

Rectal Reaction Following Radiation Therapy of Cervical Carcinoma:

Particular Reference to Subsequent Occurrence of Rectal Carcinoma

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THERE IS an extensive literature considering acute and chronic radiation effects on the rectum following radiation therapy directed at carcinomas of the uterine cervix and endo-cervix. Ingleman-Sundberg² and Todd⁶ wrote classic contributions. We are concerned with the rare occurrence of primary adeno-carcinoma of the rectum in the field of post-irradiation damage. This phenomenon was essentially unreported until Smith⁴ reported three cases and Slaughter³ reported one. It seemed odd that Todd and Ingleman-Sundberg found no instance in a series which included 3,392 cases at the Radium-Hemmet during the period 1914-1937.

Material

From records of the Tumor Institute at the Swedish Hospital we found six cases of adeno-carcinoma of the rectum and rectosigmoid occurring subsequent to radiation therapy of cervical carcinoma.

During the period from 1935 to 1961 there were 813 treated cases of carcinoma of the cervix and 100 of carcinoma in cer-

vical stumps of 1,057 cases examined at The Tumor Institute. In reviewing subsequent rectal carcinomas we will present the associated incidence of rectal wall damage such as proctitis, stenosis and recto-vaginal fistula and evaluate the incidence of rectal cancer with regard to the expected incidence of second cancers.¹

Most patients had little trouble immediately following completion of radiation. Somewhere between the fifth and ninth month clinical symptoms arose either on the basis of ulceration (with painful defecation, and the passage of mucous and blood) or stenosis with obstruction.

In nine instances of stenosis colostomies were necessary in eight after failure of conservative measures.

Ulcers associated with proctitis were at the level of the cervix on anterior rectal wall. Nine of 11 of these required operations for relief and correction. The cytological changes described by Warren were evident.⁷

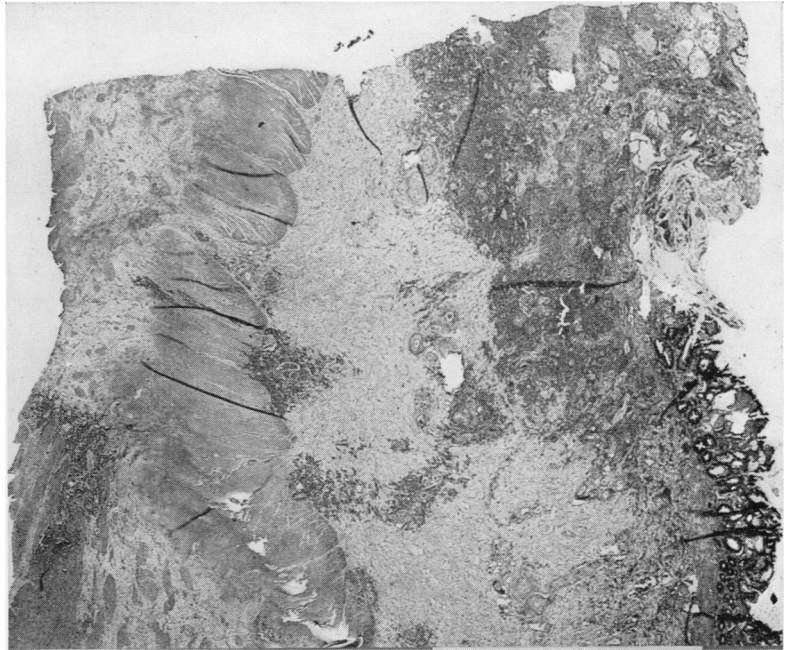
Six patients who ultimately developed recto-vaginal fistulae had variable courses. One was successfully treated with primary resection and anastomosis. In view of difficulties experienced by patients treated by colostomy, primary resection with anastomosis is the procedure of choice. Two patients had colostomies for chronic ulcers

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FIG. 1. Segment of rectosigmoid colon with focal necrosis and ulceration consistent with radiation change.



with pain and bleeding prior to the development of recto-vaginal fistulas. The time lapse from colostomy to fistula was 3½ years in one and 16 years in the other. Two patients developed recto-vaginal fistula prior to colostomy, the only therapy applied.

Adeno-carcinomas of Rectum and Recto-sigmoid Occurring Subsequent to Radiation Therapy of Carcinoma of Cervix Uteri

There were six cases of adeno-carcinoma of the rectum and recto-sigmoid subsequent to irradiation therapy. The clinical courses of most followed the pattern described by Smith.⁴ Early reactive proctitis was followed by a latent symptomless period before symptoms of secondary proctitis appeared. This intermediate period varied from 2½ to 18 months. The secondary proctitis tended to subside after a period of 2 years. At this time there was usually residual induration in the recto-vaginal septum and parametrial areas. The rectal and recto-sigmoidal carcinomas appeared after periods of from 14 months to 25 years.

The following case reports are presented in brief with detailed consideration of two cases. Details of the roentgen dosage and technic of therapy are omitted although Ingleman-Sundberg² believes that the degree of damage was directly proportional to the amount of radiation delivered. Strickland and Gregory,⁵ after quantitative analyses of dose delivered and effect, concluded that "Rectal damage would appear to depend on some factor in addition to the dose level to which the rectum is raised, during the course of treatment."

Case Reports

Case 1. A 25-year-old woman with Grade III epidermoid carcinoma of the cervix was treated in 1936 with little early rectal reaction. Six months later there was a severe episode of rectal bleeding, diarrhea, tenesmus and bearing down rectal pain. After a quiet interval of 2½ years another episode of bleeding and abdominal cramps subsided. At this time there was induration in the right hemipelvis. Ten years after completion of therapy induration appeared in the left hemipelvis. There were no further rectal symptoms until 19 years after original irradiation. Then a 9 months' period of diarrhea, bloody mucous and frank rectal bleeding ensued. An adeno-carcinoma of the recto-

TABLE 1. *Severe Benign Complications of Therapy*

Total Cases Treated	913
Rectal Ulceration	11
Stenosis	9
Recto-vaginal Fistula	6
Perforated Sigmoid	1

TABLE 2. *Subsequent Second Carcinomas Following Therapy for Carcinoma of the Cervix*

Total Patients Treated	913
Adeno-ca Rectum and Rectosigmoid	6
Breast	6
Ovary	2
Fallopian Tube	1
Urethra	1
Vulva	1
Anus	1
Stomach	1
Lung	1
Thyroid	1
Sarcoma	2
Lipo and Neurofibroma	
Concurrent Malignancy	2
Cervix and Rectum	
Cervix and Lymphosarcoma	

sigmoid was found in a rubbery, thickened segment. A low anterior resection was done. The patient is living and well 26 years after initial treatment.

Case 2. A 65-year-old woman had epidermoid, Grade III, Stage 1 carcinoma of the cervix; therapy was completed in 1956. An early proctitis with tenesmus and frequent stools subsided in 2 weeks. Two and one half months after completion of therapy a 3 months' period of tenesmus and frequent stools with urgency and a bloody mucous discharge followed. At no time was there induration in the septum. She continued to have attacks of mild "colitis." Four years post-therapy an adenocarcinoma of the rectum with hepatic metastases was found. She died 7 months after operation.

Case 3. A 59-year-old woman had epidermoid, Grade III, Stage II carcinoma of the cervix; treatment was completed in 1955. There was no early reaction suggesting proctitis. Eighteen months post-therapy an episode of rectal bleeding subsided and then recurred at 23 months. An elastic induration of the recto-vaginal septum persisted. Five and one-half years post-therapy a colonic obstruction due to an adenocarcinoma of the rectum with hepatic metastases was operated upon by a low anterior resection. Three months following operation a second obstruction required colostomy. She died 3 months later, 6 years post-irradiation.

Case 4. A 44-year-old woman had epidermoid, Grade II, Stage 1 carcinoma of the cervical stump;

TABLE 3.

Case	Interval Irradiation to Occurrence Tumor	Type Tumor	Grade	Extent Invasion	Radiation Effect
I. L. H. 25 yrs.	19 yrs.	Epid. ca Cervix Papillary Adeno-ca Rectum	III II	Dukes B	4+
II. B. L. 65 yrs.	4 yrs.	Epid. ca Cervix Adeno-ca Recto-sigmoid	III II	Dukes A	Biopsy Only
III. R. H. 59 yrs.	5½ yrs.	Epid. ca Cervix Adeno ca Rectum	III III	Dukes C	2+
IV. S. P. 44 yrs.	14 mos.	Epid. ca Cervix Adeno ca Rectum	II	Dukes B	4+
V. Z. P. 42 yrs.	14 yrs.	Epid. ca Cervix Papillary Adeno-ca Rectum	III II	Dukes A	1+
VI. G. D. 45 yrs.	25 yrs.	Epid. ca Cervix Adeno-ca Rectum	II	Dukes B	2+

* Dukes Classification A. Invasion muscle only.

B. Invasion to serosa.

C. Invasion through serosa with node involvement, etc.

therapy was concluded in 1958. Her immediate post-radiation postoperative course is unknown, as she returned home to Alaska. Fourteen months post-therapy an adeno-carcinoma of the rectum was diagnosed and resected in a Public Health Hospital. The patient is living and well.

Case 5. A 42-year-old woman had a history of a brownish vaginal discharge for one year and intermenstrual bleeding for 3 months. On Physical Examination there was a rounded, firm, moderately movable mass extending down into the pelvis from just below the umbilicus. The cervix was replaced by a large, bulky, ulcerated friable mass extending into posterior and right lateral fornices.

Irradiation treatment was completed in May 1938. There was no immediate rectal reaction. One year later she had repeated episodes of five to six bowel movements daily of normal formed stools associated with slight bleeding. There was a rubbery induration of the recto-vaginal septum which persisted. Two and one-half years later, after a symptom-free interval, she again had periods of occasional diarrhea with bleeding.

She remained symptom free until March 1952, 14 years after completion of therapy. She was examined in May 1952 when bloody stools and tenesmus recurred.

At Sigmoidoscopic Examination in May 1952, an irregular, shaggy mass resting on a sessile base 12 cm. from the dentate line on the anterior rectal wall 2.5 cm. in diameter was found.

A biopsy taken from the inferior margin of this ulcerated tumor was interpreted as glandular papilloma. Since grossly the lesion was a classical adeno-carcinoma. Combined abdomino-perineal resection was carried out.

Pathology Report: Specimen consists of an anus, portion of rectum and sigmoid colon. The entire specimen measures 36 cm. in length. Twelve cm. from the pectinate line there is a tumor which measures 2.5 cm. in diameter. The tumor has a rough papillary surface, is attached on a sessile base and appears to be slightly infiltrating the underlying wall. It does not extend entirely through the serosa, however. There are no enlarged nodes. The remaining portions of the colon show a loss of normal folds. The mucosal surface is slick and glistening. No other abnormalities are noted. Representative portions are selected for section.

Histologic Examination: Sections show a papillary structure composed of immature and atypical glandular structures which have invaded the stalk and underlying submucosa but has not extended into the muscularis. There is a moderate amount of subserosal fibrous tissue with telangiectatic

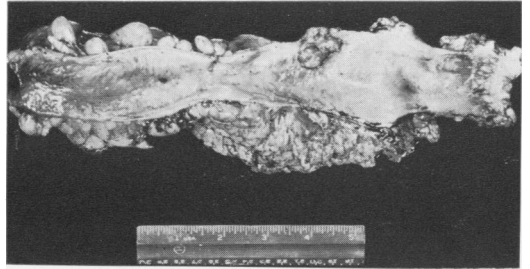


FIG. 2. Gross specimen illustrates the marked fibrosis of the rectal wall adjacent to the tumor and the stenosis of the lumen proximal to the tumor.

changes in the wall blood vessels consistent with old radiation damage.

Diagnosis: *Papillary Adenocarcinoma of Rectum with Early Invasion.* The patient is now 29 years post-irradiation, in excellent health without evidence of cervical or rectal disease. A proper biopsy was not possible due to fibrotic fixation of the recto-vaginal septum. Todd² suggested biopsy risked producing a recto-vaginal fistula because of radiation damage and ischemia in the area of biopsy.

Case 6. A 45-year-old woman had spotty vagi-

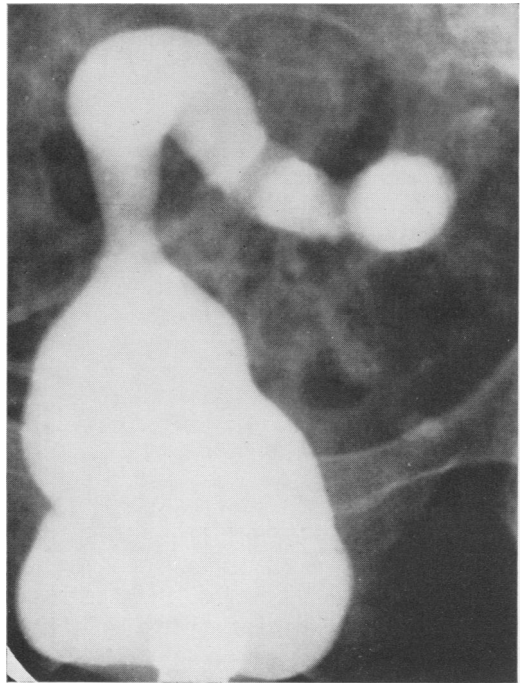


FIG. 3. On barium enema x-ray, a smooth, fixed narrowing in the rectosigmoidal area over a distance of 2 cm. was interpreted to be consistent with late radiation fibrosis with stenosis.

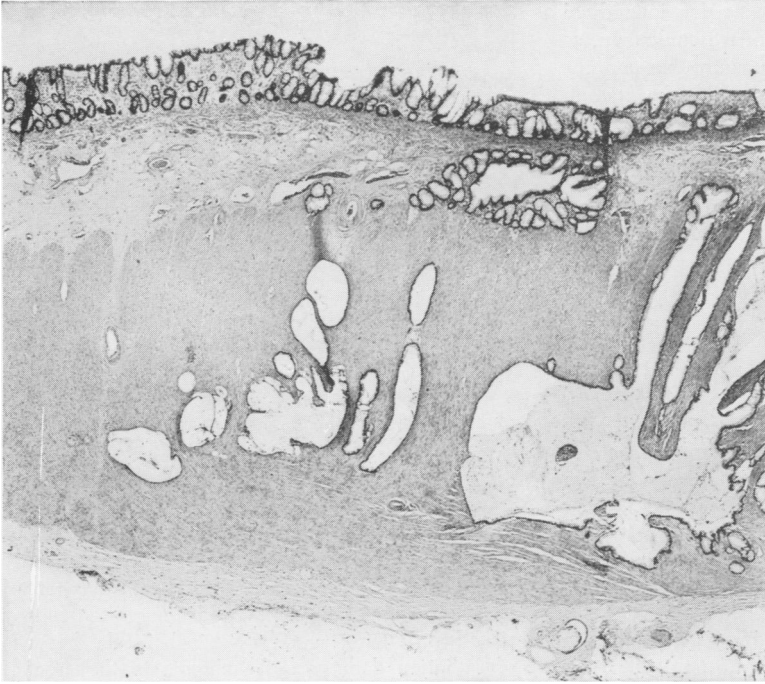


FIG. 4. *Microscopic Diagnosis:* Well differentiated mucinous adenocarcinoma of colon and radiation reaction.

nal bleeding and menorrhagia for 8 weeks duration.

On physical examination, a firm cervix was enlarged to twice normal size and there was a firm, friable ulcerated mass on the posterior lip. The uterus was enlarged to $1\frac{1}{2}$ times normal size, firm but movable.

Irradiation therapy was completed on 6 July 1936. There was complete healing of the cervical lesion with relatively little rectal reaction. Nine months post-therapy she had bearing down lower abdominal pain, frequent loose stools and bright red rectal bleeding which subsided.

Twenty months post-therapy painless rectal bleeding occurred. On sigmoidoscopic examination the rectal mucosa of the anterior wall was smooth and pale. There was telangiectasis and scarring 13 cm. from the anus and a marked stenosis beyond which the scope could not be passed. The bleeding subsided.

By June 1961, 25 years after radiation therapy she complained of increased difficulty with defecation. Stools were more frequent, three to four daily associated with cramping abdominal pain. The stools were normal but streaked with blood. On sigmoidoscopic examination, at the 10 cm. level there was a marked, fixed narrowing of the rectal lumen to 1 cm. The scope could not be advanced beyond this point. No tumor could be seen.

On barium enema x-ray, there was a smooth, fixed narrowing in the recto-sigmoidal area over a distance of 2 cm. interpreted as consistent with late radiation fibrosis with stenosis. On July 10, 1961 low anterior resection of the involved segment was performed.

Pathology Report: The specimen consists of a segment of colon 9.5 cm. in length with a moderate amount of mesentery attached. The serosa for the most part is smooth and glistening; however, 1.5 cm. from one resected margin there is slight puckering of the serosa and the adjacent mesentery is hemorrhagic and slightly indurated. The wall of the specimen is not thickened. The mucosa is slightly edematous, partially smooth and glistening and in some areas shows a slightly pebbly appearance. In the region of the puckering of the serosa the mucosa shows a narrow linear depressed area which involves the entire bowel circumference. In this same region the circumference of the bowel measures 3 cm. whereas the remaining bowel circumference measures 5 cm.

Histology: Sections of the colon in the area of the stenosis show smaller and slightly dilated glandular structures extending from the mucosa through all coats of the bowel wall into the serosal fat. These glandular structures are lined for the most part by well differentiated columnar cells which show abundant mucin production. There is no evidence of blood vessel or lymphatic involvement by tumor. The submucosa of the remaining

colon is edematous. There is a moderate amount of subserosal fibrous tissue containing small blood vessels, many of which are telangiectatic.

The immediate postoperative course was uneventful and she was discharged from the hospital only to return in late August, 1961 with an ileal-rectal fistula. An attempt at surgical correction ended in death. There was no evidence of persistence of either of the primary carcinomas at autopsy.

This case points out that a long-standing stenosis distal to an adeno-carcinoma in a field of previous radiation therapy can obscure the presence of this new malignant lesion.

Discussion

It is not certain that adeno-carcinoma of the rectum occurring after radiation therapy of uterine cervical carcinoma is a cause and effect relationship. Nor does irradiation therapy of cervical cancer involve a significant risk of benign complications or malignant disease.

All rectal and recto-sigmoidal carcinomas which follow irradiation of the uterine cervix may not be recognized or reported. The long interval between irradiation and occurrence of the carcinoma may obscure a possible association. Furthermore microscopic evidence of radiation damage to rectal mucosa may have diminished to a non-recognizable degree.

Conclusions

Six cases of carcinoma of the rectum and recto-sigmoid subsequent to irradiation therapy of carcinoma of the uterine cervix have been reported.

The interval between irradiation therapy and appearance of a rectal neoplasm of up to 25 years suggests that patients with: *early proctitis, secondary proctitis, stenosis or induration of recto-vaginal septum* should be followed and examined for the presence of a rectal or recto-sigmoidal carcinoma.

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