**Introduction**

Early gastrointestinal complications of radiotherapy for pelvic lesions are quite common and usually present no problem in their recognition and differentiation from either delayed effects of irradiation or recurrence of malignancy (Requarth and Roberts \(^{26}\) and Anderson, Witkowski and Pontius \(^{2}\)). These early complications are characterized by acute inflammation, tenesmus, pain, bleeding and diarrhea, ordinarily occurring within a few weeks to a month following completion of x-ray therapy. Commonly, the symptoms subside within a few months. However, delayed irradiation damage, such as the development of fecal fistulas and intestinal obstruction, may occur many years following completion of radiation therapy for malignant disease of the pelvis.

Craig and Buie \(^{9}\) report a series of 200 cases of irradiation proctitis following x-ray therapy for carcinoma of the cervix. In their series symptoms occurred in 43% of the cases within one month, 27% developed symptoms in one to six months and 16% of the cases developed symptoms following a period of one year. The remaining 14% of the cases manifested symptoms: several years from the completion of treatment, with one case having a delayed interval of seven years.

In one case an ileovesical and ileoileal fistula developed 14 years following irradiation for carcinoma of the cervix. These fistulas resulted in longstanding morbidity and prostration. Following surgical correction of the fistulas, rapid improvement and weight gain occurred (Simpson and Spaulding \(^{25}\)). Late complications of radiation therapy are therefore less well known and more frequently confused with recurrent carcinoma. In a series of 621 cases irradiated for carcinoma of the cervix, the chief complications were obstructive phenomena, mainly due to adhesive fibrous bands. Proctitis and rectovaginal and vesicovaginal fistulas were also frequently encountered.\(^{18}\) Hoffman\(^{14}\) reported on eight cases of stenosis of the ileum following irradiation for carcinoma of the uterine cervix and the successful surgical correction by resection of the diseased segment. In addition he reported on five cases of ureteral stenosis, many years following irradiation for carcinoma of the cervix and the uterine body, with successful treatment by means of free implantation of the ureter after resection of the stenotic segment, utilizing an end-to-end anastomosis. Perkins and Sput \(^{19}\) discussed nine cases of irradiation stenosis of the rectosigmoid and transverse colon. The histologic findings were characterized by obliterator vasculitis with subendothelial foam cell deposits, leading to ischemic changes with riecosis of the wall and subsequent perforation. The finding of subendothelial swelling, fibrosis and foam cell deposition within small caliber arteries and arterioles leading to stenosis with subsequent necrosis and fibrosis of the affected organs has been recognized by numerous investigators as the basic cause of the irradiation ulcer and other types of irradiation injury, in particular, the delayed type of irradiation damage.\(^{12,22,24,29,31,32}\)

That fibrosis is indeed very important, in producing shrinkage of the length of the bowel segment is shown by Spratt et al \(^{26}\) in experimental studies in dogs. From an, exteriorized 5 cm long small bowel segment exposed to 4,000 rads, in one sitting, only a string of scar tissue of 2 mm length remained eight months following irradiation. Brick \(^{3}\) in a series of 100 cases concluded that the maximum safe level for the stomach and bowel is 4,000 roentgens and for the colon 4,500 roentgens. Brown differentiates the delayed effects of irradiation, which are often and quite understandably confused with a recurrence of tumor, from the immediate irradiation effects,
such as tenesmus, proctitis, bloody stools and diarrhea. These delayed changes comprise bowel obstruction, fecal fistulas, and fibrous bands. In most instances the obstruction is secondary to incarceration rather than to stenosis of the lumen. There is also progressive vascular obliteration of the small caliber vessels. Those patients have often a conspicuously “frozen pelvis,” and therefore often give an impression of having a recurrence of tumor. Surgery for any reason in those cases increases the incidence of morbidity (Robinson21).

Although morbidity following irradiation is quite common, mortality is a rather uncommon complication and has been reported only twice following relatively small dosages of x-rays, leading to small bowel necrosis after 1,500 roentgens (Cathie6). It is the purpose of this paper to report a case where increased individual susceptibility to irradiation with a fatal outcome followed full dose irradiation therapy for carcinoma of the cervix subsequent to hysterectomy:

REPORT OF A CASE

In March 1959, a 35-year-old white housewife underwent a total hysterectomy because of carcinoma of the cervix. The specimen revealed extensive residual intraepithelial squamous cell carcinoma of the cervix with an area of microinvasion (Fig. 1). Postoperatively the patient had a course of cobalt radiation therapy. She received 4,000 roentgens anteriorly and 3,500 roentgens posteriorly, using a total of four portals over a period of six weeks. This treatment was tolerated well.

In April 1961, more than two years after the operation and irradiation, she complained of left lower quadrant pains. In June she complained of epigastric pain with occasional episodes of vomiting. By July she had lost five pounds, had bloody stools and her complaints had become more severe. Because of the persistence of bloody stools, an exploratory laparotomy was performed. At operation there was an area of necrosis and fibrosis involving approximately eight inches of the lower ileum. This segment of small bowel, was resected and an anastomosis was made between the ileum and the ascending colon, leaving a blind segment of terminal ileum in place. A side-to-side colostomy anastomosis of the sigmoid was performed because of a stenotic and fibrotic segment in the lower portion. An external fecal fistula developed near the anastomosis, but drainage from it gradually diminished. In August, however, the fecal fistula recurred, leading to additional abdominal surgery after continuous draining of the fistula for one month. The fistula was resected and a colostomy stoma was constructed using the lowest remaining portion of the descending colon.

In March 1962, having gained eight pounds since her preceding surgery, she was readmitted for the purpose of resecing all involved segments of small and large bowel and reconstruction of the continuity of the gastrointestinal tract. The previously bypassed small atrophic terminal ileum was resected along with the adjacent cecum and ascending colon up to the previous ileocolic anastomosis. There was marked fibrous reaction of all the tissue in the pelvis making dissection difficult. The upper rectosigmoid and part of the’ descending colon were resected with an anastomosis performed between the descending colon and the rectum in order to reestablish the continuity of the intestinal tract and enable her to have normal bowel movements. Shortly thereafter a fecal fistula developed between the site of the anastomosis and the suprapubic region. In May repair of the fecal fistula was attempted. Dihiscence of the coloproctic anastomosis was found and a diverting ileostomy was made. From October 23 to October 29, 1962, she was hospitalized because of weakness, carpopedal spasm and other musculoskeletal signs.

On admission her hematocrit was 40%, hemoglobin 13 gm%, white cell count 23,700/cu mm, BUN 43%, phosphorus 7.2 mg%, potassium 6.7 mEq/l, calcium 3.9 mEq/l, sodium 132 mEq/l, chloride 72 mEq/l and CO2 combining power was 25 mEq/l. She improved after having received several blood transfusions as well as intravenous fluids, calcium, high caloric diet and symptomatic treatment.

Two days later she was readmitted because of dehydration, weight loss, continued vomiting, muscle cramps and an episode of unconsciousness when she was found at home with mucus exuding from her mouth and with a
blood pressure of 80/40 mm of mercury. She again received intravenous fluids, calcium and other therapy, but continued to vomit and to be extremely weak and unable to care for herself.

On this admission her hematocrit had been 45%, WBC 8,700, serum potassium 2.9 mEq/l, sodium 144 mEq/l, chloride 98 mEq/l and C02 18 mEq/l. The serum calcium was 4.0 mEq/l and phosphorus 1.7 mg%.

On October 13th the BUN had been 42%, the serum phosphorus 3.6 mg%, albumin 3.1 gm and globulin 4.6 gm%. The calcium on repeat examination was 4.6 mEq/l and magnesium 1.0 mg% (serum magnesium normal level is 1.5-2.5 mg%). Urine calcium was 0.025 mEq/l, urine sodium was 0.75 mEq/l and the urine potassium 32.5 mEq/l. She weighed only 70 lbs at this time. She was treated with massive volumes of plasma intravenously as well as electrolytes, including sodium, potassium, calcium and magnesium. Between November 12 and her discharge on November 24, her intake and output were recorded and she was weighed daily. At discharge her weight was 77.5 lbs. The vomiting and nausea had disappeared. She was eating and drinking well, walking around and felt much stronger. Fluid intake had varied from three to nine liters. The output from the ileostomy varied between 5000 and 9000 cc for 24 hours. The BUN had fallen to 17 mg% and her serum creatinine was 0.5 mg%.

An interesting aspect of the case was the comparative electrolyte and nitrogen concentrations in the ileostomy fluid, the urine and the blood. Her urine output averaged only 180-200 cc per day during the last ten days of hospitalization. The initial urine sodium concentration was 0.75 mEq/l (the serum sodium was 132 mEq/l) thus showing that the renal tubules reabsorbed sodium very effectively. The ileostomy fluid sodium varied from 20-55 mEq/l and the potassium averaged 20 mEq/l. The ileostomy fluid also contained 20 mEq/l of urea nitrogen, 20 mg% of creatinine and 25 mg of uric acid. These amounts varied considerably in several specimens taken at several times.

About three weeks after being dismissed she was seen at her home in shock and barely conscious. At this time she was transferred to another hospital where she was admitted to a renal electrolyte clinic. She returned to this hospital clinic twice because the doctors intended to reestablish the continuity of her intestinal tract. However, on February 5, 1963 she again had suffered severe nausea and vomiting for three days and was in shock. She was hospitalized, received massive infusions of plasma and electrolytes and water balance was reestablished. Attempts to diminish the volume discharged from the ileostomy by means of various drugs were unsuccessful. At this time she was placed on a gluten free diet because she developed a nontropical sprue syndrome. She became hypotensive on several occasions but was rescued each time by the administration of blood and plasma, restoring it to a normal level. The attending surgeon found it impossible to reestablish the continuity of the intestinal tract owing to unhealed areas in the sigmoid colon, evident on proctoscopy. In the course of her hospitalization she did not improve, lost hope of recovery and requested on several occasions that all treatment be discontinued. A progress note on February 17 stated that all therapeutic efforts had been ineffective. On the 18th the patient was again found in shock and requested to be left alone when arrangements were made to treat her. She expired on the same day.

AUTOPSY FINDINGS

The body was that of a middle-aged and extremely emaciated white female. Externally nothing remarkable was noted on the head, neck, chest or extremities. The abdomen was flat. There were numerous midabdominal scars from previously performed surgeries. There was a patent ileostomy stoma in the left lower quadrant. The stoma was moist, edematous and moderately hemorrhagic, but the lumen was patent. Internally nothing remarkable was noted within the neck region. The heart and lungs were essentially normal. The abdomen contained no free fluid. There were numerous dense adhesions between the abdominal wall and the small bowel loops and remaining large bowel. There was surgical absence of the terminal ileum, proximal portion of the ascending colon and sigmoid colon with adjacent portions of the descending colon and rectum, as well as the uterus and adnexae. Dense adhesions between the pelvic floor and the urinary bladder were also observed. Around the sacrum and promontory, dense fibrous layers were observed which fused with the root of the mesentery. Most of the small bowel loops were thick-walled and had a pipe-stem consistency. There was no lymphadenopathy and no gross evidence of tumor recurrence. The liver, spleen and pancreas as well as the esophagus, stomach and duodenum appeared essentially normal.

MICROSCOPIC FINDINGS

The cardiorespiratory system revealed no abnormalities. The liver, spleen, pancreas, stomach, esophagus and duodenum were essentially within normal limits. Significant changes, however, were apparent on mi-
Fig. 2. — Left. Bowel with denuded mucosa and submucosa inflammatory infiltrates. (H. & E. 100x).

Fig 3. — Right. Subserosal ans perivascular fibrosis and narrowing of the vessel lumen. (H. & E. 100x).

Fig. 4.— Left. Subendothelial fibrosis of the capillary with severe stenosis of the lumen. (H. & E. 450x).

Fig 5.— Right. Vessel with severe subendothelial fibrosis and foam cell deposits. (H. & E. 450x).

Fig 6.— Left. Submucosal space with fibrosis showing a stenosing arteriole and dilated capillaries. (H. & E. 100x).

Fig 7.— Right. Submucosal space with irradiation fibroblast. (H. & E. 1000x oil immersion).
crosscopic section of the remainder of the lower intestinal tract. The serosal surfaces revealed large fibrous tags and extensive fibrosis of the entire wall of some sections. There was extensive fibrous matting of many loops. The fibrotic process extended in areas through all the layers of the individual bowel sections, resulting in complete obliteration of the submucosal space, muscularis and capillaries. The overlying mucosa was in many regions denuded and in other areas ulcerated and heavily infiltrated by inflammatory cells (Fig. 2). In other sections there was perivascular fibrosis, as well as extensive narrowing of the small vascular channels of the serosa and other portions of the gut wall (Fig. 3). The major changes of the vessels were within the subendothelial space. There were large areas of fibrosis leading in many regions to partial or almost complete stenosis of the lumina (Fig. 4). Other sections revealed foam cell deposits within the subendothelial space (Fig. 5). Some of the larger vascular channels showed fragmentation of the elastic lamellae and the internal elastica. Special stains, including trichrome stain and Van Cieson elastic stain, demonstrated marked fibrosis of the subendothelial space, leading in many areas to complete obliteration of the existing vascular channels. Some areas were encountered in which both hypertrophied and stenotic vascular channels alternated with capillaries showing dilatation of their lumina and heavy engorgement with erythrocytes (Fig. 6). The submucosal space revealed dense fibrosis with an occasional giant radiation fibroblast (Fig. 7).

**DISCUSSION**

The case presented supports the concept that the individual susceptibility of patients may vary considerably in regards to their reaction to the injurious effects of irradiation. In general, dosages of 4000-5000 roentgens are well tolerated. This has been in particular stressed by Kottmeier and Gray and Hoffman. The delayed gastrointestinal complications following irradiation therapy are primarily those of bowel obstruction, either of the rectosigmoid colon or of the ileum, and fistula formation, especially between the rectum and the vagina (Todd). The complications are normally of a localized nature and be dependent upon the nature of the tissue irradiated. The onset of symptoms may occur at any time, from several months after the completion of treatment to many years. It is difficult to explain the pathogenesis of a fibrotic stricture or fistula which appears 10, 15 or even 25 years after complete healing of an acute inflammatory radiation reaction. It is probably due to a combination of decreased tissue reserve available for repair and reduced circulation, viability and nutrition. Other injurious effects such as inflammation and bacterial action are certainly contributing factors. It is interesting that in some cases a fecal fistula will close if a successful diversion of the fecal stream is accomplishable by a colostomy or ileostomy. The time element, however, is apparently important since months are often required to make a fistula close. In many instances bowel obstruction occurs due to incarceration behind adhesive bands which formed as a consequence of irradiation. The delayed complications follow intrinsic, as well as extrinsic irradiation, either from radium application through the vagina or external radiation therapy utilizing cobalt or x-ray treatment. In many of those treated, a frozen pelvis results, giving the impression of tumor recurrence. The differential diagnosis is often quite difficult and cannot be solved until death has ensued. The presented case illustrates an increased susceptibility of the individual to irradiation, resulting in an extensive degree of fibrosis, fecal fistula and inability of the tissues to heal, therefore making surgical correction of the fecal fistula difficult or impossible. Surgery in previously irradiated tissues is followed by an extensive degree of morbidity as well as mortality (Robinson). In many cases after successful resection of a stenotic segment secondary to irradiation, complete recovery will result. In other cases, and in particular in this one, different bowel loops are affected, even if they are distant from the area of irradiation. The resulting complications, secondary to metabolic disturbances, mainly of nutrition, water and electrolytes, are stressed by the hospital course of the patient. It is well accepted that the delayed effects of irradiation relate to occlusive vascular phenomena and subsequent fibrosis. This case illustrates, however, that metabolic disturbances leading to sprue like symptoms may characterize, somewhat, late as well as early complications. Such metabolic irradiation changes may relate to depolymerization of mucopolysaccharides and connective tissue ground substances which lead to defective absorption of nutritional essentials such as glucose, thionine and pyridoxine. The decrease in these substances leads to edema and increased capillary permeability. Other important changes are destruction of mitochondria and other cell components as well as nuclei. These changes can be produced by 3000 rads. The reduced absorption is directly related to a reduction or absence of mitochondria. Other factors relating to decreased absorption in the early as well as the late phases of the radiation syndrome are the disruption and degranulation of the mast cells with release of heparin, histamine and 5-hydroxy-tryptamine. The latter two lead to the formation of leaks in the endothelium of small blood vessels.
Studies carried out with high resolution autoradiography after administration of thymidine, labelled with radioac-
tive tritium, on the gastrointestinal epithelium of previ-
ously irradiated animals, showed reduction of DNA syn-
thesis directly proportional to the amount of irradiation
delivered. These changes are seen with doses as low as 200 rads.13

Micromolecular changes can be demonstrated electro-
microscopically in the mucosal villi secured by biopsy
by means of Crosby’s sound. The biopsies were done in
patients suffering from carcinoma of the cervix and con-
sequently irradiated with small doses. After 100 rads, the
authors noticed the presence of large-sized granules of
dishomogenous structure which are not seen in normal
mucosa. The authors tentatively submit the hypothesis
that the granular formations probably represent different
metabolic conditions in the structure which make up the
enzymatic patrimony of the cells.26

**COMMENT**

The presented case illustrates a patient who succumbed
two and a half years later to the effects of bowel compli-
cations after radiation therapy for microinvasive carcino-
ma of the uterine cervix. Following a two and a half year
interval essentially free of complications, she developed
signs and symptoms suggestive of bowel obstructions,
possibly due to recurrence of the tumor.

The autopsy revealed no evidence of recurrence of tu-
mor in any of the sections and the most striking features
were severe fibrosis of the entire wall of the individual
bowel loops and ischemic ulcerations of the mucosa
at many points. Fecal fistulas were found which were
also the result of ischemia and subsequent necrosis of
the tissues. The smaller vascular channels and the ar-
terioles were significantly involved and showed striking
narrowing of their lumina secondary to subendothelial fi-
brosis and foam cell deposits with stenosis. The remain-
ing portions of the bowel wall were in areas completely
fibrotic and matted with the surrounding tissues. The
case stresses the difference in individual susceptibility
to irradiation as well as the poor wound healing and the
increased hazards of surgery in previously irradiated tis-
sues.21 It is to be anticipated that as methods of irradia-
tion treatment improve and more accurate dosimetry is
developed and also when better knowledge is gained
of cancer and radiation biology, the incidence of those
complications will continue to decline as it has in the
past.7 Utilization of irradiation treatment in the control of
malignant disease of the abdominal or pelvic organs has
always been associated with some injury to the gastroin-
testinal tract in a small proportion of patients. The use of
irradiation treatment is a double edged sword which will
result in injury to the surrounding normal tissues. This
must be accepted as a calculated risk, therefore irradia-
tion therapy should be used very judiciously and only
with very strict indication. Some authors have estimated
the incidence of gastrointestinal complications for pel-
vic irradiation to be from 1% to 17% (Brown14). These
figures, however, can only be of relative value because
of differences in techniques, differences in evaluating
the degree of injury and the heterogeneity of the patient
population. The actual incidence of complications which
will result in permanently disabling conditions requiring
surgical intervention is approximately in the order of 2%
(Brown14). Gastrointestinal complications attributed to ir-
radiation have most frequently followed the application
of intracavitary radium therapy in treatment of cancer of
the uterine cervix or uterus. The problem is an increas-
ing one because of the increased availability of radiation
therapy operating at super voltage levels.10,16

There is apparently a considerable degree of unex-
plained variability and susceptibility of the response of
the individual patient to irradiation therapy. Also the
incidence and the variety of complications as well as the
effectiveness of tumor control appear to be in general
related to time-dose-volume relationships. In this regard
the larger the total dose or the volume irradiated or the
more rapidly the treatment is delivered, the more promi-
nent will be the gastrointestinal complications.30

The gastrointestinal tract has irradiation sensitivities
second only to that of the bone marrow (DesJardins10).30
The small intestine is in particular susceptible to radia-
tion injury compared to the colon, but is ordinarily less
frequently the site of complications in the clinical prac-
tice, because of the fact that the small bowel is a less
fixed organ than the colon. Fixed daily portals or radium
placements used in radiation therapy will expose a given
loop of small bowel less frequently to irradiation than is
the case with the large bowel and only a fraction of the
total dose applied will strike the small bowel. On the
other hand, in patients who have had previous abdomi-
nal or pelvic surgery or a combination of irradiation and
surgery, loops of small bowel may become immobilized
by adhesions and therefore receive the total delivered
dosage. In those patients, a much higher incidence of ir-
radiation complications involving morbidity and mortality
of the small intestine is to be anticipated (Conrad8 and
McIntosh and Hutton17).
The paper presents a case of microinvasive carcinoma of the uterine cervix, treated with a combination of surgery followed by a full course of tumor dose irradiation. The postirradiation complications, the difference of individual susceptibility, as well as the strict indication for irradiation are stressed. The course of events strongly suggests that in cases of in situ carcinoma of the uterine cervix, even with microinvasion, surgery alone would be more beneficial to the patient than a combination of surgery and irradiation. Since such treatment seems to have much greater morbidity and mortality than surgery alone. On the other hand, in cases of advanced carcinoma of the pelvic region, irradiation certainly is indicated, since at this stage the development of delayed irradiation damage will trail the inevitable course of advanced pelvis carcinoma.

Zusammenfassung

Riassunto
Questo lavoro presenta un caso di microinvasione carcinoma tosa del cervice uterino, trattato mediante chirurgia e dosis total de irradiación. Se enfatizan las complicaciones post-irradiación, diferencias en tolerancia a la misma, e indicaciones, estrictas. La experiencia sugiere en forma determinante que en los casos de carcinoma in situ del cuello uterino, aún con microinvasión, la cirugía por sí sola es de más beneficio que el tratamiento combinado, debido a que tél último presenta mayor morbilidad y mortalidad. Por el contrario, en casos avanzados del área pélvica, la irradiación debe utilizarse, ya que durante este estadio los efectos secundarios pueden ser menores a los de un carcinoma pélvico avanzado.

Resumen
Se presenta una caso de carcinoma microinvasor del cuello uterino, tratado mediante cirugía y dosis total de irradiación. Se enfatizan las complicaciones post-irradiación, diferencias en tolerancia a la misma, e indicaciones, estrictas. La experiencia sugiere que en los casos de carcinoma in situ del cuello uterino, aún con microinvasión, la cirugía por sí sola es de más beneficio que el tratamiento combinado, debido a que tél último presenta mayor morbilidad y mortalidad. Por el contrario, en casos avanzados del área pélvica, la irradiación debe utilizarse, ya que durante este estadio los efectos secundarios pueden ser menores a los de un carcinoma pélvico avanzado.

Sumário
O presente trabalho apresenta um caso de microcarcinoma invasivo do cólo uterino que foi tratado por um processo combinado de cirurgia seguida de um curso completo de irradiação. São expressadas as complicações post-irradiação, as diferenças da susceptibilidade individual, bem como as indicações estritas da irradiação. O curso dos eventos firmemente sugerem que em casos de carcinoma “in situ” do cólo uterino mesmo com microinvasão, a cirurgia isoladamente pode ser mais benéfica para a paciente do que a combinação da cirurgia e a irradiação, desde que tal tratamento parecer ter uma morbidade e mortalidade maior que a cirurgia isoladamente. De outro lado, em casos de carcinoma avançados da região pélvica, a irradiação certamente é indicada, desde que este estágio dedesenvolvimento dos danos tardios da irradiação seguirão inevitavelmente o curso do carcinoma pélvico avançado.

References


