PATHOLOGY AND PATHOLOGIC DIAGNOSIS OF RADIATION LESIONS IN THE GASTRO-INTESTINAL TRACT *

SHIELDS WARREN, M.D., and NATHAN B. FRIEDMAN, M.D.†

(From the Laboratories of Pathology of the New England Deaconess Hospital and the Collis P. Huntington Memorial Hospital, and the Department of Pathology, Harvard Medical School, Boston, Mass.)

The occurrence of lesions in the stomach and intestine as a consequence of radiation therapy is well known. Their nature, frequency and pathogenesis are dealt with in a current review [1] and in other publications,[2] so that material will not be repeated here. The purpose of the present paper is to review the radiation reactions of the gastro-intestinal tract studied in this laboratory and to present the pathologic findings in detail. It is hoped to emphasize those features which may be useful as diagnostic criteria of radiation reaction. With the increasing use of radiation therapy in high doses, lesions are being frequently encountered with which pathologists should be familiar. A determination on pathologic grounds whether a given lesion is entirely or in part due to radiation may have importance for further therapy.

The 38 cases employed for study were selected from a considerably larger group in our files. The cases selected were those in which the lesions showed a marked radiation reaction and in which the details of radiotherapy were available. An outline summary of these cases is presented (Table I).

The lesions may be grouped (Table II) according to their location in the gastro-intestinal tract and the nature of the reaction. They include ulcers, fistulae and strictures. A reaction comprising fibrosis and scarring, with thickening and induration of the bowel wall in the absence of ulceration, has been termed "sclerosis." Sclerosis alone may be marked enough to cause a stricture. Many reactions combined ulceration and stricture formation.

Many of the lesions developed at sites distant from neoplastic tissue but some occurred at the site of a partially or completely destroyed tumor and must be considered as "mixed" lesions. For example, in the bases of some ulcers exhibiting radiation reaction there was widespread infiltration of neoplastic tissue. However, since the radiation in most cases had been directed at a malignant process, many of the radiation lesions were in proximity to neoplastic tissue although they themselves were free of tumor. For example, in one case rectal ulceration characteristic of radiation reaction was present, while the

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† Littauer Fellow in Pathology.

TABLE I

Summary of 38 Cases Showing Radiation Lesions of the Gastro-Intestinal Tract

Primary disease	Radiotherapy		Duration of treatment (if multiple courses)	Interval from completion of treatment to time of pathologic examination	Method by which tissue was obtained	Radiation lesion		Neoplastic infiltration as part of lesion
	Roentgens	Milligram or millicurie hours				Site	Nature	
1. Tumor of stomach	5,400	.....	.....	1 week	Resection	Stomach	Ulcer with chronic perforation	Nodules of necrotic and unidentifiable tumor in base of ulcer; leiomyoma (?)
2. Generalized giant-follicular lymphoma	3,000	.....	17 months	2 months	Necropsy	Stomach	Ulcer	Probable regressed lymphoma at site
3. Carcinoma of cervix recurrent following panhysterectomy	7,200	.....	.....	7 months	Necropsy	Ileum (adherent in pelvis)	Ileo-vaginal fistula	Present
4. Carcinoma of rectum	8,900	.....	26 months	3 months	Necropsy	Small intestine (adherent to retroperitoneal metastases)	Ulcer	Present
5. Carcinoma of retained cervical stump	.....	3,500	.....	1 month	Resection	Ileum (adherent to cervical stump)	Sclerosis with stenosis	None
6. Carcinoma of cervix	.....	4,700	.....	7 years	Resection	Ileum (fresh adhehesions to broad ligament; laparotomy 1 year earlier for gastro-intestinal symptoms and not adherent then)	Multiple (2) ulcers with stenosis	None

7. Carcinoma of cervix	.....	4,900	.....	7 years	Resection	Ileum (adherent to pelvic brim)	Multiple (2) ulcers with stenosis	None
8. Carcinoma of cervix	6,000	4,000	.....	8 months	Resection	Ileum (adherent to pelvic brim)	Multiple (5) ulcers with stenosis	None
9. Carcinoma of cervix	13,000	3,500	17 months	7 months	Resection	Small intestine (free loop)	Ulcer with stenosis	None
10. Carcinoma of retained cervical stump	.....	3,500	.....	3 months	Resection	Small intestine (adherent to cervical stump)	Entero-cervical fistula	None
11. Carcinoma of cervix	7,600	3,400	3 months	2 months	Necropsy	Ileum (adherent to uterus)	Ileo-uterine fistula	None
12. Carcinoma of rectum	1,500	7,800	.....	3 months	Necropsy	Jejunum (adherent to rectum)	Ulcer	None
13. Generalized Hodgkin's disease	1,900 and additional treatment dose unknown	.....	4 years	1 month	Necropsy	Small intestine	Multiple ulcers with perforation	Probable regressed Hodgkin's tissue at site
14. Ewing's tumor of ilium	3,500	.....	4 months	Immediate	Necropsy	Appendix	Sclerosis	None
15. Carcinoma of uterus	.....	6,700	2½ years	4 months	Necropsy	Sigmoid	Sclerosis	None
16. Carcinoma of rectum	.....	2,500	2 months	5 months	Resection	Rectum	Ulcer with stenosis	None
17. Carcinoma of cervix	.....	5,500	.....	11 months	Necropsy	Rectum	Sclerosis	None
18. Carcinoma of anus, recurrent following resection	.....	16,500	5 months	6 months	Necropsy	Rectum	Sclerosis	None
19. Carcinoma of cervix	.....	7,000	4 years	20 months	Necropsy	Sigmoid	Sigmoido-uterine fistula	None
20. Carcinoma of cervix	3,500	5,200	7 months	1 month	Necropsy	Rectum	Recto-uterine fistula	None
21. Carcinoma of anus	.....	900	.....	7 months	Resection	Rectum	Ulcer	None
22. Carcinoma of cervix	6,400	3,000	3 months	5 months	Necropsy	Sigmoid	Ulcer	None
23. Carcinoma of rectum	2,900	4,500	3 months	4 months	Resection	Rectum	Ulcer	None

TABLE I—*Continued*

Primary disease	Radiotherapy		Duration of treatment (if multiple courses)	Interval from completion of treatment to time of pathologic examination	Method by which tissue was obtained	Radiation lesion		Neoplastic infiltration as part of lesion
	Roentgens	Milligram or millicurie hours				Site	Nature	
24. Carcinoma of vagina	.....	8,600	.....	4 months	Resection	Rectum	Recto-vaginal fistula	None
25. Carcinoma of rectum	.....	1,600	.....	9 months	Resection	Rectum	Sclerosis	None
26. Carcinoma of rectum recurrent following local resection	.....	3,000	5 months	8 months	Resection	Rectum	Ulcer	None
27. Carcinoma of rectum	6,000	3,800	8 months	8 months	Resection	Rectum	Ulcer	None
28. Carcinoma of cervix	7,200	2,800	.....	5 months	Biopsy	Rectum	Ulcer with stenosis	None
29. Carcinoma of cervix	.....	2,800	.....	3 months	Necropsy	Rectum	Ulcer	None
30. Carcinoma of rectum	10,000	.....	5 months	9 months	Necropsy	Rectum	Sclerosis	None
31. Carcinoma of cervix	4,800	8,100	4¾ years	2 months	Necropsy	Rectum	Recto-cervical fistula	None
32. Carcinoma of cervix	4,000	3,000	2 months	10 months	Necropsy	Rectum	Sclerosis	None
33. Carcinoma of cervix	1,800	6,900	6 months	2 months	Necropsy	Rectum	Recto-vaginal fistula	Present
34. Carcinoma of rectum	2,800	3,600	2 months	2 weeks	Necropsy	Rectum	Ulcer	Present
35. Carcinoma of rectum	.....	2,600	14 months	6 months	Resection	Rectum	Ulcer	Present
37. Carcinoma of rectum	6,300	.....	.....	2 months	Necropsy	Rectum	Ulcer	Present
36. Carcinoma of rectum	.....	1,700	4 months	9 months	Resection	Rectum	Ulcer	Present
38. Carcinoma of rectum	8,400	.....	.....	1 month	Resection	Rectum	Sclerosis	Present

perirectal tissues were extensively invaded by carcinoma that arose in the cervix. In another case carcinoma of the rectum had undergone extensive necrosis following radiotherapy, while the nearby sigmoid showed typical radiation sclerosis. It is felt that such lesions should be considered as radiation reactions independent of the neoplastic process.

TABLE II

Distribution of the Lesions in the Gastro-Intestinal Tract and Their Relationship to the Presence of Neoplasm

	Radiation reaction without tumor			Radiation reaction with tumor		
	Ulcer or fistula	Ulcer with stenosis	Sclerosis or stenosis	Ulcer or fistula	Ulcer with stenosis	Sclerosis or stenosis
Large intestine	10	1	6	5	1	1
Small intestine	3	4	1	3	..	..
Stomach	..	..	..	2	..	..
Appendix	..	..	1	..	..	..

PATHOLOGIC ANATOMY

The lesions consisted of ulceration, sclerosis and combinations of the two. The process sometimes involved a segment of intestine uniformly; in other instances it was focal, with single or multiple lesions.

The bowel wall was usually thickened and indurated, with the serosa opaque and showing prominent telangiectasia. The mesentery, particularly at its point of attachment, was frequently similarly involved. The mucosa rarely appeared entirely normal, but usually, even in non-ulcerated lesions, atrophy and fixation to the submucosa were seen. The degree of ulceration ranged from confluent, irregular, superficial erosions to deep, punched-out ulcers. The persisting mucosa was irregularly heaped up and nodular in the former, while discrete ulcers were very sharp-edged. Telangiectasia occurred especially at the edges of ulcerated areas. Stenosis was sometimes due to diffuse sclerosis with general constriction of a segment, and sometimes to formation of a stricture at a site of ulceration.

Secondary changes, such as inflammatory reactions related to penetrating or perforating ulcers and fistulae, were evident. Exudation of fibrin, fibrinopurulent membranes and adhesions were encountered. Necrosis was a part of most reactions and in extreme instances the reaction approached massive gangrene of a loop of intestine.

Histopathology

Connective Tissue

The changes in the connective tissues involved the mucosa, submucosa, vessel walls, stroma of the muscle layers and the serosal or adventitial tissues. There was usually edema of some degree and in early reactions edema was sometimes the dominant stromal change. There was frequently precipitated protein as well as an exudate of fibrin, with little cellular reaction to it as it lay unchanged and unabsorbed. In more advanced stages of reaction the characteristic "hyaline" change of the collagen, in which the collagen bundles are swollen, glassy and afibrillar, was seen. The hyaline change suggests "setting" or "gelling" of the edematous connective tissue and may superficially resemble amyloid. Special staining of the hyaline connective tissue revealed that there was swelling of the ground substance but usually relatively little increase in collagen fibers, reticulin fibers, or elastic fibers. The extent of actual fibrosis in the sense of new formation of fibrous tissue accounted only in part for the increased tissue mass of the hyaline connective tissue.

The hyaline thickening and edema of the connective tissue increased the thickness of the bowel wall considerably, especially in the submucosal and subserosal layers. The attached mesenteric tissues were similarly involved. In one instance the basement membrane of the surface epithelium was hyalinized and thickened.

The fibroblasts exhibited an atypical structure reminiscent of neoplastic change. Their processes were large and distorted. The nuclei were swollen, giant, bizarrely shaped, lobulated and even multiple, with prominent nucleoli and chromatin masses standing out darkly against a pale background in "owl's eye" manner.

Vessels

In the arteries, edema of the wall was seen early; and later, hyaline change quite comparable to that seen in the connective tissue elsewhere was noted. The muscle cells were sometimes hypertrophied and distorted. Sclerosis was far less marked in the arteries than it was in the veins. Obliterative endophlebitis was sometimes extreme with occasionally some splitting and reduplication of the elastica about the periphery. Lymphatic and venous ectasia together provided the most striking vascular feature of the reaction.

The endothelial cells in general rarely showed swelling and atypical cellular forms similar to those described for the fibroblasts. Deposits of fibrin in the vessel walls were sometimes seen, and occasionally there

were thromboses. The vascular changes were present in nonulcerated lesions, but with ulceration the local inflammatory process was accompanied by more marked fibrinoid necrosis, thrombosis and vascular sclerosis.

Mucosa

In ulcerative processes the epithelial lining was destroyed. There were, however, regenerative and healing attempts which differed little from those seen in other types of ulceration. Flat or cuboidal undifferentiated epithelium grew in from the ulcer edge, while remnants of glands within the ulcerated area sometimes became hyperplastic and in them cells of the mucous type were extremely prominent.

Even when the mucosa was not ulcerated it underwent profound alteration and sometimes atrophy. Mucous stasis with overproduction was a very common finding and was far more striking than is commonly seen in other conditions. The goblet cells were large and full and were present in great numbers. The glands showed various forms of distortion to varying degrees. They became short and wide-mouthed or, conversely, sometimes became very narrow and elongated, lined by flattened epithelium, or were dilated and cystic. Among the cells were frequently seen bizarre and atypical forms, even multinucleate and giant-cell elements.

In many cells the swelling of the nucleus and the prominent nucleolus and chromatin with an "owl's eye" appearance were characteristic. Varying types of cellular degeneration were seen, ranging from hydrops to necrosis. In one specimen an unusual change was noted—a marked degree of vacuolation of the parietal cells of the stomach.

Muscle

In many instances the muscle coats were also altered. Edema and vacuolation of the fibers were sometimes present, and in instances of marked change, degeneration and atrophy of fibers were widespread. Interstitial fibrosis with hyalinized connective tissue accompanied these changes, and hyaline degeneration and swelling of muscle fibers resembling Zenker's degeneration were sometimes seen. The combination of atrophic fibers, swollen fibers and hyaline interstitial fibrosis was very striking. In one case there were large, bizarre, atypical muscle cells in the muscularis mucosae. The abnormal muscle cells in vessel walls have been previously described.

Necrosis and Inflammation

Necrosis was extensive in the ulcers. While the necrotic tissue did not always present specific features, it was sometimes characteristic in

showing a distinct, glassy, homogeneous, acidophilic structure similar to that produced by a physical agent such as the heat of a cautery.

The inflammatory reactions were quite varied and all types of cellular response were seen. Granulation tissue frequently formed in the usual manner although occasionally the degenerated hyalinized tissues remained almost avascular.

Diagnosis

Knowledge of the changes seen in radiation reactions is of value from two points of view. On the one hand these changes are of academic and biologic interest in considering lesions studied at necropsy or in surgical material. The descriptions given in this paper give a perspective of the tissue changes seen in the gastro-intestinal tract in a moderately broad selection of material. It is evident that further study of the mucosal changes and of the gastric mucosa in particular is needed.

The second and more immediately practical point of view is that of the value of these criteria in making diagnoses on biopsy material. The differential diagnosis on pathologic grounds between the extension of a malignant process and a radiation reaction may be important. A common example is the problem of an ulcerated rectum in a patient irradiated for carcinoma of the cervix. A pathologic diagnosis of "radiation reaction" rather than "chronic inflammation," if it can be made, may be invaluable in deciding what therapy should be instituted. Therefore a brief review and summary of those changes which are likely to be useful in diagnosis will be presented.

The significant changes may be divided into primary and secondary criteria, that is, those without which the diagnosis cannot be made and those which are merely supportive. It is, of course, obvious that a biopsy specimen submitted for diagnosis may represent only a small part of the lesion. The primary points to be looked for are hyalinization of the connective tissue, abnormal fibroblasts, telangiectasia and hyaline degeneration of vessel walls. These have all been described in detail and illustrated.

Hyalinization of radiation reaction may be simulated by the hyaline fibrous tissue of chronic inflammation, but with experience the peculiar swollen, glassy, afibrillar matrix of radiation reactions can be fairly well distinguished. Rapidly proliferating *fibroblasts* in organizing and healing processes and in active granulation tissue somewhat resemble those seen in radiation lesions. However, in radiation reactions they are less abundant, show little mitotic activity and tend to be stellate and large rather than of the narrow spindle-shaped variety. Abnormal nuclear

forms, too, are rarely seen in other than radiation reactions. *Telangiectasia* involving the veins and lymphatics to a marked degree is very characteristic. It may even be seen in the gross specimen or in the lesion itself prior to removal. The *hyaline degeneration of vessel walls* requires no further comment, although the frequent presence of ordinary arteriosclerosis in the tissues of individuals from the higher age groups may be confusing.

The *secondary diagnostic features* include the endothelial abnormalities, phlebosclerosis, the changes in the muscle fibers and the epithelial alterations. Atypical endothelial cells are seen far less frequently than the almost invariably present altered fibroblasts, but when they are seen, they lend support to the diagnosis. Phlebosclerosis is an important part of the vascular change, but can seldom be seen clearly in a small specimen. It is also seen, of course, in many other types of inflammatory reaction as a residue of phlebitis and consequently is not a specific finding. Stains for elastica may bring out details that would otherwise be missed and many obliterated and partially obliterated veins were overlooked in our preparations until this method was used. The degeneration of the muscle coat may be evident in sections from a complete specimen but is seldom of value in a biopsy fragment.

Finally, the epithelial changes described are not necessarily characteristic of radiation reaction. Atypical glands, hyperplasia, regenerating epithelium and even the mucous change may be seen in any process that has damaged the mucous membrane. However, swollen nuclei with prominent "owl's eye" nucleoli, and marked mucous change are far more frequent in radiation reactions.

NOTE: We are indebted for clinical data to the Surgical Staff of the Palmer Memorial Hospital, particularly Dr. George A. Leland, Jr.; and to the Staff of the Lahey Clinic, as well as to Dr. Joseph H. Marks, radiologist to the New England Deaconess Hospital, and to Dr. Max Ritvo and Dr. F. W. O'Brien.

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2. Friedman, N. B., and Warren, Shields. Evolution of experimental radiation ulcers of the intestine. *Arch. Path.*, 1942, **33**, 326–333.

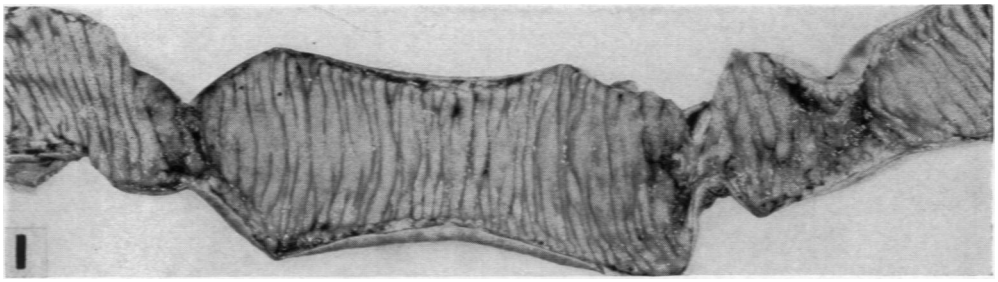
DESCRIPTION OF PLATES

PLATE 82

FIG. 1. Case no. 8. Multiple radiation ulcers and strictures of small intestine.

FIG. 2. Case no. 9. Regenerating epithelium at edge of radiation ulcer of small intestine. × 125.

FIG. 3. Case no. 1. Hyperplastic glands and mucous change in radiation ulcer of stomach. × 125.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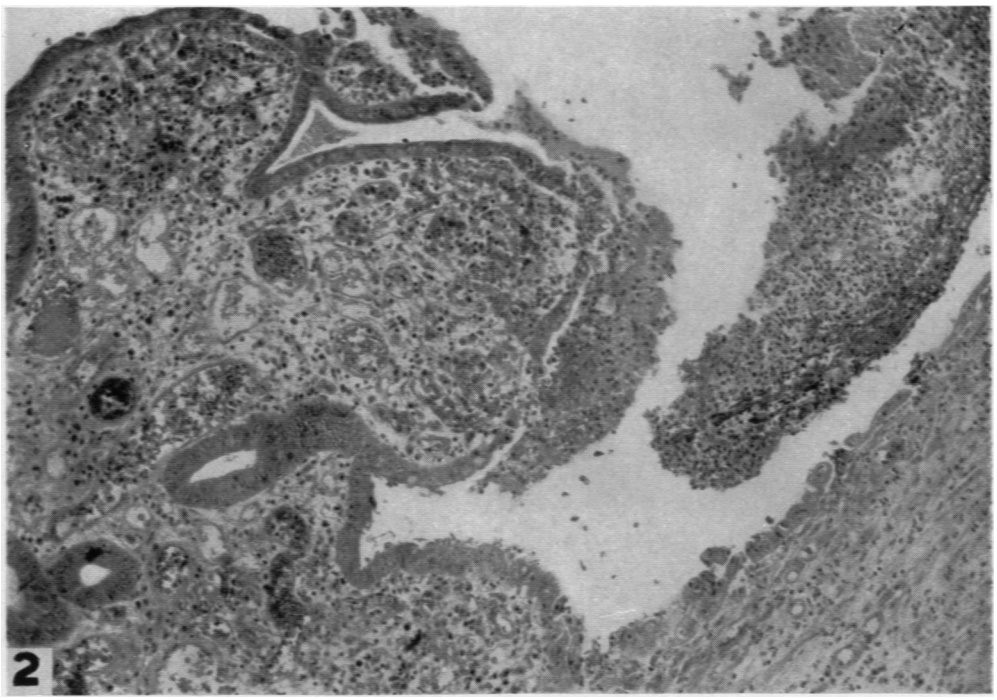
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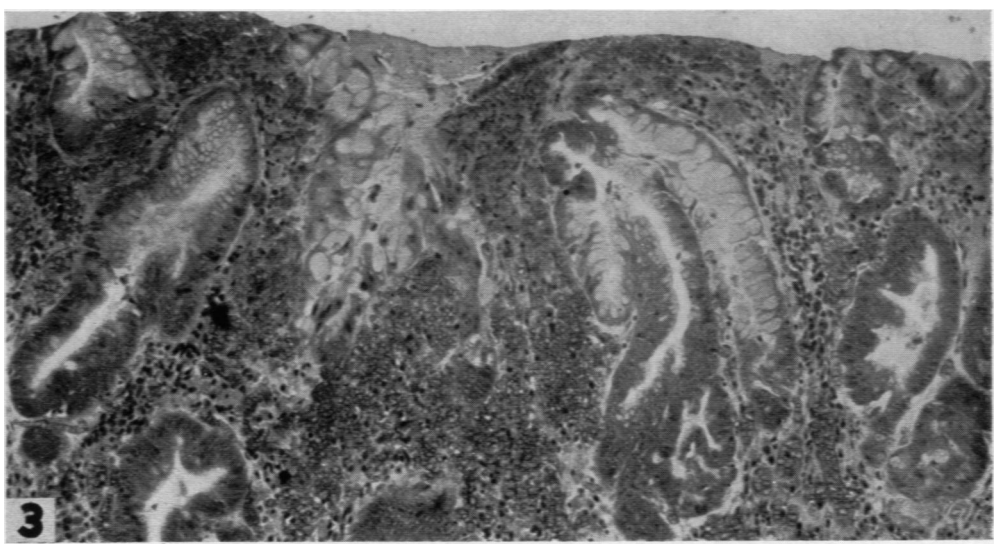
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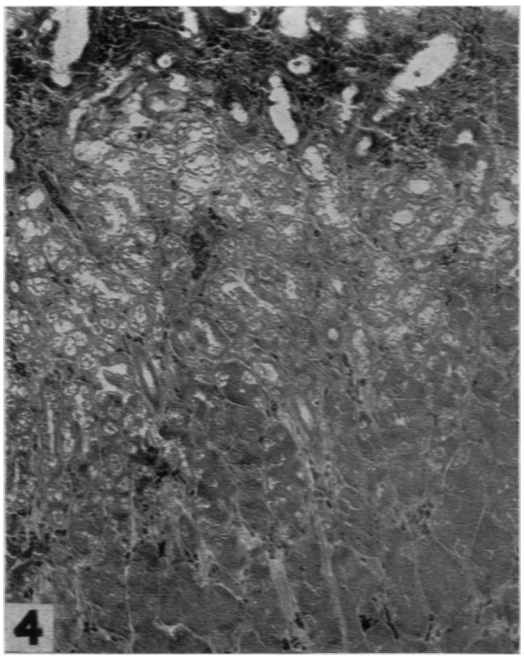
PLATE 83

FIG. 4. Case no. 1. Vacuolation of parietal cells in radiation reaction of gastric mucosa. × 125.

FIG. 5. Case no. 1. Same as Figure 4. × 500.

FIG. 6. Case no. 23. Hyalinized artery in radiation ulcer of rectum. × 200.

FIG. 7. Case no. 8. Phlebosclerosis in radiation reaction of small intestine. Elastica stain. An artery without significant change is seen. × 100.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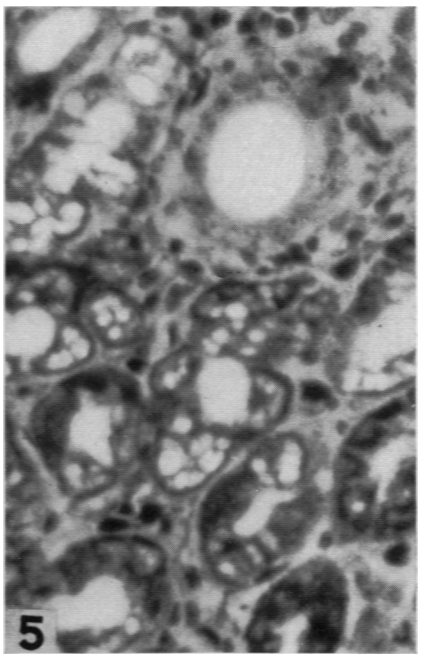
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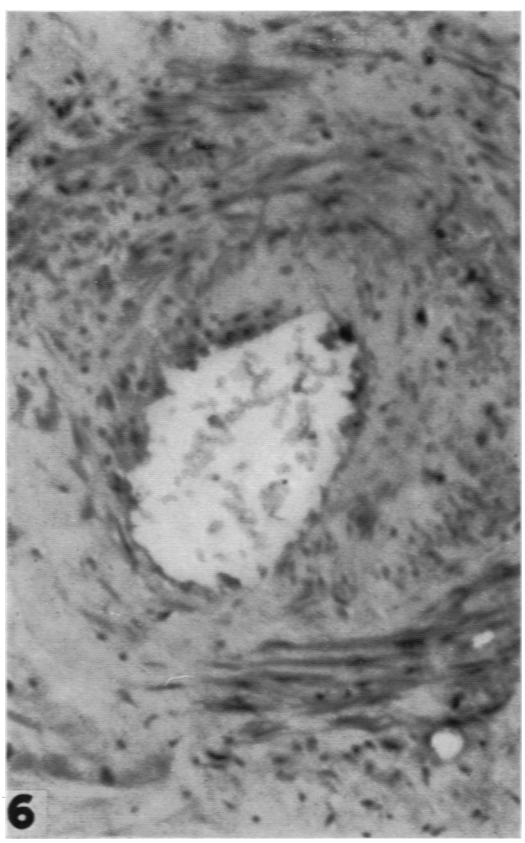
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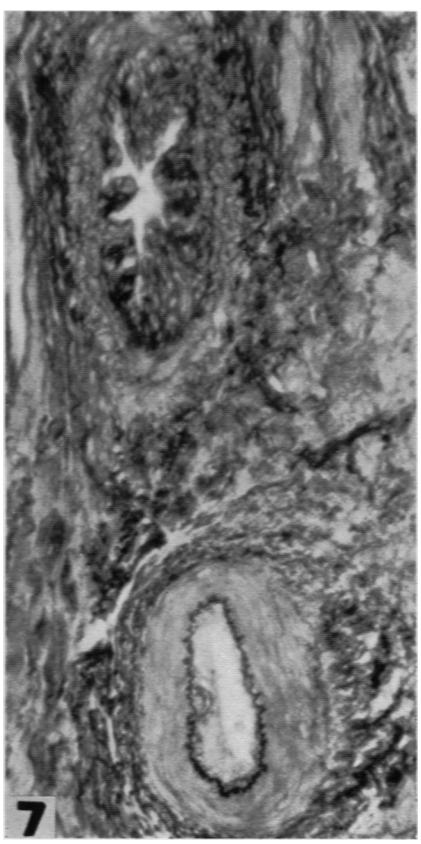
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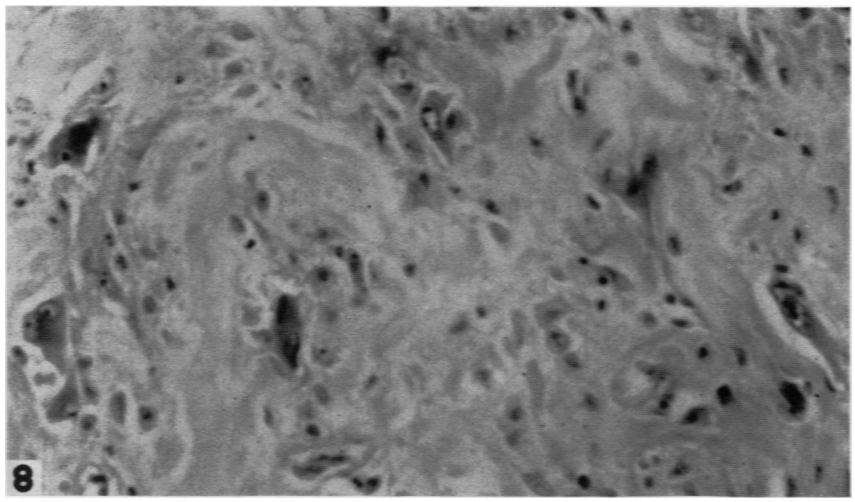
PLATE 84

FIG. 8. Case no. 29. Abnormal fibroblasts and hyalinized collagen in radiation ulcer of rectum. × 265.

FIG. 9. Case no. 9. Edema and telangiectasia of submucosa in radiation reaction of small intestine. × 55.

FIG. 10. Case no. 13. Radiation reaction in muscularis of small intestine. × 170.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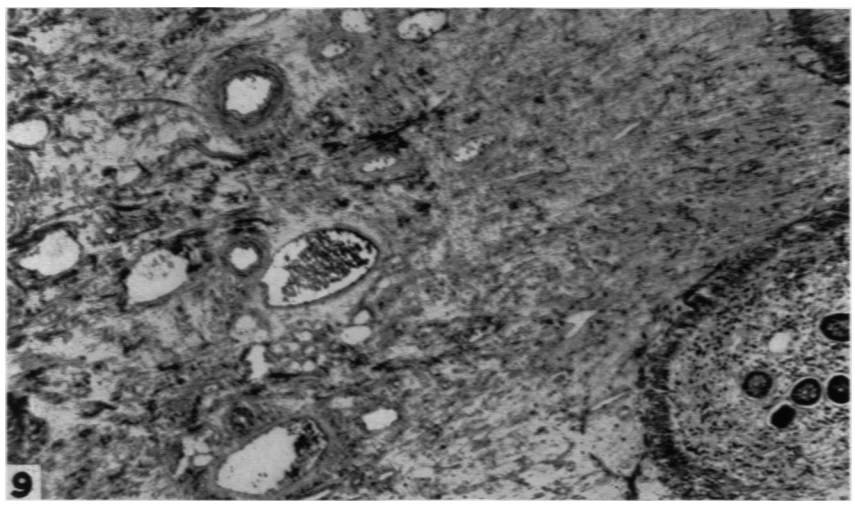
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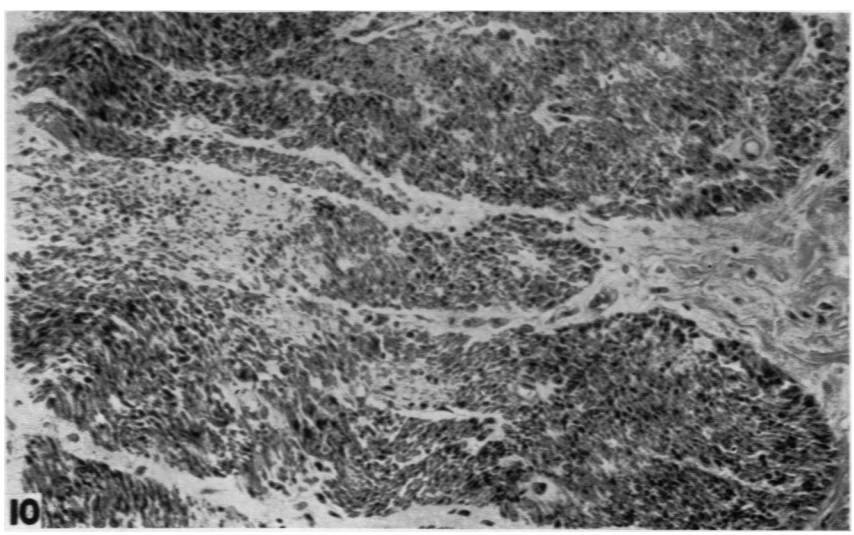
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