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Pathologic Changes Secondary to Radiation

Morgan Berthrong, M.D.

Department of Pathology, Penrose Hospital, Colorado Springs, Colorado, U.S.A.

In order to be effective in the treatment of disease, especially neoplastic disease, radiation necessarily needs to be given in large doses. When treating tumors with high radiosensitivity in tissue of relatively low radiosensitivity, few complications of therapy occur. Frequently, however, the differential of sensitivity to radiation between the neoplasm and normal tissues exposed is small and the incidence of radiation injury to normal tissues becomes significant. Nowhere is this more apparent than in treatment of neoplasms during which the alimentary canal is heavily radiated. The following discussion will describe the pathologic changes that occur in the various units of the exposed alimentary tract and in various components of those units during and especially months or years after radiation therapy. The usual rapid and effective regeneration of the rapid-renewal cell system after injury will be noted. The serious delayed manifestations of injury to the fibrovascular tissues with resulting delayed complications of ulcerations, stenoses, fistula formation, and obstructing adhesions will be emphasized. Brief discussions of several other organ systems injured by radiation will be presented.

The development of second neoplasms as a result of radiation will be briefly mentioned and discussed from three standpoints: very low levels, low levels, and high levels of radiation.

There are no pathognomonic pathological changes of radiation injury [1]! Necrotic cells are simply necrotic cells. Acute inflammation in acutely injured tissue is nonspecific. Homogenization of collagen, atypical fibroblasts, swollen endothelial cells, telangectasia of thin-walled vessels, intimal proliferation of veins and arteries with or without foam cells, abnormal epithelial atrophy or regeneration, and bizarre cell nuclear sizes or staining all may occur in reactions to injury other than radiation. An important feature of radiation injury, i.e., the loss of the volume of the capillary bed, cannot be recognized with certainty in routine histologic sections but only by special injection studies or by other morphometric techniques.

To be reasonably confident that a lesion is the result of radiation injury, the pathologist needs to see in the tissues a constellation of the more characteristic changes of radiation effects. He or she needs to know that radiation has been given, in what doses, and by what fields so that radiation can be considered as a possible etiologic agent for the abnormalities seen. After total consideration of all observations, correlated with the clinical and therapeutic record, the best the pathologist may be able to do is to say "consistent with radiation injury." In other cases, in which these facts and observations are such that other causes for the tissue changes, such as infection, physical, chemical or thermal trauma, or arteriosclerosis, can be excluded, more definite diagnosis may be rendered.

The following discussion will attempt to describe and to illustrate in some detail the morphologic features of radiation injury of various organ systems seen by the surgical pathologist with particular emphasis on the alimentary tract from which most surgical pathology specimens with radiation injury are received. It will attempt to provide insight to the problems inherent in the nonspecificity of the lesions and in the sampling of the tissues by biopsy in contrast to resected specimens. Reference to experimental models of radiation injury will be minimal except when such models have clarified perplexing areas of human acquired disease. No detailed discussion of total-body massive acute radiation sickness will be given. Most of the descriptions will concentrate on the chronic effects of radiation injury since these are the effects that usually result in specimens for study by the surgical pathologist.

Reprint requests: Morgan Berthrong, M.D., Department of Pathology, Penrose Hospital, P.O. Box 7021, Colorado Springs, Colorado 80933, U.S.A.

Acute radiation lesions are rarely biopsied and much of our knowledge of acute histopathologic changes of radiation comes from experimental studies. Most of this material will be found in greater detail in previous publications [2–4].

First, we present a very brief discussion of cell or tissue sensitivity to radiation injury. This is an extremely complex subject, studied intensively by radiobiologists, and perhaps impossible to simplify. Generally, cells are increasingly responsive, or sensitive, to ionizing radiation during the G_2 and M phase of cell division; therefore, cells undergoing rapid cell division are more often acutely injured by radiation than those less rapidly dividing or not dividing at all [5–7]. Thus, intestinal mucosa, bone marrow, endothelial, and germ cells are more radiosensitive than osteocytes, myocardial, or ganglion cells. This general principle, however, applies primarily to immediate or acute injury which, as indicated above, is not often studied by pathologists. The cells that suffer injury, not manifest for weeks, months, or even years, are those that result in the tissue changes that lead to clinical conditions that require surgical treatment, namely, fibrosing lesions of the pericardium, peritoneum, submucosa of the intestine, and especially loss of capillary bed [8, 9] and fibrosing lesions of arteries and veins which produce ischemia or even infarction of organs. The most radiosensitive cells which suffer acute injury have the capacity to repair or regenerate completely from the acute injury of radiation although cells such as the germ cells of the testes and ovaries and the bone marrow hematopoietic cells may remain permanently lost. We thus may see obstructing segments of the small intestine in the pathology laboratory 10 years after therapeutic radiation with near-normal mucosa but with massively thickened fibrosed submucosa and peritoneum and markedly narrowed arteries and veins which have caused focal and sometimes deep eroding fistula-forming ulcerations or even infarction.

Alimentary Tract

Since the alimentary tract so often receives large doses of ionizing radiation during the treatment of malignant disease, either of the tract itself or of adjacent organs, practicing pathologists will study more specimens from the alimentary tract with radiation injury than from any other organ system. Perhaps the majority of these will be from the small and large intestine or rectum because of their inclusion in fields of therapy for cancers of the uterus, bladder, prostate, or periaortic nodes, but lesions of radiation injury of the oral tissue, salivary glands, esophagus, and stomach will also be encountered [10, 11].

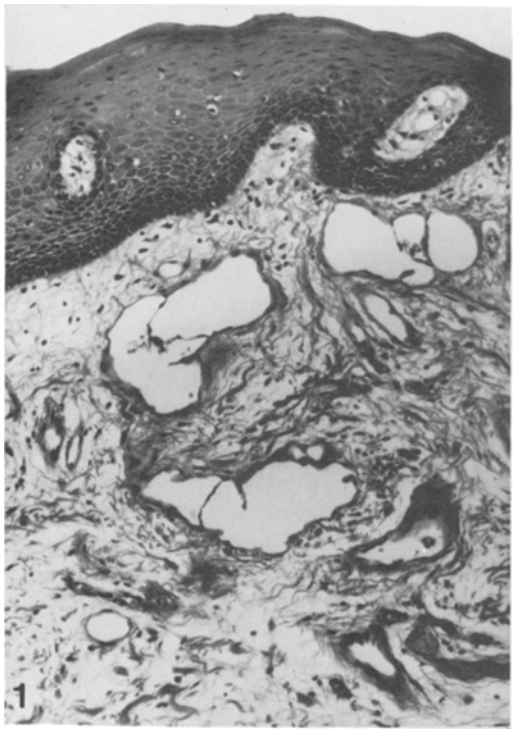
During the course of radiation therapy, clinical symptoms of the acute cell injury often develop, i.e., soreness of the oral mucosa, dysphagia, diarrhea, tenesmus, or melana. Biopsies are only rarely taken at this time and our knowledge of the morphologic changes that may be present is scanty, surmised from animal experiment studies, as well as from occasional biopsy or chance autopsy observations in humans. The acute radiation injury that results in such clinical symptoms has affected the rapid-turnover cell systems of the epithelial mucosa and perhaps the endothelial cells especially of the capillary bed. Mucosal cells, however, rapidly regenerate, particularly when the radiation therapy is appropriately protracted and often by the time the therapy is completed, or shortly thereafter, have regenerated to a near-normal mucosal layer.

Most of the injury by radiation to the alimentary tract that results in biopsy or surgical resection or is studied at autopsy is the consequence of delayed reactions which develop in the fibrovascular tissue months or years after completion of the therapy. Progressive loss of the capillary bed and fibrosis of the submucosa and serosa may lead to obstruction of the intestine. Progressive vascular intimal fibrosis which often narrows vessel lumina significantly causes ulcerations, fistulas, and infarctions. Impaired regeneration of the radiated mucosal epithelium may contribute to the erosions and ulcers, but it seems that progressive fibrosis and vascular lesions leading to ischemia are most important.

Oral Cavity

With radiotherapy from 5,000 to 7,000 rad in 5 to 7 weeks at the rate of 200 rad per day, acute lesions develop beginning by the second or third week of treatment. Acute cell necroses may be seen in the basal epithelial layer, a total loss of cells from the epithelium may occur, and edema as well as vascular dilatation will be found in the submucosa. Depolymerization of the mucopolysaccharide intercellular matrix may be an important factor leading to the edema. If the mucositis progresses, by the fourth week, superficial erosions may be found covered by a pseudomembrane of fibrin. Mucosal regeneration will be underway by the end of the radiation treatments and will often be complete 1 month after therapy [12]. Biopsies are rarely performed. In about 1% of treated patients, radiation therapy will need to be interrupted because of the severity of acute reactions in the oral mucosa.

Far more commonly, pathologists will study delayed radiation changes in specimens biopsied for chronic ulcers in the oral cavity or resected for recurrent neoplasm. In these cases, the pathologist will find the buccal and lingual mucosa or the mucosa of the floor of the mouth to be similar.



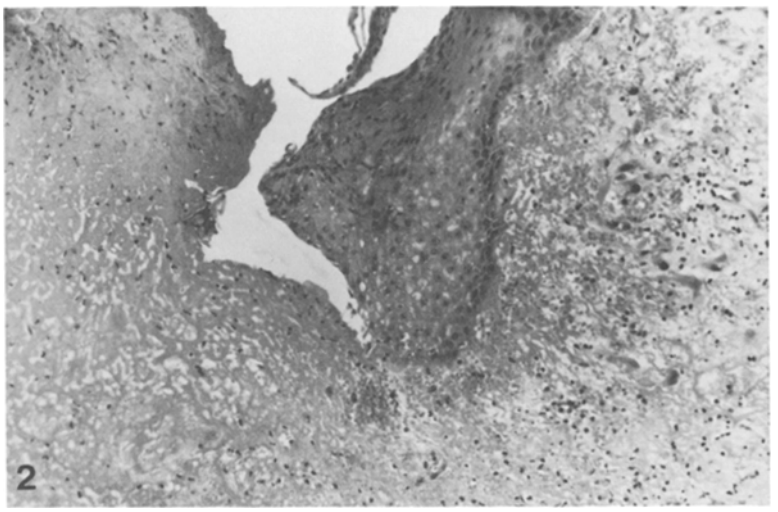


Fig. 1. Thick squamous epithelium covers submucosa with telangiectatic vessels and atypical fibroblasts.

Fig. 2. An ulceration of the tongue with its amorphous fibrinoid base shows minimal inflammation and atypical fibroblasts at the right. The squamous epithelium appears normal.

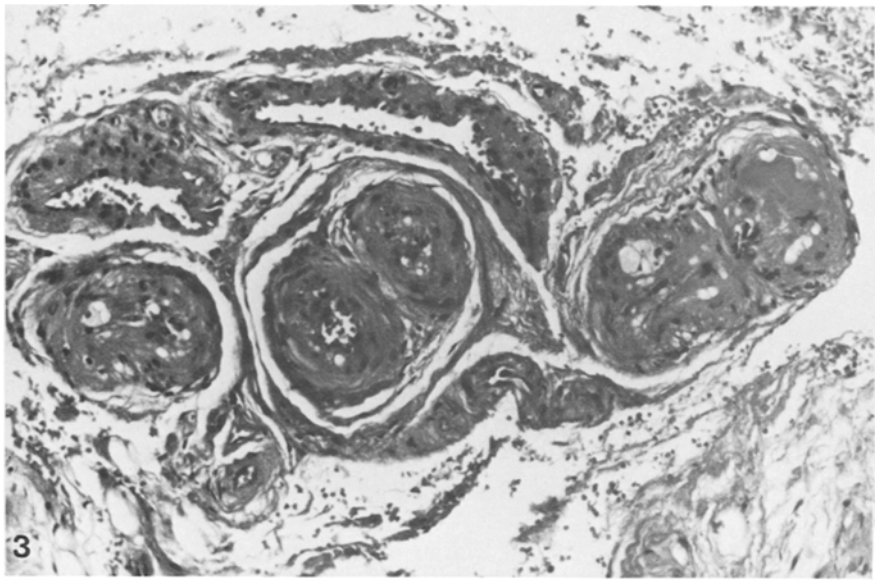
Atrophy of the squamous epithelium will be common, especially of the basal layers. Parakeratosis of the surface is often noted. Sometimes the epithelial layer is thicker than normal with prominent parakeratosis. Apparently, the epithelial layer is less resistant to traumatic injury ulcerating more readily after injury. Severe submucosal fibrosis is usually prominent with the collagen bundles indistinct as if homogenized or obscured by intercellular fluid. Atypical "radiation" fibroblasts are usually numerous and telangiectatic vessels of capillary or lymphatic type are noted (Fig. 1). Depletion of total capillary bed is difficult to recognize in routine sections.

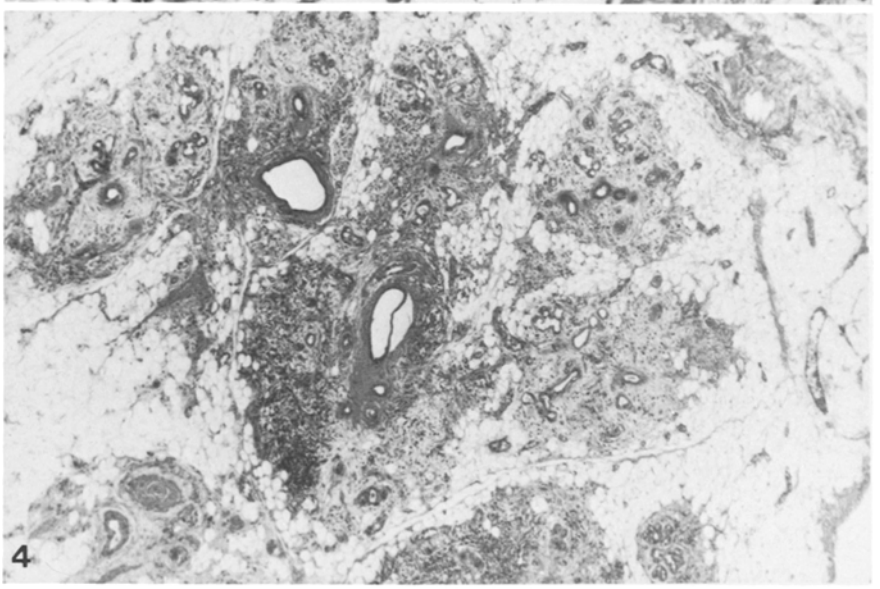
Ulcerations formed may be quite deep with totally necrotic ulcer crater blending gradually with chronic granulation tissue and extensive fibrosis in deeper layers. The granulation tissue is not unusual except for atypical endothelial nuclei and bizarre fibroblasts. Perhaps there is a less intense inflammatory cell infiltrate than in nonirradiated ulcers (Fig. 2). Such ulcers have been described in 31% of patients followed for years after oral radiation [13] but more recent studies have shown 22% of treated patients will develop postradiation oral ulcers [14].

Minor salivary gland clusters are usually atrophic, especially the acini which may be completely lost. Ducts may be dilated and plugged with inspissated secretion. Squamous metaplasia of ducts is often noted [15]. Since the minor salivary gland atrophy is often associated with similar changes in the major glands, xerostomia is common. Dental caries, as well as dry mouth symptoms, may develop owing to the xerostomia.

Skeletal muscle fibers may be surrounded by fibrosis and muscle cell regeneration will be seen in these areas. Other skeletal muscle bundles, however, may be near normal. Arteries often show severe intimal fibrosis which narrows the lumina markedly. Foam cell plaques in the intima are less common [16] (Fig. 3). Some arteries will show loss of media with fibrosis, disruption of elastica, and with organized recanalized thrombi. These vessels resemble a healed necrotized vasculitis. In all, the vascular lesions often seem to be sufficiently severe as to be responsible for the other lesions of atrophy, fibrosis, and especially the ulcerations.

The vascular lesions may also contribute to the radio-osteonecrosis that may be present in the mandible or maxilla. Direct radiation injury, loss of capillary bed, trauma, and infection all may also contribute to dead bone, disappearance of osteoblasts and focal bony resorption [17]. Some attribute the onset of bone necrosis to dental extractions, but there is controversy in this subject. Radio-osteonecrosis occurs in from 14% to 33% of patients radiated for oral cancer [13, 14]. In some series, 40% of patients with post-radiation osteonecrosis of the maxilla and/or mandible required surgery [14].





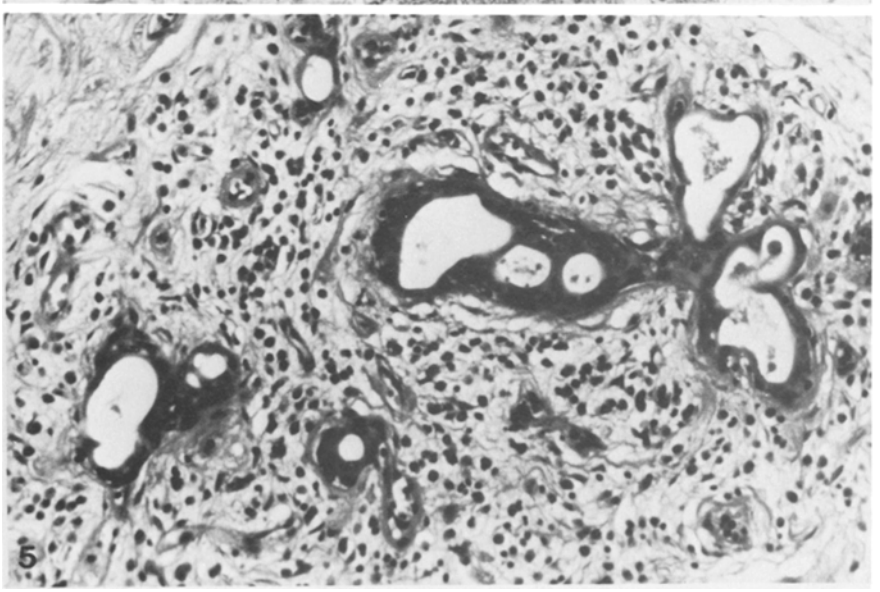


Fig. 3. Thick-walled, narrow-lumened arterioles with occasional subendothelial foam cells lie deep in oral submucosa.

Fig. 4. Under low power, a parotid gland has lost most of its acini. Remaining ducts lie in dense fibrous tissue.

Fig. 5. Remaining salivary gland ducts are atypical and mimic adenocarcinoma.

Fig. 6. Esophageal mucosa 20 days after heavy radiation is completely necrotic with a submucosal necrotic and thrombosed vessel to the left.

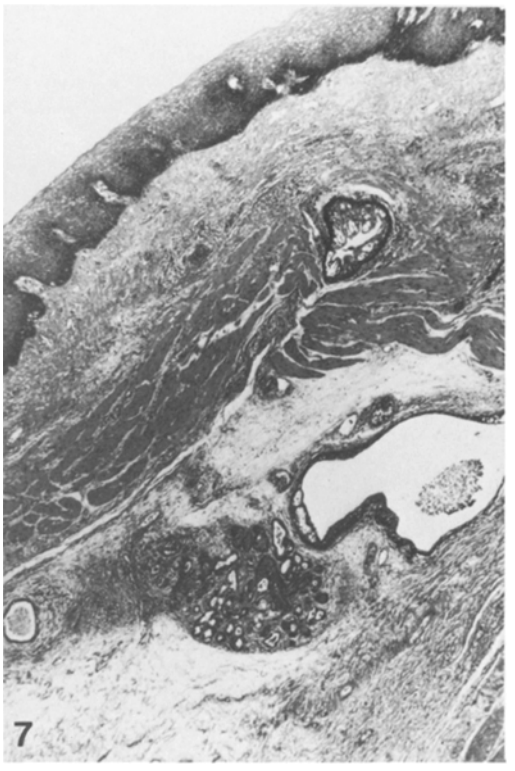


Fig. 7. Thickened parakeratotic esophageal mucosa covers fibrotic submucosa and cystically dilated gland ducts with squamous metaplasia.

Salivary Glands

The salivary gland epithelium, whether of the minor or major glands, has a long cell turnover with 40–65 days for serous acini and 95 days for ducts. Mucus goblet cells also have a long cell turnover. It is thus surprising that after only 100 or 200 rad, functional changes may occur with a dry mouth and elevated serum amylase. After perhaps 1,000 rad, the glands may be tender and swollen and histologically show loss of zymogen granules in the serous epithelium and focal cell necroses [18]. Granular cell debris may be seen in dilated ducts. Saliva is described as viscous and tenaceous, probably the result of loss of serous secretions [12].

Delayed changes in salivary gland tissue follow 5,000 rad administered in 5 or 6 weeks, and are severe after 7,000 rad in 6 or 7 weeks. Permanent xerostomia will be present in 5% of the former and 50% of the latter [19]. Regeneration with improvement in xerastomia when it occurs may take 6–12 months. Chronic histologic changes we have seen from 1 to 6 months after from 5,000 to 7,000 rad are atrophy or even loss of serous glands, preservation but atypism of mucus glands or goblet cells, cystic dilatation of ducts with mucous plugging and sometimes squamous metaplasia of ducts, often nearly normal intercalated ducts, fibrosis of interstitial tissue with atypical fibroblasts, hyaline arterioles, telangiectasia of thin-walled vessels, and arterial thickening with intimal proliferation and vascular narrowing as described under the oral cavity (Fig. 4). After particularly heavy doses all salivary gland acini may be lost and we have noted, as have others, ducts which persist in the dense scar that may resemble adenocarcinoma [20] (Fig. 5).

Esophagus

Since the esophageal mucosa has about the same cell turnover rate as oral mucosa, it is not surprising that patients being radiated for neoplasms of the lung, mediastinum, or esophagus develop clinical consequences of acute radiation injury to the mucosa consisting of substernal burning or dysphagia. Little is known about the histologic changes seen in this acute phase. In the few cases we have studied at this stage there is acute cell damage particularly of the basal cell layer, as well as edema and vascular dilatation of the submucosa. In a recent case of ours, a 66-year-old female died 20 days after the completion of 3,000 rad of therapy with a 4 mille electron (ME) linear accelerator, 1 year after receiving 3,000 rad in the same area. The esophagus showed extraordinary acute necrotizing lesions of small blood vessels, and complete necrosis of the mucosa and panesophagitis which in part may have been the result of superimposed infection (Fig. 6). Necrotic small blood vessels with fibrin thrombi, probably veins, were numerous in the submucosa. These seemed to be of the same age as the mucosal necrosis.

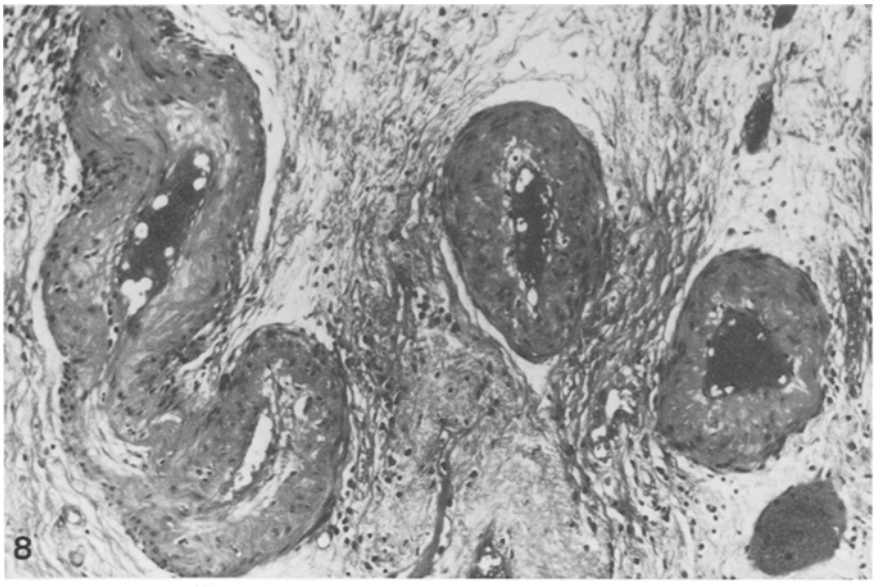


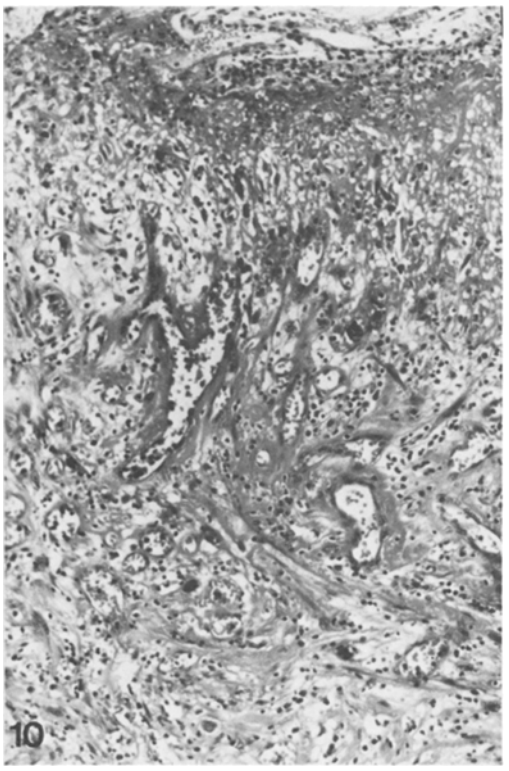
Fig. 8. Markedly narrowed small arteries with hyaline-scarred walls are shown in the esophageal wall.

Fig. 9. Under low power, a gastric ulcer complicating radiation presents the characteristic layers of a peptic acid ulcer.

The tolerance dose for delayed effects is approximately 6,000 rad in 6 weeks or less if fractionated [21]. Also, the frequency and severity of esophageal injury may be increased if chemotherapy is given concomitantly. From Seman and Ackerman's excellent study [22], as well as from our own material, the esophagus will show at 6 months to many years after radiation: mucosal atrophy or, more often, hyperplasia and thickening of the mucosa with parakaratosis; severe fibrosis of the submucosa with hyalinization of the collagen; and submucosal mucous gland changes of atrophy, fibrosis, duct dilatation, and sometimes duct epithelial squamous metaplasia (Fig. 7). Vascular lesions of intimal proliferation and narrowing are frequently prominent (Fig. 8). It is difficult to detect capillary loss in routine studies. Erosions of the surface mucosa or even deep ulcerations are probably ischemic although unimpaired mucosal regenerative capacity may have contributed. Presumably as a result of healing, mucosal bridges across the esophageal lumen may result [23]. Tapering strictures over significant segments of the damaged esophageal wall may develop as early as 4 months posttherapy. Fistulas to trachea, bronchi, or aorta have been described. These usually occur at sites of contiguous neoplasm or at sites of previous or subsequent surgical procedures. Radiographic studies will show esophageal motility alterations in a large percent of patients receiving therapeutic doses to the esophagus [24].

Stomach

It has long been known that relatively low dose radiation, i.e., 1,500–1,600 rad, given in 10 daily doses to the entire stomach causes a significant



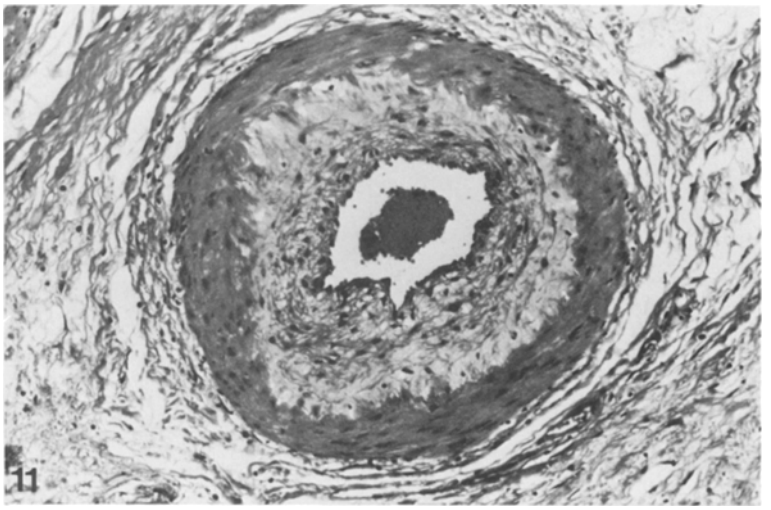


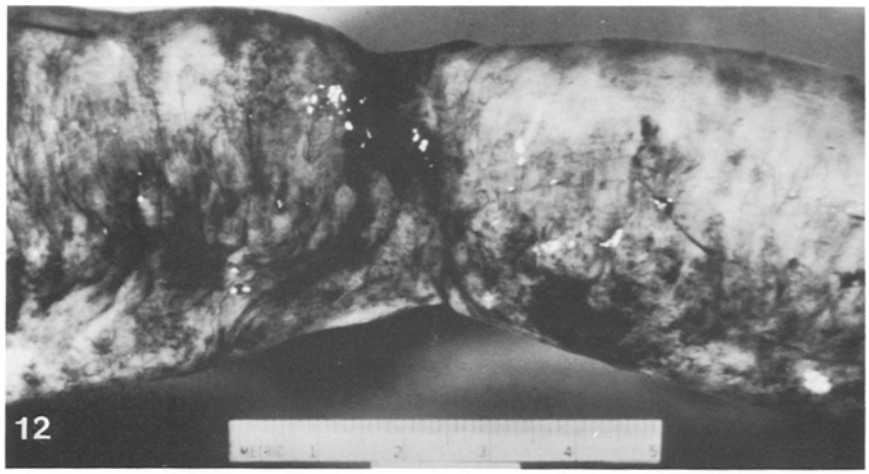
Fig. 10. The granulation tissue in the ulcer base beneath the fibrinoid layer to the right shows atypical endothelial and fibroblastic cells.

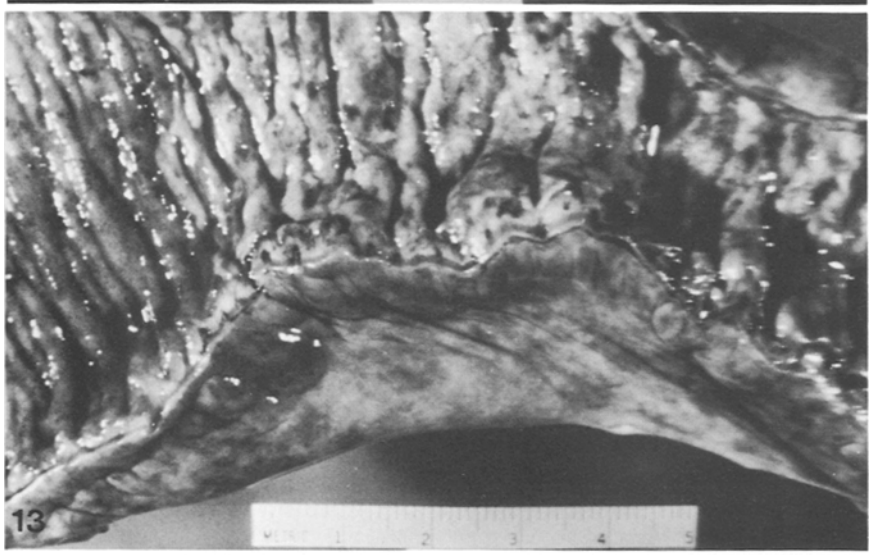
Fig. 11. A medium-sized artery in the gastric wall shows intimal fibrous proliferation with a few atypical cells, a characteristic postradiation vascular lesion.

reduction, sometimes for many years, of gastric acidity and has been used in treatment of peptic ulcer disease [25, 26]. Following these doses of radiation, there is a loss of chief cell and parietal cell granules. Focal cell necroses in the gastric pits occur, but regeneration here is rapid so that by the end of 10 days, gastric mucosa appears normal by light microscopy [27]. Secretion and particularly the pH may remain low in some patients for years. Occasionally, in those patients who have persistent low gastric acidity, atrophic gastric mucosa also persists. Many other patients have a gradual return to normal gastric secretion. At 11 months, gastric acidity is at pretreatment levels in 30% and at 30 months in 60%. While no ulceration or neoplasia was found in 3,000 patients treated in this manner at one institution, recent reports of adenocarcinoma of the stomach following such treatment have been described.

High-dose gastric radiation of 5,000–6,000 rad for neoplasia of the stomach or adjacent organs results in acute erosions in some patients during treatment because of the rapid-cell turnover rate and consequent radiosensitivity in the upper portions of the gastric gland isthmus and contiguous portion of the gastric gland pits. These cells have a turnover rate of from 2 to 6 days while the long convoluted gastric glands which contain the parietal and chief cells below the pits and isthmus have a much slower turnover rate [29]. Biopsies of acute changes are rarely observed.

The tolerance dose of the stomach for development of delayed changes is approximately 5,500 rad with the frequency of complications increasing above this dose. Ulcers, sometimes with perforation, are the predominant complication. Ulcers that develop after radiation are alleged to be nonpeptic in type which would be the case only if total gastric radiation had eliminated the parietal cells. In our patients, however, only partial gastric mucosa radiation had been administered and we found characteristic chronic peptic acid ulceration (Fig. 9). The ulcers show granular necrotic debris on the surface with the typical fibrinoid layer beneath. The granulation tissue which formed the base of the ulcers demonstrated atypical fibroblasts and endothelial cells (Fig. 10). Hyaline fibrosis may replace the gastric muscularis beneath the ulcers. Deep in the gastric wall severe vascular changes are seen with massive fibrosis of surrounding tissues. These vascular lesions are similar to those described above (Fig. 11). Other cases have shown more acute but also typical peptic ulceration with a minimal inflammatory response suggestive of those described as "stress" ulcers. Two of these patients have died with rapid, almost asymptomatic progression of these peptic ulcers to perforation and hemorrhage. Radiation changes in vessels and fibroblasts were characteristic. Chemotherapy administered with radiation may result in more severe tissue and cellular injury. Indeed, we now have seen a number of patients who, with combined radiation and hepatic





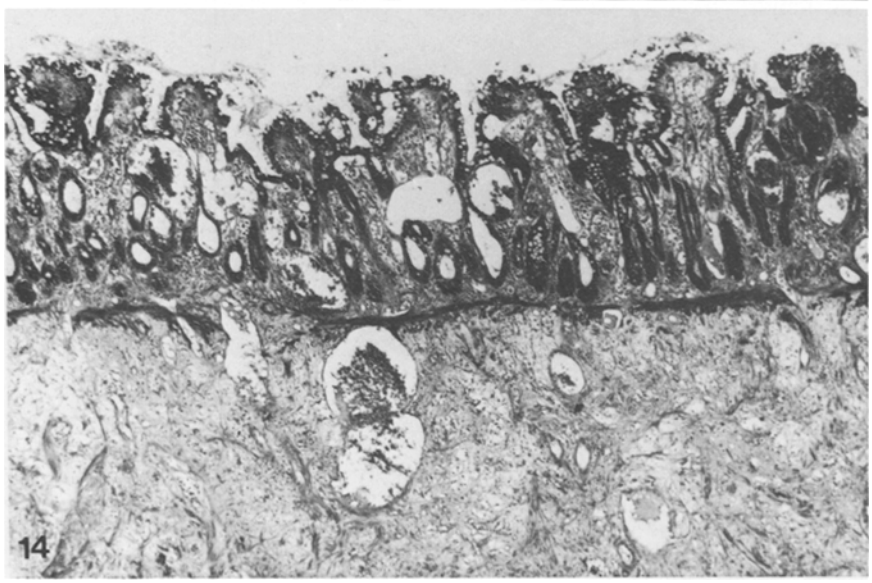


Fig. 12. A stenosed segment of ileum removed for subacute intestinal obstruction shows mottled opaque peritoneal thickening without "creeping fat."

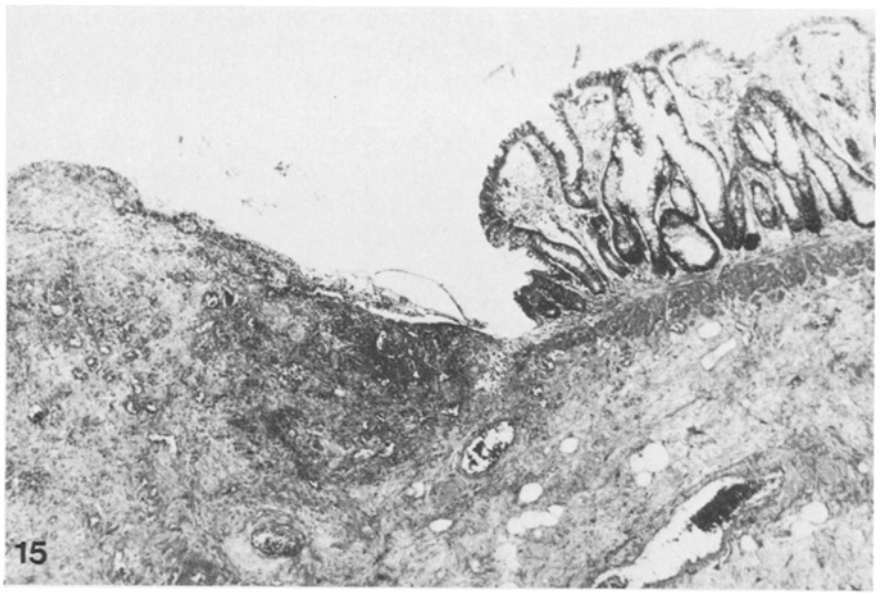
Fig. 13. The opened segment shows loss of regular mucosal folds, superficial erosions, and the prominent gray line of submucosal fibrosis.

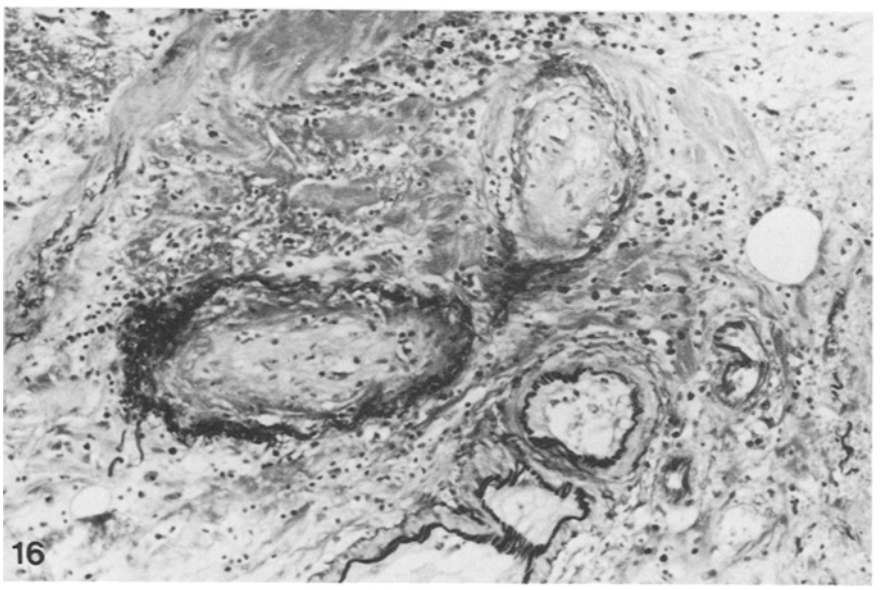
Fig. 14. Telangiectatic vessels are seen in the distorted small intestinal mucosa and in the thickened submucosa.

artery chemotherapy infusion, developed gastric and duodenal peptic ulcers, the margins of which showed mucosal cellular atypia highly suspicious of carcinoma [30].

Small Intestine

A common, serious, and life-threatening complication of therapeutic radiation is subacute or chronic





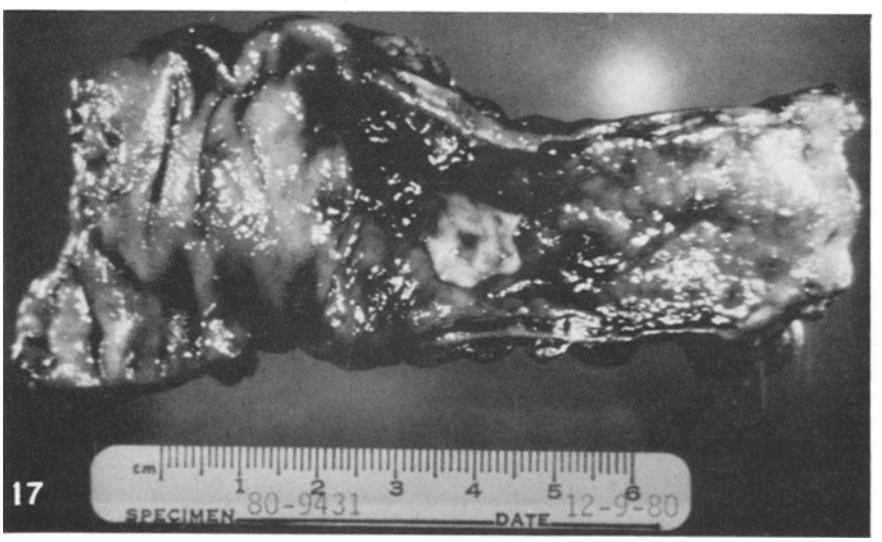


Fig. 15. The small intestinal ulcer is nonspecific, but is so circumscribed as to suggest an ischemic origin.

Fig. 16. Veins in the scarred small intestinal submucosa show occlusive intimal fibrosis. A small arteriole (bottom, center) is almost normal.

Fig. 17. This heavily radiated rectum reveals severe mucosal change with ulceration.

radiation enteropathy. With whole-body radiation, the mucosa of the small intestine, because of the extremely rapid cell turnover rate, is diffusely denuded and results, in combination with leukopenia, in overwhelming sepsis [31]. If bone marrow function is preserved, death still may occur due to fluid and electrolyte loss. With therapeutic radiation, however, the dose is fractionated. While acute crypt epithelial cell injury with nuclear pyknosis and karyorrhexis occurs after each dose, regeneration is active betwen fractions and the mucosa, during therapy, usually shows only atrophy with crypt dilatation and a loss of villi; superficial erosions are uncommon [32]. Patients may manifest nausea, vomiting, pain, and diarrhea, usually not sufficiently severe to require cessation of therapy. Malnutrition may develop and impaired absorption of fats and bile salts and protein loss has been demonstrated [33, 34]. Two to three weeks after irradiation is completed, the mucosa may appear normal although villous atrophy and abnormal crypts may persist.

Delayed effects, which become clinically evident in patients from 6 months to 25 years later, occur in perhaps 20–30% of patients who have received 5,000–6,000 rad and even more often when more than 6,000 rad have been administered. Patients who had prominent acute symptoms during therapy may have a greater incidence of late complications [35]. Not all patients with symptoms require surgical treatment, but in one study 31 of 89 symptomatic patients eventually required surgery. If patients who received radiation had had previous intraperitoneal injury, radiation damage occurred with greater frequency, presumably because normal small intestinal motility was altered and loops fixed by adhesions in the fields of radiation received a disproportionately greater share. Approximately one-half our patients with radiation enteropathy who required surgery had had some intra-abdominal disease or surgical procedure prior to radiation. A recent study indicated that slender women were more susceptible to enteric radiation injury [36].

We have observed the following changes in the small intestines resected with radiation enteropathy for intermittent small bowel obstruction, severe abdominal pain, diarrhea, or less commonly, intestinal fistulas.

Grossly the involved segments of small intestine are mottled gray and red, usually with multiple fibrous adhesions. Not infrequently, loops of small intestine are fused by fibrous adhesions with resulting kinked loops. Sometimes the surgeon had removed multiple adherent loops of ileum from the pelvic cavity by sharp dissection. The fat of the mesentery never extends over the surface of the intestine as in regional enteritis (Fig. 12). Tapered strictures are the rule rather than sharply circumscribed ones. Fistulous tracts between loops of small intestines may be difficult to locate because of the narrow tortuous paths. The walls of the involved intestine are thickened and when opened the gray fibrous thickening of the submucosa and serosa stand out in sharp contrast to the brown muscularis and red mucosa. The mucosal folds may be nearly normal but are more often irregular, cobblestone-like, even with focal ulcers (Fig. 13). The ulcers are often at the point of most severe stricture. Fistulas may be traced into another loop of intestine but holes that may indicate fistulas must be distinguished from surgical trauma since these lesions may be very difficult to resect and tears are frequent.

Microscopically the stained sections are pink (eosinophilic) since inflammatory cell infiltrations are usually sparse. The mucosa is variable in thickness, sometimes atrophic without villi. Other areas have blunt thickened villi, perhaps with dilated telangectatic vessels in the lamina propria (Fig. 14). The surface epithelial cells may be near normal although enlarged; hyperchromatic nuclei may be noted; and distinct brush borders are often lost. The lamina propria seems to have fewer mononuclear cells than usual.

The muscularis mucosa is often normal although it may suggest hypertrophy and may show fibrosis. Obviously, it will be lost at sites of ulceration (Fig. 15).

The submucosa is thickened by broad, homogenized sheets of collagen in which atypical fibroblasts and telangectatic vessels are often seen. Small veins in the submucosa are often thick walled with intimal fibrosis occasionally occluding the lumina of the veins (Fig. 16). In early lesions, fibrin may be seen beneath the endothelium. Arterioles are less involved but may show some hyaline thickening of the media and occasionally a foam cell will be noted in the intima. The submucosal ganglia are nearly normal with perhaps slight distortion of nerve fibers by fibrosis; the ganglion cells seem uninvolved.

The muscularis propria is essentially normal with only occasional strands of fibrous tissue. The myenteric nerves and ganglia are essentially normal.

The serosa is markedly thickened by hyaline fibrosis in which atypical fibroblasts are noted. Arteries are more severely involved than veins both in the serosa as well as in the mesentery. Intimal fibrous plaques, or less frequently intimal foam cell plaques, narrow the lumina. Sometimes the intimal elastic lamella and smooth muscle media are intact but other arteries may show healed destructive lesions of the full thickness of the wall with organized thromboses. An occasional vessel is totally

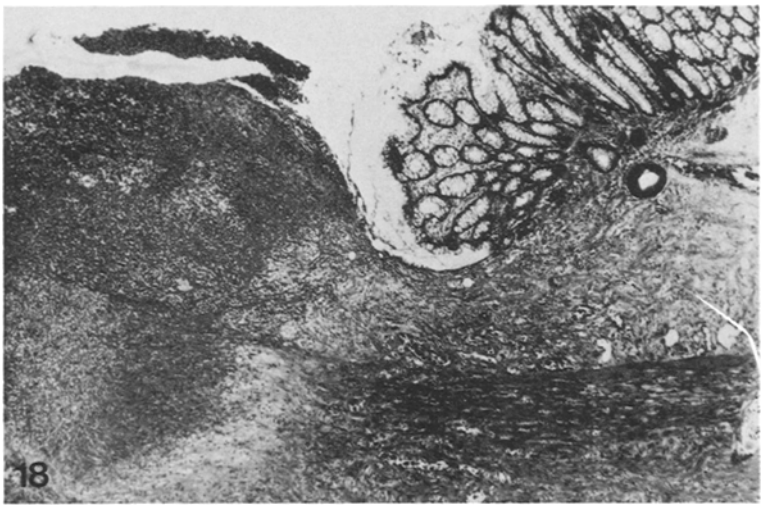


Fig. 18. Another colonic radiation ulcer is suggestive of an ischemic colitis ulcer. The muscularis on the right becomes abruptly necrotic at the base of the ulcer.

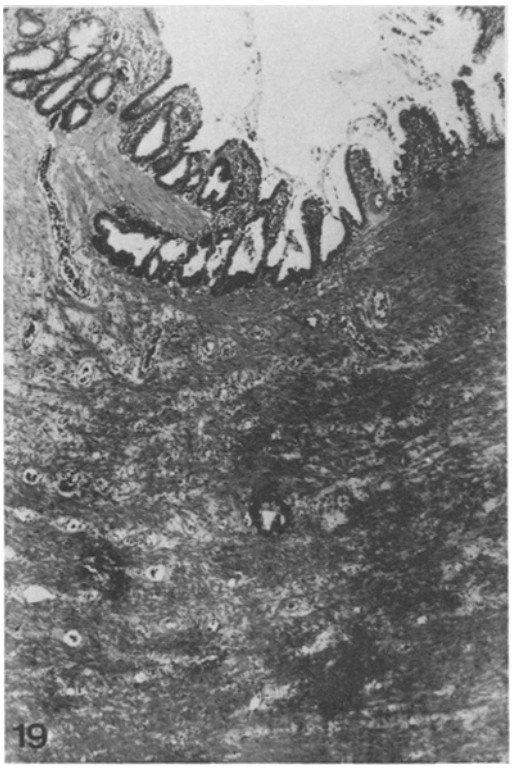


Fig. 19. A strange postradiation colonic lesion shows atypical colonic mucosa lying directly on the muscularis and a gland deep in the muscle. Under high power, the epithelium is benign.

occluded and stains show wrinkled elastica surrounding an occluding intimal fibrous mass with complete loss of a muscular media.

At either end of a tapered stricture the lesions described gradually diminish so that at 8 to 10 cm proximally or distally, the small intestine may be histologically normal although serosal fibrosis may be more widespread.

Large Intestine

The colonic mucosal cell turnover rate is slightly less rapid than the small intestine but still is an extremely radiosensitive cell. Also because of the anatomic location of the rectosigmoid and its fixation in the pelvis, acute radiation proctitis is quite common, although rarely biopsied, and usually does not interrupt radiation therapy. Acutely, mucosal cells will show atypia, karyorrhexis, loss of mucous production, and occasionally crypt abscesses with eosinophils [37]. Atrophy of the mucosa develops during course of the therapy. The submucosa is edematous with some fibrin. Perhaps a month after radiation, half the biopsies may be normal although atrophy may persist.

In rabbits, Friedman showed that diverting the fecal stream prevented the severity of colonic ulcerations of acute radiation colitis [38]. Reduction in passage of food, of pancreatic secretions or bile in rats also reduces the severity of acute injury [39, 40]. These experiments suggest that acute radiation injury to the mucosal cells results in increased susceptibility to the incidental trauma of normal bowel functions.

After from 6 months to 30 years, patients who have colon or rectal radiation may present with pain of intestinal obstruction or bleeding. The strictures are usually long and tapered. The mucosa may be near normal or atrophic with loss of goblet cells and with nuclear atypia. Ulcers are found, sometimes deep and even occasionally, perforated. The ulcers are probably the consequence of radiation vascular lesions which cause ischemic injury to cells already impaired of regenerative capacity (Fig. 17). A recent study by Gilinsky et al. emphasizes the complication of bleeding from radiation proctosigmoiditis for they found surgery necessary in 24 of 88 patients with radiation proctitis and persistent bleeding although many of these had bowel dysfunction and pain as well [41]. Repeated transfusions were sometimes necessary in patients for as long as 18 months after radiation.

The anatomic abnormalities found in specimens of chronic radiation colitis or proctitis are quite similar to those of the small intestine. Mucosal atrophy with reduction in goblet cells, nuclear atypia, and telangectasia are frequent. While reduction in lymphocytes in the lamina propria is frequent, normal lymphoid nodules may persist or regenerate. Some specimens may show remarkably normal mucosa. When erosions or ulcers are seen,

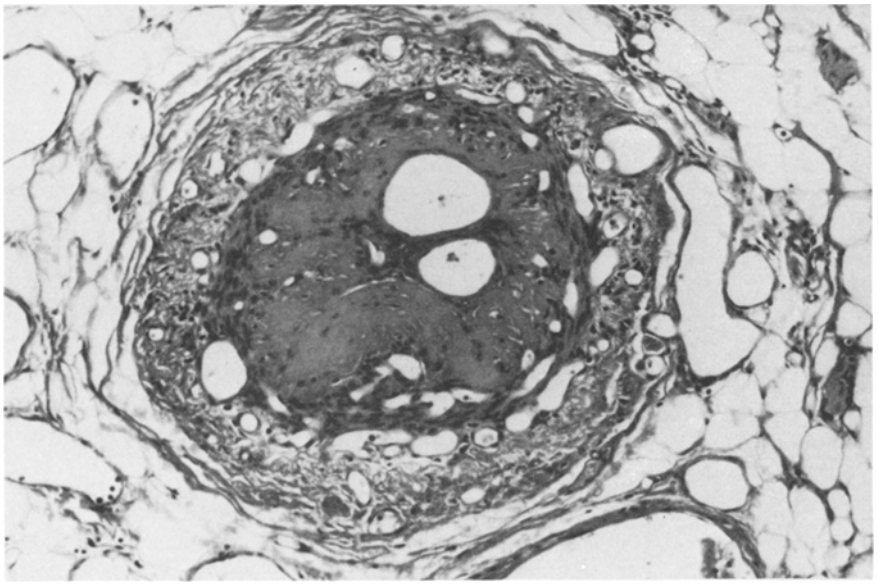


Fig. 20. A vessel in the serosa of a postradiation colon shows what appears to be a healed necrotic vasculitis, another common postradiation change.

aside from fibroblastic and endothelial cell atypia, the inflammatory response may be nonspecific (Fig. 18). Carr et al. with injection studies and microradiographic techniques beautifully demonstrated the loss and distortion of the normal microcirculation of the mucosa [10].

Typically, again the submucosa is scarred by hyaline, homogenized collagen, atypical fibroblasts, sclerosed veins, telangectatic capillary or lymphatic-like vessels, and sparse inflammation. The submucosal ganglia and nerves are usually preserved although they may be distorted by the fibrosis. Sometimes the muscularis mucosa and submucosa are lost and the mucosal layer rests directly on the muscularis propria. This possibly is the result of broad, deep ulcers which may have occurred during the acute injury period with regeneration of mucosa over the exposed muscularis propria. Such regeneration may have caused an interesting abnormality of the mucous glands which was seen in one of our patients. Mucous glands were found deep in the muscularis (Fig. 19). These glands were well differentiated and in no way resembled carcinoma. This peculiar penetration of the muscularis by normal glands was in no way related to diverticula or previous deep ulcerations since the muscularis was intact without fibrosis. Black, in a fine experimental study of radiation colitis, described a somewhat similar change of colitis cystica profunda which developed after controlled radiation of rat colons [42]. We have recently seen a more severe example of this change in a sigmoid colon radiated 12 years before. Numerous large mucous glands, occasionally cystic and distorted, were present deep in the muscularis propria which was otherwise normal. It was thought to be carcinoma by capable surgical pathologists, but the cells were essentially normal and the patient has remained well. Another similar case has been recently reported [43]. The mechanism by which these mucous glands "invade" the muscularis remains obscure.

The chronic changes of radiation otherwise spare the muscularis although mild focal fibrosis may be present. The serosa and the perirectal connective tissue, however, show severe fibrosis often with the peculiar homogenization of the collagen and the bizarre fibroblasts of radiation injury. Arteries in this area usually reveal all the changes of intimal fibrosis, or destruction of the walls with recanalized thrombi (Fig. 20), or foam cell intimal plaques all seen in the arteries of the entire alimentary canal postradiation. Veins are less involved but intimal fibrosis may be found. The vascular lesions are sufficiently severe to suggest an ischemic pathogenesis for severe mucosa ulcers. One of our patients, excessively radiated a second time and who showed both acute and chronic vascular lesions, had acute infarction of a significant segment of the rectosigmoid.

Adenocarcinoma of the colon may also be found in patients who have received colonic radiation. The intervals of time between the radiation and the development of the carcinoma has been reported as from 5 to 10 years. Such carcinomas are not known to be different from the usual ones arising in the colon. The added risk of developing carcinoma after therapeutic radiation to the colon has been variously estimated at 1.2 to 8 times normal [44], but is still subject to statistical scrutiny. At least 49 cases have been reported, perhaps the first described by

Black and Ackerman [45]. Importantly, there is experimental evidence for this association since Black found 14 adenocarcinomas in colons of 96 rats radiated [42].

Pancreas

With radiation of the upper abdomen, the pancreas or portions of it will be included in the fields. Since cells of the pancreatic acini and islets of Langerhans are cells with extremely *low* turnover rates and most cells are in the postmitotic phase, they should be radioresistent to acute injury. One might predict, however, considering the similarity of the pancreas to the salivary glands, that following acute irradiation pancreatic enzyme excretion might be acutely diminished. Indeed, experimentally, Pieroni has shown a fall of enzyme and bicarbonate excretion in dogs for months after radiation of the pancreas [46]. Isolated reports of injury have been described in humans, consisting of atrophy or loss of acini, fibrosis, and with preservation of more resistant islands of Langerhans.

Our cases of radiation injury of the pancreas are all of the chronic or delayed type and in these cases no records of exocrine pancreatic excretion derangements are available. The patients did not have clinically evident diabetes mellitus. The characteristic change was massive fibrosis replacing pancreatic lobules. Islets of Langerhans were remarkably well preserved in the scar. Atypical fibroblasts were often present. The pattern of fibrosis replacing the acini but leaving intact islets suggests ischemia and vascular lesions identical to those described in the alimentary tract are common in the fibrosed pancreas of radiation injury. Adjacent malignant neoplasia did not explain these lesions and were not always present in such areas of the pancreas. Major pancreatic ducts showed minimal change. Similar changes have been reported [47, 48].

Female Genital Tract

While the radiated uterus, fallopian tube, and ovaries rarely produce complications that demand surgical correction, the surgical pathologist often studies these organs postradiation since combined preoperative radiation and surgical removal is appropriate therapy for many cancers of the uterus.

The cervix, after 4,500 rad of external beam therapy and/or 3,000 rad or more of brachytherapy will show, a few days to a few weeks after treatment, nearly complete erosion of the squamous epithelial surface. The superficial acute erosion shows dilated vessels of acute granulation tissue, minimal cell infiltrate, and edema. Later, at a month or more after radiation, regeneration of the epithelium usually occurs, the cells of which show enlarged slightly atypical nuclei, usually with normal nuclear-cytoplasmic ratios. Persistent necrosis of the surface also has been observed at this stage. Fibrosis, telangectatic vessels, and bizarre fibroblasts may be present. The endocervical mucosa may show some abnormal gland structure, but the mucus-forming cells appear more resistant.

The endometrium reveals a varied picture. Nine days after heavy radiation only a few islands of living but bizarre cells are present, the rest is necrotic. Most observations are made after a 1–2-month interval when endometrial glands are either atrophic, often cystic, or are composed of cells with abnormal nuclei and eosinophilic cytoplasm. Sometimes the cells and gland structure are so bizarre as to make separation from adenocarcinoma difficult. Necrotic cancer may show calcification and foreign body reaction. Atrophic endometrial stroma is the rule but a few bizarre nuclei may be seen.

One interesting case of ours showed an in situ adenocarcinoma of the endometrium 12 years after radiation therapy for squamous carcinoma of the cervix. The cervical mucosa was dysplastic and perhaps indicated a precancerous lesion but no residual carcinoma was present.

The myometrium is quite resistant and radiation injury may not be apparent. The blood vessels and connective tissue of the uterus may show the same changes as described in the alimentary tract though some of these changes are difficult to separate from the endarteritis obliterans routinely seen in postparturate or postmenopausal uteri. Atrophic fallopian tube mucosa is noted with flattened cells and atypical nuclei. The submucosa is hypocellular and fibrosed. Ovarian atrophy and fibrosis is marked at these therapeutic doses. Ovarian vascular fibrosis may be indistinguishable from vascular endarteritis obliterans of senile ovaries but foam cell plaques and organized thrombi may suggest postradiation vascular lesions.

Pericardium

Radiation injury to the pericardium with its resulting progressive fibrosis is one of the more common causes of constrictive pericarditis today [49]. The greatly thickened pericardium is adherent to the epicardium, as well as to mediastinal tissues. Histologically dense collagenous connective tissue is nonspecific except for the suggestive atypical fibroblasts, telangectatic vessels, and peculiarly homogenized collagen. Continued active granulation tissue, which is organizing fibrinous exudate, may be present on the inner side of the pericardium years after the radiation occurs.

Urinary Tract

While the urinary bladder seems resistant to the delayed effects of radiation injury following therapeutic radiation to the uterus, therapy for carcinoma of the bladder usually causes significant injury.

The bladder is often severely contracted with a fixed low volume. The mucosa is atrophic, sometimes with atypical transitional cells. Extensive fibrosis of the submucosa and of the muscularis is characteristic. While carcinoma may be persistent, eradication of the tumor is not uncommon. We have seen a number of autopsies with local cure of carcinoma of the bladder but distant metastases which proved fatal. The ureters may show submucosal and mural fibrosis sometimes sufficient to result in obstruction, hydroureter, and hydronephrosis.

Radiation-Induced Neoplasia

Since early in this century there have been observations of neoplasms developing in previously radiated tissues. Early radiologists found multiple skin cancers on unprotected hands. Osteosarcomas occurred in bones of radium-dial painters who ingested from 15 to 125 mcg of radioactive material weekly. The incidence was low, considering that in 1 year, 1919, over 2 million radioactive dials were painted, but the incidence of osteosarcomas was significant [50]. Furthermore, Sharpe followed 42 former dial painters for 25 or more years and found that malignant tumors of various types had developed in 26 [51]. Finally, the high incidence of usually rare liver and splenic tumors was noted in patients who had received thorotrast.

Possible radiation-induced tumors can be considered in 3 groups according to the quantity of exposure to radiation.

Very low levels of exposure, from 10 to 100 rad may increase the incidence of cancer but that increase is so small that it takes millions, or tens of millions of individuals to obtain statistically significant differences. Estimates suggested are that 1–3% of all cancers are "due" to the 0.1 REM per year or 5–10 rad of radiation per lifetime that humans receive [52]. If 1 million persons each received 1 additional REM there would be an estimated 100 additional cases of cancer over the expected 200,000. (The maximum exposure at Three Mile Island was 0.1 REM or 0.7 additional cases of cancer among 2,000,000 people.)

Low- or medium-level exposure, i.e., 100–1,500 rad, appears to result in an increase in incidence of cancer to exposed organs. Relatively large numbers of individuals are still needed to appreciate the increase. An increase in thyroid carcinomas in individuals radiated as children for thymic enlargement, etc. [53], an increase in lung or breast carcinoma in individuals followed for years by fluoroscopy for pneumothorax treatment for tuberculosis [54], and an increase in leukemia patients treated for ankylosing spondylitis by spinal radiation [55] are 3 examples.

Finally, large or therapeutic levels of radiation have been repeatedly reported to result in cancers of exposed tissues. Frequently reported are esophageal carcinoma after lung or mediastinal radiation [56], colon adenocarcinoma after uterine cancer therapy [44], bone sarcomas after bone radiation [57], and various soft tissue sarcomas in areas of therapeutic radiation [58]. Statistical proof of the radiation cancer induction is often lacking and case reports are sometimes poorly documented. Strict criteria should be used to suggest such causal relationships: (a) documented proof of radiation dose and fields; (b) adequate latent period, *at least* 3, preferably 5 years, from time of radiation to onset of tumor; (c) occurrence of the tumor in the radiation field; and (d) unequivocal evidence that the tumor is a different one than the originally treated neoplasm.

The incidence of high-dose radiation-induced neoplasia is not known, is certainly quite low although probably significant and probably varies with the organ radiated, the age of the patient at which time radiation occurred, and the type of radiation, i.e., higher with old 200–250 KV and with high linear energy transfer alpha particles and neutrons than with gamma radiation.

The neoplasms that may result from high-dose radiation are not histologically or biologically different from spontaneous neoplasms in that organ, although the soft tissue sarcomas may show more atypical bizarre cells than usual.

Résumé

Pour traiter efficacement la maladie, en particulier les affections néoplasiques, l'irradiation nécessite l'emploi de doses importantes de rayons. Lorsque le traitement s'addresse à des tumeurs très radiosensibles siègeant au niveau de tissu peu radiosensible, les complications sont rares. Très souvent cependant la différence de sensibilité entre le tissu tumoral et le tissu normal est peu importante; c'est alors que les lésions secondaires à l'irradiation sont à redoute. Elles sont particulièrement fréquentes lorsque l'irradiation de la tumeur est susceptible de s'étendre au tractus digestif. Cet article décrit les modifications pathologiques qui peuvent se manifester au niveau des différentes parties du tube digestif et de leurs éléments constitutifs des mois ou des années après l'irradia-

tion. La régénération habituelle rapide et efficace du système cellulaire est soulignée. Les manifestations pathologiques tardives et sérieuses au niveau du tissu fibro-vasculaire qui sont à l'origine des complications: ulcérations, sténoses, fistules, adhérences occlusives sont décrites. De courtes discussions sont consacrées aux autres organes susceptibles d'être lésés par l'irradiation. Enfin la question de tumeurs qui peuvent être provoquées par l'irradiation est également prise en considération, et ce, en fonction de son intensité que célle-ci soit très faible, faible ou forte.

Resumen

La efectividad en el tratamiento de la enfermedad neoplásica implica la necesidad de administrar irradiación en dosis elevadas. Pocas complicaciones se presentan cuando se emprende el tratamiento de tumores de gran radiosensibilidad ubicados en tejidos de baja radiosensibilidad. Sinembargo, con frecuencia el diferencial de sensibilidad a la irradiación entre el neoplasma y el tejido normal expuesto es pequeño y la incidencia de lesión por irradiación en los tejidos normales viene a ser significativa. Esto es especialmente aparente en el tratamiento de neoplasias que implique irradiación extensa del tracto gastrointestinal. La discusión en este trabajo describe los cambios patológicos que ocurren en las diferentes unidades del tracto gastrointestinal expuesto, así como en los variados componentes de tales unidades durante, y especialmente meses y años después, de la radioterapia. Es notoria la capacidad de rápida y efectiva regeneración del sistema de veloz recambio celular que se presenta después de la lesión. Se hace énfasis sobre las graves consecuencias tardías manifestadas por ulceración, estrecheces, fístulas y adherencias obstructivas. Se presenta una breve discusión sobre los otros sistemas orgánicos que pueden ser lesionados por la irradiación. El desarrollo de neoplasias secundarias como resultado de la irradiación se menciona brevemente, y se analiza desde tres puntos de vista: muy bajos niveles, bajos niveles y altos niveles de irradiación.

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