History and Management of Radiation Induced Injury of the Gastrointestinal Tract

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Radiation therapy has provided a powerful and effective modality for control of cancer. Infrequent complications of radiation have been recognized and, as with surgery, accepted as the penalty for cure of life-threatening neoplastic disease. Complications, especially skin injury, have been reduced by modern supervoltage therapy and other improvements in methodology. However, injuries of the gastrointestinal and genitourinary tracts have remained a problem of substantial surgical importance.[4, 12, 16, 22]

The present report is a retrospective analysis of the experience at University Hospitals of Cleveland with radiation induced injury of the gastointestinal tract. One hundred patients, who sustained significant injury between 1922 and 1968, have been analyzed in detail. Only patients whose hospitalization was related to or prolonged from injury are included. In addition to a disturbingly high mortality, we found radiation induced injury of the gastrointestinal tract was associated with some important, previously undescribed, systemic relationships.

Previous reviews have demonstrated the protean manifestations of intestinal injury.[1, 5, 10, 21, 26, 34, 35, 42, 50] Since many patients who receive pelvic radiation will have transient gastrointestinal symptoms, it is difficult to compare complication rates.[21, 23] During the past 15 years at this institution, the frequency of gastrointestinal complications following radiation therapy for cervical cancer was 11.6 per cent, results comparable to that observed in the contemporary literature.[30]

The injuries, often multiple, comprised proctitis in 44 patients, rectal ulcer in 10, rectal stricture in 19, rectovaginal fistula in 29, colitis in 17, ileitis or jejunitis in 25, and rectal polyps in one and a rectal carcinoma in one that were possibly induced by radiation (Table 1). Twenty-two postmortem examinations and 56 surgical specimens were reviewed. Of the 100 patients, 83 were eligible for 5-year follow-up and 54 for 10-year follow-up.

Clinical Features

Ninety-seven injured patients received radiation therapy for a malignant tumor; the remaining three had benign diseases (Table 2). Ninety-five of the patients were women. At the time of radiation, the age of the patients averaged 52 years, ranging from one to 77 years. A previous supracervical hysterectomy had been performed in 14, adnexal surgery in 12, and an appendectomy in 10.

Of the 100 patients, 43 had no significant medical illnesses at the time of radiation

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TABLE 1. *Radiation Induced Injury of the Gastrointestinal Tract in 100 Patients*

Proctitis	44
Rectal ulcer	10
Rectal stricture	19
Rectovaginal fistula	29
Colitis	17
Enteritis	25
Rectal neoplasm	2
Total	146

therapy. In the remaining 57, hypertension was identified in 39, arteriosclerotic heart disease in 15, diabetes in nine, intestinal disease in six, prior cancer in three, rectal disease in three, tuberculosis in two, and syphilis in two. Twenty per cent were regarded as obese. Ten had pelvic inflammatory disease. Anemia was not prominent; nor were urinary tract infections or azotemia particularly notable in the injured patients.

In 78 of the 100 patients, the intent of treatment was for cure. External radiation alone was administered to 17 injured patients, radium alone in six, and the remainder had combinations of both. Sixteen of the 100 patients had surgery combined with radiotherapy.

Of the 100 patients, the present status of six is unknown. Death was attributed to cancer in 28 patients (mean follow-up—3.0 years), radiation complications of the gastrointestinal tract in 22 (mean follow-up—7.0 years), other radiation complications in three (mean follow-up—7.0 years), cardiovascular disease in six (mean follow-up—3.2 years) and other causes in four (mean follow-up—14.1 years). Of 83 patients eligible for 5-year follow-up, 27, or 33 per cent, are living, and 56, or 67 per cent, are dead.

Etiological Factors in Study Group

Since there was no way to assess the population base at risk from which the 100 injured patients were derived, some possible etiological factors in injury were examined in a subset of 34 consecutive injured patients who were treated here for carcinoma of the cervix from Jan. 1, 1956 to Dec. 31, 1965. The study group of injured patients was contrasted with 227 consecutive uninjured patients treated here for cancer of the cervix during the same interval. Comparisons, except for obesity and age, were based on four-cell chi-square tests (Table 3).

A significant ($p < 0.025$) relationship was found between the presence of hypertension at the time of radiotherapy and injury to the gut. In addition, there was a correlation ($p < 0.05$) between the presence of diabetes, cardiovascular disease, or both, and radiation injury. A history of pelvic inflammatory disease did not bear a relationship to radiation injury, but a previous supracervical hysterectomy had a significant ($p < 0.025$) bearing on subsequent gastrointestinal damage. Other abdominal surgery could not be correlated with injury.

Age was compared by a t-test and was not different. Weight at time of admission for radiation therapy was examined by tables of expected weight for age and height.[8] The results showed both injured and uninjured patients to be overweight by these standards; no difference was found between the two groups in degree or frequency of obesity. Nor was there any difference in racial distribution between the two groups. No difference was found be-

TABLE 2. *Basis for Radiation*

Carcinoma of cervix	75
Carcinoma of endometrium	9
Carcinoma of vagina	5
Carcinoma of bladder	2
Hepatoblastoma	1
Seminoma	1
Carcinoma of vulva	1
Carcinoma of prostate	1
Carcinoma of ovary	1
Lymphosarcoma	1
Chronic cervicitis	1
Radiation castration	1
Fungal vaginitis	1

tween the two groups in clinical staging; however, significant differences in histological grading were identified.

Radiation Factors

Radiation factors were examined by one of the authors who was familiar with radiotherapeutic technics and unaware of other etiological elements being assessed. A retrospective analysis of factors contributing to serious radiation complications was hazardous. Records were inadequate to assess accurately such features as equipment, therapists and the spatial relationships of radiation dosage. For this reason, a select group of parameters were evaluated in injured patients treated for carcinoma of the cervix.

The distribution of five histological grades of cervical cancer was examined with respect to anatomical stage of involvement (Table 4). Of 75 patients, 59, or 79 per cent, had Stage I or II involvement, and 16, or 21 per cent, had Stage III or IV involvement. The distribution of histological grades was compared with similar information from another group of patients with confirmed carcinoma of the uterine cervix at this institution. A significant increase in small cell cancer in injured patients was associated with an accompanying decrease in large cell nonkeratinizing carcinoma ($p < 0.001$). Previous studies have demonstrated a variation in radiosensitivity and radiocurability for different grades of cervical carcinoma.[48, 49] Small cell carcinoma has been associated with the worst prognosis by stage when compared with other types of cervical carcinoma.

TABLE 3. *Study Groups with Carcinoma of the Cervix*: Injured Patients (34) *vs.* Uninjured Patients (227)

	Corrected Factors
Obesity	n.s.
Age	n.s.
Race	n.s.
Pelvic inflammatory disease	n.s.
Clinical staging	n.s.
Hypertension	$p < 0.025$
Arteriosclerosis or diabetes	$p < 0.05$
Supracervical hysterectomy	$p < 0.025$

Of the 75 patients with cervical carcinoma, 67 were treated by external pelvic radiation (Table 5). Four of 21, or 19 per cent, treated by orthovoltage received a total central tissue dose in excess of 4,000 rads. Of 46 patients treated by pelvic supervoltage, six, or 13 per cent, received a total central tissue dose in excess of 9,000 rads. External therapy by the two modalities was considered high if the dose to mid-

TABLE 4. *Histological Grade of Cancer in All Injured Patients with Carcinoma of Cervix vs. Uninjured Control Series.*

	Stage of Anatomical Involvement								
	Radiation Complication Group							McDonald House Control Group	
Type of Cancer	I	II	III	IV	Not Staged	Total	%	%	p
Keratinizing	3	8	2	—	—	13	17.3	15.8	n.s.
Large Cell	1	15	3	—	—	19	25.3	55.7	<0.01
Small Cell	7	9	3	2	—	21	28.0	5.5	<0.01
Adenocarcinoma	5	3	—	—	—	8	10.8	15.4	n.s.
Mixed carcinoma	1	—	—	—	—	1	1.3	7.6	n.s.
Not available	3	4	1	1	4	13	17.3	0	—
	20	39	9	3	4	75	100.0	100.0	

TABLE 5. *More Than 4,000 Rads CTD Was Considered High Orthovoltage (O.V.); More than 9,000 Rads CTD Was Considered High Supervoltage (S.V.T.)*

	Evaluation of External Therapy Dosage			
Stage	Total O.V.	High O.V.	Total S.V.T.	High S.V.T.
I	5	1	12	0
II	13	3	25	3
III	1	0	8	3
IV	2	0	1	0
	21	4	46	6

plane pelvis exceeded the above levels when supplemented by central radium therapy.

Intracavitary radium therapy was employed in 67 of the 75 patients with carcinoma of the uterine cervix (Table 6). Nonrigid applicators of the Fletcher or tandem and cervical pack type were used in 24 patients whereas a rigid Ernst applicator was used in 43 patients. Seven patients, or 29.1 per cent, with nonrigid radium applications, and eight, or 18.6 per cent, with Ernst radium application were considered to have high radium dosage. Thus, 20.0 per cent of all patients with cervical carcinoma received radium applications in excess of 7,000 rads, or mgh. (milligram-hours), for one application, or 9,000 rads, or mgh., for two applications.

Several factors emerged that appeared to complicate cervical radium application (Table 7). Thirteen patients had past or recent pelvic surgery. Intercurrent infection or pyometra complicated six radium applications. Trauma by vaginal-cervical laceration or perforation occurred in four patients. High midline dosage to bowel or bladder resulted from a narrowed vagina which prevented complete expansion of the Ernst applicator or from vaginal ovoid therapy in 31 patients.

Of 75 injured patients with carcinoma of the cervix, 18, or 24 per cent, had residual or recurrent invasive carcinoma encountered prior to or at the time of detection of the radiation complication. The presence of recurrent cancer was thought to increase the likelihood of fistula formation. Approximately 50 per cent of injured patients with confirmed recurrent or residual cancer had the small cell variety of cervical carcinoma which has the poorest results from radiation therapy.

The Progression of Radiation Injury of the Gut

Radiation Proctitis, Rectal Ulcer, Rectovaginal Fistula and Rectal Stenosis

Patients with rectal injury lent themselves to classification into two groups. Group I injuries comprised 52 patients with proctitis, rectal ulcer and stenosis. Group II injuries consisted of 29 patients who developed rectovaginal fistulas. While there was an intersection of different kinds of rectal injury, the Group I injuries were more varied, more ambiguous in the relationship between symptoms and findings, and more likely to be reversible. Group II injuries were sharply defined historically and virtually irreversible by local management.

Both groups were contrasted by assessment of possible etiological factors. Age,

TABLE 6. *More Than 7,000 Rads, or mgh, for one Application, or More Than 9,000 Rads, or mgh, for Two Applications Was Considered a High Dose*

	Cervical Radium Therapy			
Stage	Total Non-rigid Applicator	High Dose Non-rigid	Total Rigid Applicator	High Dose Rigid
I	4	0	14	1
II	14	4	25	5
III	3	2	3	1
IV	0	0	1	1
Not Staged	3	1	0	0
	24	7	43	8

TABLE 7. *Factors Contributing to Radium Complications*

Factors	Stage I	II	III	IV	Total
Cervical stump	2	3	1	—	6
Recent pelvic surgery	2	3	1	1	7
Intercurrent infection	2	1	—	—	3
Pyometra	1	2	—	—	3
Vaginal laceration	1	1	—	—	2
Perforation	—	1	1	—	2
Ernst not opened completely	3	13	—	—	16
Vaginal ovoids only	5	9	1	—	15
	16	33	4	1	54

race, previous supracervical hysterectomy, clinical staging, and the dosage of radium and/or external radiation were not different in the two groups. The incidence of obesity was significantly greater in Group II injuries ($p < 0.05$). The incidence of cardiovascular disease appeared more frequent in the group with rectovaginal fistula, but the differences were not significant ($p < 0.10$).

Most Group I injuries were identified within the first year after radiation therapy (Fig. 1). However, in 14 patients definitive injury was not evident for two or more years after primary therapy. Symptoms of diarrhea, bleeding and tenesmus did not correlate well with the extent of rectal pathology. The presence of crampy abdominal pain was unusual in pure rectal injury and generally could be related to more cephalad enteric injury.

Radiation induced rectal ulcers were usually noted 4 to 12 months after initiation of radiotherapy. Rectal ulcers were located on the anterior rectal wall at the level of the cervix. Rectal ulcers were usually single, less than 4 cm. in diameter, shallow with a yellowish-grey necrotic base and flat edges, and were readily distinguishable from cancer. Serial proctoscopy revealed that rectal ulcers were reversible and not necessarily precursors of rectovaginal fistula. Nor was there evidence that biopsy hastened or resulted in development of a fistula.

Rectal stenoses were located higher than ulcers, usually 8 to 12 cm. from the anal verge. In this series, the presence of ulcers and stenoses were noted simultaneously, there being no evidence that one progressed to the other. The degree of stenosis did not correlate well with the severity of the symptoms.

Group II injuries comprised 29 patients who had rectovaginal fistulas. Patients who had biopsy or clinical evidence of cancer in or near the fistula were not included in the study. The average interval from initiation of therapy to onset was 22 months, ranging from 3 months to 12 years. Prior to development of a fistula these patients

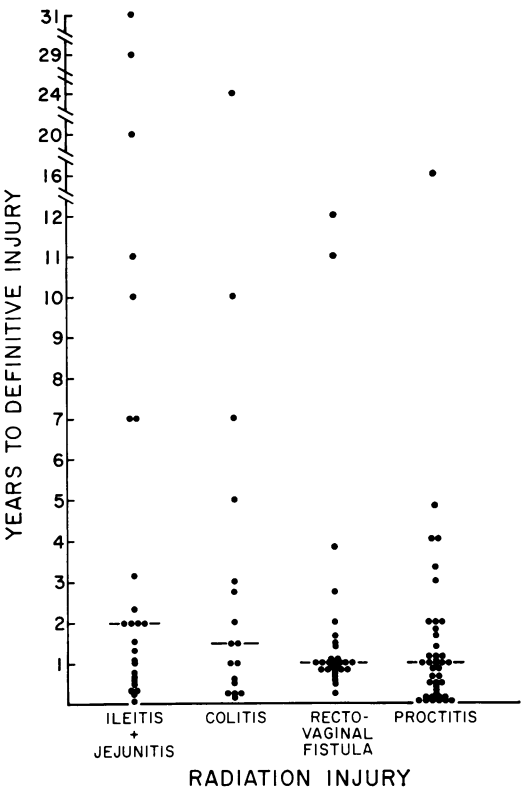

FIG. 1. Interval, in years, from primary radiation therapy to definitive gastrointestinal injury. The horizontal bar indicates the mode.

TABLE 8. *Results of Management of Small Bowel Injury*

	Non-Surgical	Bypass	Lysis	Resection
Died from carcinoma	1	0	0	2
Died from radiation injuries	1	0	0	5
Died from operation	0	1	1	2
Dead, unrelated cause	0	0	0	4
Alive, symptomatic	4	1	0	3
	6	2	1	16

had symptoms similar to Group I but generally more severe. In several patients the onset was heralded by days to weeks of vaginal bleeding, occasionally massive. The diagnosis of a rectovaginal fistula was not difficult. However, one patient had an additional ileovaginal fistula, the diagnosis of which was made only after a colostomy failed to stop vaginal drainage.

Most patients with rectal ulcer or stenosis were controlled by medical measures. Of the total group of 100 patients, a colostomy was performed in 27. The indications were rectovaginal fistula in 21, rectal stenosis in two, sigmoid obstruction in two, incontinence from destruction of the anal sphincter in one, and perforation of a carcinoma in one. Of 17 sigmoid colostomies, only eight were uncomplicated. Four required revision because of gangrene, two required revision due to stenosis, two required revision due to hemorrhage and one had further hemorrhage which was not treated surgically. Four descending colon colostomies and seven of eight transverse colon colostomies were uncomplicated.

Colostomy provided some symptomatic relief in all but three patients. In no patient was there spontaneous healing of a rectovaginal fistula. Three patients underwent colostomy closure because of apparent healing; in each the fistula recurred promptly. Surgical repair of the fistula was equally frustrating; in only one patient, after several attempts, was there successful closure of both the fistula and the colostomy.

The follow-up of both groups is similar. In Group I, 21 of 47 followed patients are living: seven died from complications of radiation therapy; 15 died from recurrent carcinoma; and, four died from unrelated causes. In Group II, seven of 28 followed patients are living; eight died from complications of radiation therapy; ten died from recurrent cancer; and three died from unrelated causes.

Radiation Enteritis

In this series, 34 patients sustained significant injury to the intestine exclusive of the rectum. Injury was confined to the small bowel in 17, to the colon in nine, and to both small and large bowel in eight. Thus, 25 patients had radiation induced ileitis or jejunitis and 17 had colitis. In 21 of 25 patients with small bowel injury, either operative or autopsy findings verified the nature of the pathologic process. In the remaining four patients, barium examination of the small bowel (as well as symptomatology) demonstrated radiation injury. Thirteen of the 34 patients had associated rectal injury and 15 had associated urinary tract injury, which, in several, was the major life threatening lesion.

Ten of 17 patients in the colon injury group had previous lower abdominal surgery, in contrast to only four of 17 patients who had small bowel injury alone. Commonly, a loop of injured sigmoid colon was adherent to the uterus or to the cervical stump after a previous supracervical hysterectomy.

The presenting manifestations of small bowel injury were those of ileitis or partial to complete obstruction in 14, intestinal ischemia or necrosis in eight, and enteric fistula in three. The presenting findings of colonic injury were colitis in seven, stenosis or obstruction, usually sigmoid, in seven, necrosis in two, and a sigmoid vaginal fistula in one.

In some instances, patients had a spectrum of recurrent abdominal pain and diarrhea for long periods of time, but many were well until several weeks or months before the complication occurred. Symptoms of crampy post-prandial abdominal pain, often with nausea or vomiting, accelerated until an acute episode of complete obstruction, necrosis or perforation intervened. In the small bowel injury group the interval from radiation therapy to surgery averaged 6.5 years, ranging from one month to 31 years, and in the colon injury group 5.7 years, ranging from six months to 24 years (Fig. 1). In nine patients, the clinical manifestations of injury occurred 5 or more years after radiation therapy; sigmoiditis at 5 years; ileal perforation at 7 years; colonic necrosis and jejunal obstruction at 7 years in the same patient, sigmoid stenosis at 10 years; ileal obstruction at 10 years; ileal obstruction at 11 years; ileal perforation at 20 years; sigmoid stenosis at 24 years and ileal perforation at 29 years in the same patient; and jejunal obstruction at 31 years. In six of the nine patients there was evidence of deteriorating cardiovascular disease at the time of manifestation of injury. In another patient with chronic radiation ileitis who did not require surgery, gastrointestinal symptoms worsened when she discontinued digitalis and improved when congestive heart failure was corrected. A brief case report of one of the injured patients is illustrative.

Case Report

Case 1. In 1923, at age 12, the patient had a left testicular tumor treated by orchidectomy and abdominal radiation. The radiation factors are unknown. In 1943, 21 years later, the patient, now a physician, experienced the onset of intermittent episodes of crampy, periumbilical pain associated with diarrhea and partially relieved by vomiting. By July, 1952, these episodes were occurring every few weeks. He was hospitalized in December, 1953, for a partial small bowel obstruction which resolved with conservative measures. An upper gastrointestinal barium x-ray examination revealed an abnormal jejunal mucosal pattern. The attacks continued and the patient began losing weight. In 1954 he experienced a paroxysmal atrial fibrillation which required digitalization. An exploratory laparotomy in Sept., 1954, at age 43, revealed the entire jejunum to be pale with thickening and edema of the serosa and with dilated subserosal lymphatics.

The patient was readmitted in Jan., 1958, because of a partial small bowel obstruction. Stools were frequent, yellow and foamy. The obstruction was relieved by passage of a Miller-Abbott tube. The patient was now experiencing angina pectoris. In Nov., 1958, he was readmitted because of increasing abdominal symptoms. A duodenal ulcer was noted on x-ray examination and he was explored. A subtotal gastrectomy with gastrojejunostomy was performed. In addition the proximal jejunum was noted to be scarred and contracted; a 75 cm. segment of jejunum was resected. Histological examination showed focal fibrous and fibrinous peritonitis with marked sclerosis of the vessels of the stomach, jejunum and duodenum.

He was readmitted in April, 1960, with hypertensive cardiovascular disease, congestive heart failure and pericarditis of unknown etiology. He continued to experience abdominal pain. In July, 1963, 40 years after radiation therapy, and 5 years after jejunal resection, he died of a myocardial infarction. At autopsy he had severe generalized arteriosclerosis. The vessels in the jejunum showed a radiation vasculitis. There was also evidence of radiation nephritis.

Of 25 patients with small bowel injury, surgery was necessary in 19 and nonoperative management was used in six (Table 8). The latter group had a persistent ileitis or a chronic partial small bowel obstruction. All six patients continued to be symptomatic throughout the follow-up period.

TABLE 9. *Patients Who Sustained Perforation*

Age at Primary Radiation Therapy	Diagnosis	Radiation Factors	Interval to First Symptoms	Interval Primary Radiation Therapy to Surgery
1. 30	Ca. cervix	Radium & gold 6,732 mgh	5 yr.	29 yr.
2. 48	Ca. ovary	SVT-5,067 CTD	3 yr.	7 yr.
3. 33	Ca. cervix	Radium-3,480 mgh SVT-5,040 CTD	5 mo.	6 mo.
4. 57	Ca. cervix	Radium-11,464 r SVT-2,613 CTD	2 yr.	2 yr.
5. 63	Ca. cervix	Radium-5,670 r SVT-5,056 CTD	2 yr., 2 mo.	2 yr., 2 mo.
6. 42	Ca. endometrium	Radium-4,000 r	6 mo.	1 yr., 4 mo.
7. 60	Ca. cervix	OV + Radium	20 yr.	20 yr.

Sixteen patients had an intestinal resection; one had a lysis of adhesions which was followed by perforation and death; and two had a bypass procedure which resulted in success in one and failure in the other. The gross pathology of radiation injury to the small intestine was relevant. The peritoneal cavity usually contained dense adhesions with agglutination of peritoneal serosal surfaces. Adhesions made the operation more difficult, but they were not the cause of the obstruction. Rather, the cause of obstruction was a fibrotic, grey, stenotic segment of small bowel associated with diffuse thickening of the intestinal wall.

Two patients died during the first 30 days after bowel resection, a mortality rate of 12.5 per cent. One patient died within 24 hours of operation from both peritonitis secondary to the perforation for which her intestine was resected as well as other extensive radiation damage. A second patient died within 30 days of other radiation complications.

The remaining 14 patients survived resection of the small bowel. However, only six can be regarded as successfully treated insofar as the operation achieved the purpose for which it was intended without further complications to the small intestine. All of these patients are now dead:

After Intestinal Resection

Basis for Surgery	Interval to Postop Perforation	Presentation of Perforation	Subsequent Management	Result	Associated Conditions
Perforation	1 mo.	Multiple fistula	Jejuno-colostomy Desc. colostomy	Alive	Radiation stenosis of colon Rectal stricture Hypertension
Perforation	3 wk.	Pelvic abscess	Drainage only	Alive	Had colostomy for lymphogranuloma Megaloblastic anemia Hypertension and anemia
Intestinal obstruction	1 mo.	Ileocutaneous fistula	None	Died	R. V. Fistula Hypertension. No cancer at autopsy
Perforation	3 mo.	Enterocutaneous fistula from cecum	Resection	Died	Severe diabetes ASHD Died of gangrene of leg. No cancer at autopsy.
Perforation	6 mo.	Peritonitis	Resection	Died	R. V. Fistula, colitis, severe vascular disease. No cancer at autopsy
Vesico-vaginal fistula	3 mo.	Fistula in loop	Resection	Died	Radiation destruction of pelvic viscera hypertension
Obstruction	4 mo.	Peritonitis	Exteriorization	Died	Congestive cardiac failure. No cancer at autopsy

three died within 2 years of other radiation complications; two died ultimately of recurrent cancer, and one died 5 years later of a recurrent myocardial infarction. Of the remaining eight patients, seven developed a perforation of the intestine postoperatively, and one had an obstructed ileal anastomosis requiring an ileotransverse colostomy.

The seven patients who developed an intestinal perforation following resectional surgery are amplified in Table 9. The interval from resection to appearance of perforation ranged from three weeks to six months, therefore, perforation could not be attributed to a technical failure of surgery. Rather, the evidence supported continuing progression of vascular occlusion. Of the seven patients, three had evidence of heart failure or severe peripheral vascular disease at the time of perforation, one had hypertension and a severe megaloblastic anemia, and three had documented hypertension.

Of 17 patients with radiation injury to the colon, seven were treated medically. These were patients with a colitis or limited stenosis without obstruction. Symptoms subsided in three and continued in four. Death occurred ultimately from hemorrhage cystitis in one and small bowel injury in one.

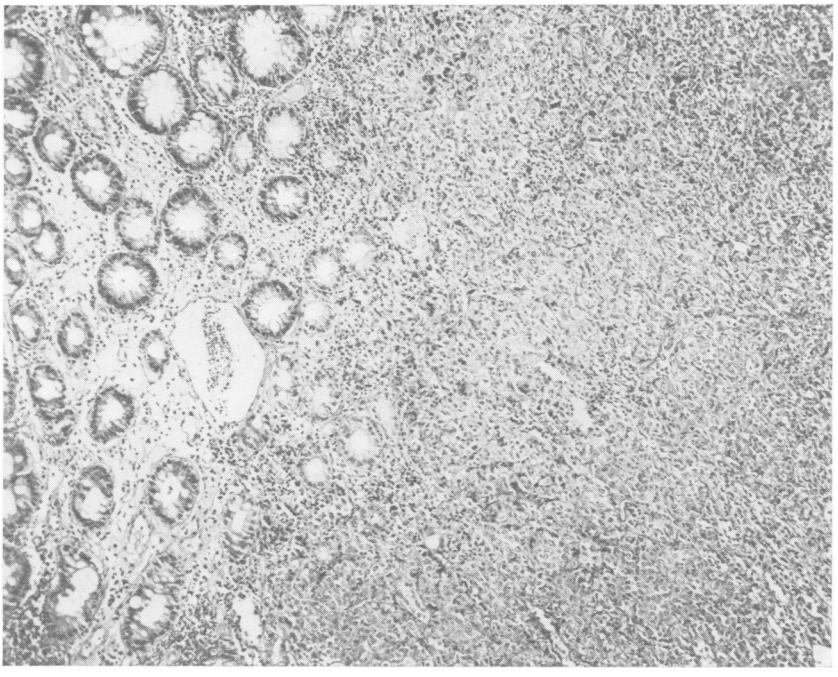

FIG. 2. Photomicrograph (×80) of undifferentiated rectal carcinoma in a patient with rectal stenosis 31 years after radiation therapy for carcinoma of the cervix.

Ten patients with colon injuries had surgery performed. A colon resection was done for perforation in two patients and for sigmoid stenosis in one. One of these patients who also had a small bowel injury died of peritonitis and two survived. A colostomy was performed in two patients for sigmoid obstruction. Five patients, mentioned previously, had a colostomy for rectal stricture or fistula with associated colon injury.

Radiation Induced Polyps and Cancer

Several reports of radiation induced rectal neoplasms have appeared in the literature.[3, 31, 36, 39, 40] Two patients in this series developed rectal neoplasms many years after their radiation therapy. One patient developed recurrent adenomatous rectal polyps on the mucosal surface of a radiation induced rectal stenosis 26 and 29 years after radiation therapy for carcinoma of the cervix. The other patient is described briefly in the following summary:

Case 2. In 1936, at age 40, the patient had carcinoma of the cervix treated with radium and external orthovoltage therapy. Following treatment she experienced persistent diarrhea and tenesmus with the passage of pencil-sized stools. A rectal stenosis was identified by proctoscopy. In 1964 at age 68, she had a right ureteral calculus. In 1965, she developed fecal incontinence, associated with crampy abdominal pain and 20 to 25 bowel movements a day despite treatment with antispasmodics and steroids. Hypocalcemia was present. In July, 1967, 31 years after radiation therapy, she was admitted to University Hospitals with acute peritoneal signs. Exploration revealed a rectal perforation, secondary to a rectal carcinoma. The terminal ileum was thickened and narrowed. A sigmoid colostomy with a distal mucous fistula was performed. Sigmoidoscopy revealed a hard, fixed ulcerated mass occluding the rectum at 9 cm. and fixed to the lateral pelvic walls. Biopsy of the mass was interpreted as an undifferentiated carcinoma of the rectal mucosa (Fig. 2). She died from metastatic rectal cancer in Sept., 1968.

Other Radiation Injury Associated with Gastrointestinal Injury

There was a close relationship between gastrointestinal and genitourinary injury;

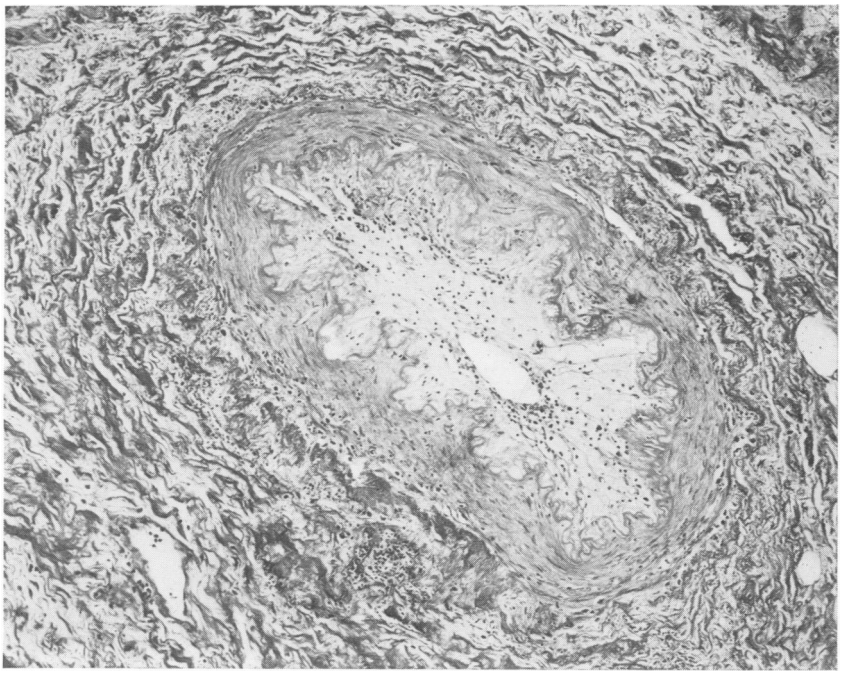

FIG. 3. Photomicrograph (×80) of an ileal arteriole demonstrating occlusive radiation vasculitis with severe tissue fibrosis. The vasculitis and fibrosis is characteristic of radiation injury.

55 of the 100 patients had associated urinary tract injury. Forty-four patients had cystitis, of whom 16 were regarded as severely injured. Nine had vesicovaginal or ureterovaginal fistulas, and eight had ureteral obstruction. Four of the eight with ureteral obstruction also had a rectal stenosis in conjunction with a diffuse pelvic fibrosis, a syndrome that was distinguished with considerable difficulty from recurrent cancer.[18]

Thirteen patients had orthopedic complications. In four, pathological fractures occurred, and in one, osteitis pubis was present. Almost all of these patients had been treated prior to the use of modern technics.

Discussion

Radiation of the gastrointestinal tract produces an immediate and potentially reversible effect on the sensitive generative epithelium of the intestinal mucosa [32] and a more prolonged and progressive obliterative vasculitis.[37, 45, 46] Vascular damage includes endothelial proliferation, endarteritis, hyaline rings and subendothelial foam cell formation (Fig. 3). It was the vascular occlusion induced by radiation that was critical in the pathogenesis of ulcers, strictures and necrosis which developed months or years after primary therapy.

An inter-relationship between low splanchnic blood flow and radiation vasculitis was evident from several aspects of the study. There was a significant difference in frequency of hypertension, diabetes and cardiovascular disease between injured patients with carcinoma of the cervix and an otherwise comparable group of uninjured patients. Those patients who sustained perforations of the intestine after intestinal resection for radiation injury all had varying degrees of cardiovascular disease. When the patients with rectovaginal fistulas were contrasted with those who had less severe rectal injury, there was a suggestive but not significant increase in frequency of cardiovascular disease in the more severely injured patients. Finally, the co-author, who examined the radiation factors and was un-

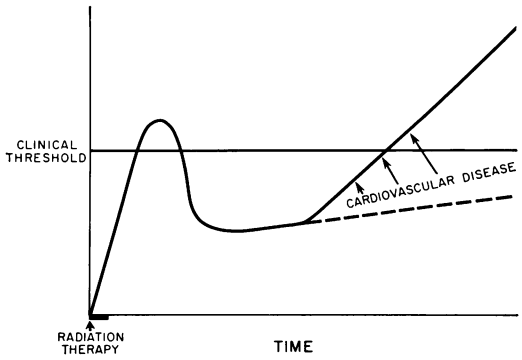

FIG. 4. A model, after Rubin and Cassarett,[35] suggesting a pattern for radiation injury; early transient symptoms, a latent period of subclinical activity, and precipitation of clinical symptoms, often by onset of cardiovascular disease.

aware of other elements being assessed, identified 17 patients in whom radiation therapy appeared by all standards to be within a tolerable range. Of those 17 patients, 12 had hypertension or other cardiovascular disease. A relationship with radiation injury has been suggested by previous authors regarding luetic as well as arteriosclerotic vascular disease.[17, 43]

The presence of a decreased cardiac output or the arteriolar narrowing of hypertension,[25] diabetes, or arteriosclerosis appeared to increase both the probability for radiation injury at the time of primary therapy as well as the likelihood for clinical manifestation of a severe injury later. In certain patients wtih radiation injury of the gut, a subclinical activity of disease persisted until advent of decreased splanchnic oxygenation from cardiovascular disease. At that time clinical symptoms became apparent and the intestinal disease progressed rapidly to necrosis (Fig. 4). These observations suggest an analogy to the mucosal infarction syndrome without vascular occlusion by emphasizing the necessity of supporting splanchnic flow and oxygenation.[9]

A persistent subclinical injury is probably more frequent than has been suspected. Without having overt symptoms, the majority of patients receiving pelvic radiation will have transient malabsorpiton[33] and transient alteration in the proliferative kinetics of the intestinal epithelium.[44] The effects of radiation on the regenerative capacity of the liver are quite latent.[47]

Radiation therapy was sometimes excessive or administered under circumstances known to increase the risk for injury. A high dose of external therapy to the midpelvic plane was noted in 13 per cent of patients also receiving radium therapy. A high radium dosage was found in 20 per cent of all patients receiving a cervical radium application. Difficult radium applications because of previous pelvic surgery, intercurrent infection, trauma at the time of radium insertion, or an inadequate distribution of radiation causing a high central dosage to bladder or rectum, were noted frequently in patients with carcinoma of the cervix. Injured patients were more likely to have had a previous supracervical hysterectomy which resulted in fixation of the radiosensitive viscera to the cervical remnant, difficulty in achieving an ideal pelvic dose distribution, and loss of fibromuscular shield to protect the bowel. The cellular pattern of the primary tumor was related to radiation injury of the gut. In the injured patients there was a fivefold increase of the small cell cancers which yield a poor prognosis after irradiation therapy.

In this series the injured patients were not more likely to have had pelvic inflammatory disease. Injured and uninjured patients had the same age distribution at the time of radiation therapy, a similar degree of obesity, and the same racial distribution.

Previous authors classified rectal injuries into three or four categories.[7, 15, 38] For several reasons, a two group classification, based on the presence or absence of fistula, was preferred. Proctitis, ulcers, and stenosis were frequently mixed. Some pa-

tients were asymptomatic even in the presence of ulcers or stenoses. Conversely, patients may be very symptomatic with minimal pathologic lesions.[20] Further, several patients in our series demonstrated spontaneous healing of ulcers. Healing of ulcers and regression of stenoses have been noted by others.[7, 38, 43] Rectovaginal fistulas, however, showed no tendency to heal spontaneously. The variability in behavior precluded classification in any other practical fashion.

Transient proctitis is a frequent side effect of pelvic radiation. Persistence for more than a month after completion of therapy merits investigation by proctoscopy. Even if overt urinary tract symptoms are absent, assessment of that system is indicated by the high frequency of associated genitourinary involvement. Patients with proctitis are generally managed effectively with a low residue diet, sedation, antispasmodics,[6] stool softeners and general supportive measures. Oral steroids and steroid enemas or suppositories are useful in severe injuries.[24] The benefit derived from long term use of sulfonamides has been impressive.[29, 41]

Rectal stenosis can usually be managed by the above measures as well as by instrumental or digital dilatations. Colostomy may reduce symptoms but does not alter the progression of radiation vasculitis. Accordingly, colostomy was deferred as long as possible in Group I injuries. Occasionally, excision with a low rectal anastomosis may be appropriate, but only if acute inflammatory changes have subsided, the distal rectum is uninvolved, recurrent cancer is not present and proximal diversion of the colon is achieved.

A primary determinant for subsequent therapy in severe rectal injury is the possible presence of residual or recurrent carcinoma. Radiation fibrosis in the pelvis closely simulated recurrent cancer. Pain was not a discriminating feature. There should be no reluctance to biopsy, but cytology and rectal biopsy may be difficult to evaluate owing to radiation change.

The appearance of a rectovaginal fistula heralds a complicated course of management. The local repair of radiation induced rectovaginal fistulas is not rewarding. A few patients with small fistulas may do well without any surgical management. In some, repeated failures or extensive local radiation damage may dictate a permanent, defunctionalizing, descending colon colostomy to achieve local control of pelvic symptoms. If severe genitourinary injury is present, exenteration may be necessary.[2, 42]

Radiation induced injury of the small and large bowel provided the greatest diagnostic and therapeutic challenge. Numerous reviews have emphasized these progressive and potentially lethal injuries.[4, 10, 11, 13, 14, 19, 26–28, 34, 42, 50, 51]

Radiation enteritis should be regarded as a possible cause of abdominal pain after radiation therapy to the abdominal viscera. Several patients in this series had a diagnosis of a functional bowel syndrome for some time before perforation occurred. On the other hand, biopsy proof of cancer should be obtained before attributing the patient's symptoms to recurrent tumor. The patient who appears well and maintains his body weight but continues to have pain usually has a radiation reaction, not recurrent or persistent cancer. The presence of crampy, periumbilical pain with diarrhea or with obstructive symptoms suggests ileal involvement. Identification of steatorrhea or other signs of malabsorption, e.g., hypocalcemia, was helpful in making a diagnosis of ileal injury. Both a barium enema and a small intestinal barium examination should be obtained, particularly in the presence of enteric fistulization. Apparent radiological normality may be evident in the presence of severe circulatory compromise secondary to vasculitis.

Radiation damage tends to occur at points of fixation in the intestine. Involved intestine appears as matted loops; the serosal surface is opaque, the consistency firm, and the mesentery contracted. Multiple filmy adhesions are ordinarily present.

A most important principle is that the degree of involvement from radiation injury is far more than is evident on gross inspection. In our patients the high late mortality after resection was due principally to the combination of residual injured intestine and advancing cardiovascular disease. In general, a wide resection is preferable to a wide bypass; both are superior to limited procedures. A meaningless dissection of adhesions should be avoided and no attempt made to free intestine unless its removal is intended. Contemporary advances in the management of nutritional problems after extensive intestinal resection are successful enough to permit removal of all intestine in the field of pelvic radiation. Since involvement of both terminal ileum and cecum is common, a right colectomy with an extensive ileal resection may be required. Frozen section examination of the margins of resection is valuable.

But individualization in management is essential. Surgery for relatively minor complaints should be avoided. In the presence of stenotic, obstructed bowel fixed in a badly fibrosed pelvis, an intestinal bypass must be favored. If severe peritonitis is present or proximal margins uncertain, exteriorization of the involved intestine is advisable. In some patients, especially with enterovesical fistula, an exenteration or loop will give optimum chance for survival.[2, 42] In all instances cardiovascular function must be maintained at optimum levels.

Summary

One hundred patients who sustained significant radiation induced injuries of their gastrointestinal tract before and after the introduction of supervoltage therapy had been analyzed. The injuries comprised proctitis in 44 patients, rectal ulcer in 10, rectal stricture in 19, rectovaginal fistula in 29, colitis in 17, ileitis or jejunitis in 25, and rectal polyps in one and a carcinoma in one that were possibly induced by radiation. Urinary tract injury was frequently associated. Death was attributed to recurrent cancer in 28 patients and to radiation injury of the gastrointestinal tract in 22.

When a subset of 34 injured patients with carcinoma of the cervix was contrasted with 227 uninjured patients treated during the same 10-year interval, gastrointestinal damage and progression of injury correlated significantly ($p < 0.025$) with hypertension, less so with diabetes or arteriosclerosis, and not at all with age, race, or clinical staging. Small cell cancer of the cervix or a previous supracervical hysterectomy was observed more frequently in injured patients.

In 25 patients, gastrointestinal injury was not manifested for at least two years after therapy. A delayed appearance of a complication often related to the advent of cardiovascular disease. There was an additive relationship between low splanchnic blood flow from systemic vascular disease and radiation vasculitis.

Limited surgery was attended by a high mortality and a high complication rate, particularly late intestinal perforation. The evidence favored an extensive intestinal resection in the management of small bowel injury.

References

1. Ashbaugh, D. G. and Owens, J. C.: Intestinal Complications Following Irradiation for Gynecologic Cancer. Arch. Surg., 87:100, 1963.
2. Barber, H. R. K. and Brunschwig, A.: Pelvic Exenteration for Extensive Visceral Necrosis Following Radiation Therapy for Gynecologic Cancer. Obstet. Gynec., 25:575, 1965.
3. Black, W. C. and Ackerman, L. V.: Carcinoma of the Large Intestine as a Late Complication of Pelvic Radiotherapy. Clin. Radiol., 16:278, 1965.

4. Brick, I. B.: Effects of Million Volt Irradiation on the Gastrointestinal Tract. Arch. Int. Med., **96**:26, 1955.
5. Colcock, B. P. and Hume, A.: Radiation Injury to the Sigmoid and Rectum. Surg. Gynec. Obstet., **108**:306, 1959.
6. Conard, R. A.: Effect of X-Irradiation on Intestinal Motility of the Rat. Amer. J. Physiol., **165**:375, 1951.
7. Craig, M. S., Jr. and Buie, L. A.: Factitial (Irradiation) Proctitis. Surgery, **25**:472, 1949.
8. Davenport, C. B.: Body Build and Its Inheritance. Publication 329, Carnegie Institute of Washington, 1923.
9. Drucker, W. R., Davis, J. H., Holden, W. D. and Reagan, J. R.: Hemorrhagic Necrosis of the Intestine. Arch. Surg., **89**:42, 1964.
10. Fabrikant, J. I., Anlyan, W. G. and Creadick, R. N.: The Management of Radiation Injuries to the Intestines. South Med. J., **52**: 1186, 1959.
11. Frank, R. C. and Pohle, E. A.: Late Radiation Reaction in the Small Intestine Manifested 8 Years After Therapy. Ann. Surg., **133**:104, 1951.
12. Frick, H. C., Taylor, H. C., Jr., Guttmann, R. J., Jacox, H. W. and McKelway, W. P.: A Study of Complications in the Surgical and Radiation Therapy of Cancer of the Cervix. Surg. Gynec. Obstet., **111**:493, 1960.
13. Gardner, C. E., Jr. and Anlyan, W. G.: Radiation Injury to the Small Intestine. Surgery, **31**:746, 1952.
14. Graham, J. B. and Villalba, R. J.: Damage to the Small Intestine by Radiotherapy. Surg. Gynec. Obstet., **116**:665, 1963.
15. Gray, M. J. and Kottmeier, H. L.: Rectal and Bladder Injuries Following Radium Therapy for Carcinoma of the Cervix at the Radiumhemmet. Amer. J. Obstet. Gynec., **74**:1294, 1957.
16. Greiss, F. C., Blake, D. D. and Lock, F. R.: Complications of Intensive Radiation Therapy for Cervical Carcinoma. Obstet. Gynec., **18**:417, 1961.
17. Ingelman-Sundberg, A.: Rectal Injuries Following Radium Treatment of Cancer of the Cervix Uteri. Acta Radiol. Suppl., 64, 1947.
18. Kaplan, A. L., Hudgins, P. T. and Wall, J. A.: Postradiation Pelvic Fibrosis Simulating Recurrent Carcinoma. Amer. J. Obstet. Gynec., **92**:117, 1965.
19. Kaplan, A. L., Hudgins, P. T. and Wall, J. A.: Injury of the Small Intestine Following Irradiation for Gynecologic Cancer. South. Med. J., **58**:1108, 1965.
20. Kaplan, B. J.: Some Clinical Aspects of Factitial Proctitis. Conn. Med. J., **20**:357, 1956.
21. Kottmeier, H. L.: Complications Following Radiation Therapy in Carcinoma of the Cervix and Their Treatment. Amer. J. Obstet. Gynec., **88**:854, 1964.
22. Lalanne, C. M. and Fajbisowicz, S.: Complications Post-Radiotherapiques dans le Cancer du Col Uterin. Ann. Radiol., **8**:697, 1965.
23. Maas, J. M.: Intestinal Changes Secondary to Irradiation of Pelvic Malignancies. Amer. J. Obstet. Gynec., **56**:249, 1948.
24. MacDonald, G. E. and Hoyt, L. H.: Corticotropin (ACTH) Gel in Treatment of Irradiation Enterocolitis. J. Amer. Med. Ass., **161**:1381, 1956.
25. Morlock, C. G.: Arterioles of the Pancreas, Liver, Gastrointestinal Tract and Spleen in Hypertension. Arch. Int. Med., **63**:100, 1939.
26. Nance, F. C., Persson, A. V. and Piker, J. F.: Radiation Injuries to the Lower Gastrointestinal Tract. Amer. Surg., **34**:21, 1968.
27. Perkins, D. E. and Spjut, H. J.: Intestinal Stenosis Following Radiation Therapy. Amer. J. Roentgenol., **88**:253, 1962.
28. Peterson, H. H. and Clausen, E. G.: Radiation Injury to the Small Bowel with Special Consideration of Surgical Complications. Gastroenterology, **31**:47, 1956.
29. Poth, E. J. and McClure, J. N.: Intestinal Obstruction: The Protective Action of Sulfasuxidine and Sulfathalidine to the Ileum Following Vascular Damage. Ann. Surg., **131**:159, 1950.
30. Powel-Smith, C.: Factors Influencing the Incidence of Radiation Injury in Cancer of the Cervix. J. Canad. Assoc. Radiol., **16–17**: 132, 1965–66.
31. Quan, S. H.: Factitial Proctitis due to Irradiation for Cancer of the Cervix Uteri. Surg. Gynec. Obstet., **126**:70, 1968.
32. Quastler, H.: The Nature of Intestinal Radiation Death. Radiat. Res., **4**:303, 1956.
33. Reeves, R. J., Cavanaugh, P. J., Sharpe, K. W., Thorpe, W. A., Winkler, C. and Sanders, A. P.: Fat Absorption Studies and Small Bowel X-Ray Studies in Patients Undergoing Co^{60} Teletherapy and/or Radium Application. Amer. J. Roentgenol., **94**:848, 1965.
34. Requarth, W. and Roberts, S.: Intestinal Injuries Following Irradiation of Pelvic Viscera for Malignancy. Arch. Surg., **73**:682, 1956.
35. Rubin, P. and Casarett, G. W.: Clinical Radiation Pathology. Volume I, W. B. Saunders Company, Philadelphia, 1968.
36. Rubin, P., Ruplansky, A. and Dutton, A.: Incidence of Pelvic Malignancies Following Irradiation for Benign Gynecologic Conditions. Amer. J. Roentgenol., **85**:503, 1961.
37. Sheehan, J. F.: Foam Cell Plaques in the Intima of Irradiated Small Arteries (One Hundred to Five Hundred Microns in External Diameter). Arch. Path., **37**:297, 1944.
38. Sherman, L. F.: A Reevaluation of the Factitial Proctitis Problem. Amer. J. Surg., **88**: 773, 1954.
39. Slaughter, D. P. and Southwick, J. W.: Mucosal Carcinomas as a Result of Irradiation. Arch. Surg., **74**:420, 1957.
40. Smith, J. C.: Carcinoma of the Rectum Following Irradiation of Carcinoma of the Cervix. Proc. Roy. Soc. Med., **55**:701, 1962.
41. Spratt, J. S., Heinbecker, P. and Saltzstein, S. L.: The Influence of Succinylsulfathiazole (Sulfasuxidine) upon the Response of Canine Small Intestine to Irradiation. Cancer, **14**:862, 1961.
42. Sugg, W. L., Lawler, W. H., Ackerman, L. V. and Butcher, H. R., Jr.: Operative Therapy for Severe Irradiational Injury in the Enteral

and Urinary Tracts. Ann. Surg., 157:62, 1963.
43. Todd, T. F.: Rectal Ulceration Following Irradiation Treatment of Carcinoma of the Cervix Uteri. Surg. Gynec. Obstet., 67:617, 1938.
44. Trier, J. S. and Browning, T. H.: Morphologic Response of the Mucosa of Human Small Intestine to X-Ray Exposure. J. Clin. Invest., 45:194, 1966.
45. Warren, S.: Effects of Radiation on Normal Tissues: VI. Effects of Radiation on the Cardiovascular Systems. Arch. Path., 34: 1070, 1942.
46. Warren, S. and Friedman, N. B.: Pathology and Pathologic Diagnosis of Radiation Lesions in the Gastrointestinal Tract. Amer. J. Path., 18:499, 1942.
47. Weinbren, K., Fitchen, W. and Cohen, M.: The Unmasking by Regeneration of Latent Irradiation Effects in the Rat Liver. Brit. J. Radiol., 33:419, 1960.
48. Wentz, W. B. and Lewis, G. C.: Correlation of Histologic Morphology and Survival in Cervical Cancer Following Radiation Therapy. Obstet. Gynec., 26:228, 1965.
49. Wentz, W. B. and Reagan, J. W.: Survival in Cervical Cancer with Respect to Cell Types. Cancer, 12:384, 1959.
50. White, W. C. and Finn, F. W.: The Late Complications Following Irradiation of Pelvic Viscera. Amer. J. Obstet. Gynec., 62:65, 1951.
51. Wiley, H. M. and Sugarbaker, E. D.: Roentgenotherapeutic Changes in the Small Intestine. Cancer, 3:629, 1950.

Discussion

Dr. Bentley P. Colcock (New Haven): Having had the opportunity to read this paper, I feel that it is the best analysis of this serious complication that I am aware of—and it is a serious complication. In this report of 100 patients, as you noticed, almost as many patients died as a result of the radiation treatment as died from recurrent cancer. In the 41 patients of ours that I reported about 10 years ago, five patients died as a direct result of the radiation treatment, and in two of those patients there was no evidence of residual cancer.

It is not only a serious problem, but it is one that we are probably going to face more often in the future. Our x-ray colleagues admit this. They feel, that, with supervoltage therapy, they have a means of destroying cancer in lymph nodes that in the past has beyond the reach of orthovoltage and radium.

The diagnosis is particularly apt to be missed because the clinical effects of the radiation injury are delayed for many months and even years after the radiation treatment. You noticed in Dr. DeCosse's paper, the interval between radiation and surgery was 6½ years for patients with small bowel injury, and 5½ years for patients with colon injury. As he pointed out, it is in these patients with small bowel and colon injury rather than the more common complication of proctitis that the greatest challenge to our diagnostic and therapeutic ability is present. Once the clinical symptoms develop, the inflammatory process goes on rather rapidly to perforation and necrosis, and it is here that we as surgeons have the opportunity to save the lives of some of these patients by first, prompt diagnosis, and, second, adequate treatment.

The key to early diagnosis is the onset of postprandial, cramplike abdominal pain in a patient who has had radiation to her pelvis. The key to a successful result is adequate surgery which includes resection of bowel, well beyond the obvious disease. I think this is an excellent paper and I congratulate the authors.

Dr. J. Englebert Dunphy (San Francisco): I would like to congratulate the authors on this excellent presentation and comment on just one aspect of it; namely, the unexplained perforation which occurs after lysis of adhesions or sometimes after resection. The perforation often occurs in an area in which the surgeon realizes he could not possibly have inadvertently damaged the bowel during the operation.

We have accumulated a great deal of evidence in our laboratory that following a laparotomy, or particularly after a bowel resection, the normal, otherwise uninjured colon and small bowel undergoes a remarkable loss of collagen. There is a marked activation of collagenase in the small bowel. There is also a marked increase of collagenase in the colon, and this can lead to loss of substance and then perforation of the normal, intact bowel.

In radiation damaged bowel resynthesis of collagen is depressed. Therefore, the effects of lysis are increased. This gives us additional reasons why we should carry out not merely lysis of adhesions around the involved area, but resection and extensive resection if we are going to operate at all.

Dr. J. J. DeCosse (Closing): As Dr. Colcock indicated, with increasing use of supervoltage radiation, I believe we are accumulating a pool of patients with subclinical injury that we are going to see as surgical patients in the coming years.

There is a second ramification of the one slide that has played a scattergram of the interval from radiation to injury and that is the inability to fully assess the impact of radiation therapy in any short-term follow-up study.