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NEOPLASMS IN RATS PROTECTED AGAINST LETHAL DOSES OF
IRRADIATION BY PARABIOSIS OR *PARA*-AMINOPROPYIOPHENONE

RESEARCH REPORT
Project NM 006 012.05.12

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NEOPLASMS IN RATS PROTECTED AGAINST LETHAL DOSES OF
IRRADIATION BY PARABIOSIS OR PARA-AMINOPROPYIOPHENONE

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ABSTRACT

Rats that survived otherwise lethal doses of radiation when protected by *para*-aminopropiophenone or parabiosis are followed along with their normal controls for the rest of their natural lives. Seventy animals have been irradiated. Of these, 22 have survived 6 months or more and in these survivors there has appeared an adamantinoma, renal carcinoma, sarcoma, adenocarcinoma of the duodenum, jejunum, and of the ileum, glioma and adenocarcinoma of colon; and a uterine sarcoma between 6 and 16 months after irradiation. During this time no tumors have developed in control animals. The high incidence of tumors in this small group of animals, and the incidence of tumor types that seldom occur spontaneously, indicate that these neoplasms were induced by whole-body irradiation.

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INTRODUCTION

This report describes a number of neoplasms observed in rats that were treated with *para*-aminopropiophenone prior to exposure to lethal doses of irradiation and in rats that were joined in parabiosis before or after such exposure. The number of animals involved is too small to permit any conclusions as to the incidence of these tumors. Their histologic characteristics are believed worth reporting, however, because spontaneous occurrence of the particular tumors observed is extremely rare. Moreover, it is hoped that this report may stimulate long-term observation of laboratory animals protected from the immediate effects of lethal doses of radiation.

MATERIALS AND METHODS

Groups of rats were exposed to single whole-body irradiation with doses ranging from 700 to 1,000 r. A number of these animals were protected against the early lethal effects of these doses by administering *para*-aminopropiophenone (PAPP) or glutathione (GSH) before irradiation, or by joining them to nonirradiated litter mates before or after exposure to X ray. The survivors were observed until death or development of symptoms of disease. Details of the experiments are described below.

All animals were female rats of the Sprague-Dawley strain raised at the National Institutes of Health. Radiation was delivered by a Picker therapy X-ray machine operating at 200 KVP (25 ma. 1.0 mm. AL, 0.25 mm. Cu, TSD 50 cm., field size 20 x 20 cm., HVL 0.8 mm. Cu., dose rate 44 r in air per minute). Half of each total dose was delivered to the dorsal and half to the ventral surface of the rat. Under these conditions the dose delivered to any part of a rat probably does not vary more than 1 percent. Actual measurements at various points of a masonite dummy differed by only ± 0.4 percent. All rats were 40 to 60 days old when irradiated, except those of the fifth experiment which were four months old.

In the first experiment, 20 rats weighing 115 to 148 grams were given PAPP, 30 mg. per kg. body weight, administered intraperitoneally as a 1 percent solution in propylene glycol (1). Twenty minutes later, these rats were exposed to 700 r whole-body irradiation. Of the 20 animals injected with PAPP, 11 survived beyond the 30th postirradiation day. Of these 11 survivors, 6 died between the 30th and 60th postirradiation day. The remaining 5 animals lived more than six months. Twenty-eight rats of comparable age and weight were exposed to the same dose without prior administration of PAPP. None survived beyond the 12th postirradiation day.

In a second experiment, 18 rats, weighing 115 to 140 grams, received 3 mg. of GSH, per gram of body weight intraperitoneally 15 minutes prior to irradiation with 700 r (2). Eighteen rats were given the same dose of irradiation without prior administration of GSH. Of the 18 animals treated with GSH, eight survived beyond the 30th postirradiation day; one each died 45, 68, 93, and 150 days following exposure. The remaining four lived more than six months. Of the 18 rats not treated with GSH, none survived beyond the 10th postirradiation day.

In a third experiment, 11 rats, weighing 85 to 117 grams, were exposed to 700 r and joined in parabiosis to nonirradiated litter mates (3). Six of the parabiotic pairs survived 30 days and were separated at that time. One of these irradiated animals died 45 days and one 111 days after exposure; the remaining four lived more than six months following irradiation. Ten rats of comparable age and weight were irradiated at the same time but not joined in parabiosis, and none of them survived beyond the 15th postirradiation day.

In a fourth experiment, 12 rats, weighing 150 to 190 grams, were exposed to 800 r and joined in parabiosis to nonirradiated litter mates. Eight pairs survived for 30 days and were separated at that time. One irradiated animal died on the 34th postirradiation day. The remaining 7 exposed rats lived more than six months. Ten rats of comparable weight and age were similarly irradiated but not joined in parabiosis, and none survived beyond the 12th postirradiation day.

A fifth experiment comprised 8 pairs of litter mates joined in parabiosis a month before irradiation. One partner of each pair was exposed to 1,000 r. Five of these pairs were killed for histologic studies within the first 5 days following exposure. The three remaining pairs were separated 16 days after exposure. One of the irradiated animals became progressively more anemic and was killed on the 20th postirradiation day. The two remaining pairs lived more than six months.

RESULTS

The tumors found in rats that survived doses of 700 to 1,000 r for more than six months are summarized in table 1. No tumors were seen in any of the rats that died earlier. Fibroadenomas of the breast, which were common in both irradiated animals and untreated litter mates, are not included in table 1 or in the subsequent discussion.

Only two of the tumors were identified by inspection or palpation during life. After the possibility of increased incidence, as well as the difficulty of diagnosis of tumors in the irradiated animals was recognized, all rats were closely observed for any signs, such as weight loss, diarrhea and rectal or vaginal bleeding, from which the existence of a visceral tumor might be suspected. Four animals exhibiting such signs were killed in the hope of obtaining tumor tissue suitable for transplantation, but no tumors were found. The remaining irradiated animals died spontaneously or were killed when moribund. In four of the irradiated animals death was caused by extensive tumor growth in vital organs. The immediate cause of death of the remaining animals was bronchopneumonia. The frequency with which irradiated animals developed pneumonia was in contrast to the rarity of such infections in animals of comparable age kept for other experimental purposes in adjacent cages. This apparent increase in susceptibility to infection was not due to a depression of the bone marrow, as was determined from study of the marrow, the peripheral blood count and the presence of massive leukocytic infiltration in the lung tissue.

Gross and Microscopic Findings in 8 Tumor-Bearing Irradiated Rats

Adenocarcinoma of jejunum. - Path. No. 57379. Whole-body irradiation, 700 r, December 27, 1950. Postirradiation parabiosis for 30 days. This rat developed a large mammary fibroadenoma and was killed on April 29, 1952, 490 days after irradiation, when the tumor had grown to a size of 10 x 8 x 6 cm. Eight inches below the pylorus, the jejunum was markedly dilated, measuring 2.5 cm. in diameter. At the caudal end of the dilated portion of the gut, the normal mucosa abruptly changed to a partly thickened area consisting of irregularly proliferating glands and villi lined with hyperchromatic cells with numerous mitoses extending to the tip of the villi and without the usual regular differentiation into goblet cells (fig. 1). Mucus production was, however, evident in some of the dilated glands that had invaded the mesentery. An adjacent mesenteric extension of the tumor consisted of a large cyst lined by columnar epithelium having multiple papillary ingrowths (fig. 2). There were no metastases to the regional nodes or other organs.

Adenocarcinoma of the ileum. - Path. No. 57363, Whole-body irradiation, 800 r, May 4, 1951. Postirradiation parabiosis for 30 days. Killed March 28, 1952, 330 days after irradiation, because of marked enlargement of the abdomen. Beginning at about 8 cm. proximal to the ileocecal valve, the ileum was markedly dilated for a distance of approximately 5 cm. and contained a polypoid tumor. The tumor infiltrated through the wall and extended in the form of a narrow cord to the bifurcation of the uterus, and along the uterine horns to both ovaries, which were largely replaced by tumor tissue. The tumor also invaded the pancreas and the adjacent splenic capsule. The polypoid tumor of the ileum consisted of glandlike cystic spaces of varying size, lined by columnar epithelium and partly filled by albuminous material with an admixture of neutrophilic leukocytes near the ulcerated surface. The tumor was sharply demarcated from the adjacent intact mucosa by the abnormal configuration of the glandular

spaces, but their epithelial lining closely resembled the normal intestinal epithelium, containing both goblet and Paneth's cells (fig. 3). An inflammatory reaction was seen only at or near the surface of the primary tumor which had penetrated and replaced the entire muscularis, producing a marked fibroblastic reaction with osteoid formation. The secondary tumor deposits closely resembled the primary lesion except for the generally smaller size of the glandlike structures and occasional proliferation of solid cords or nests of tumor cells (fig. 4). Even in these areas, however, and in groups of tumor cells invading lymphatics or veins, their differentiation into goblet or Paneth's cells was frequently maintained.

Adenocarcinoma of the duodenum. - Path. No. 57371. Whole-body irradiation, 800 r, on May 5, 1951. Postirradiation parabiosis for one month. Died April 17, 1952, 350 days after irradiation. At autopsy, a tumor mass was found in the abdomen that replaced the mucosa of both the pyloric portion of the stomach and the first part of the duodenum, and extended through the diaphragm, compressing and invading both lungs. Tumor deposits were also present along the anterior aspect of the thoracic vertebral column and in the pancreas. The structure of this tumor was indistinguishable from the one in the ileum described above. The primary site could not be determined anatomically either at autopsy or after serial sectioning of the intestinal tumor. However, the differentiation of invasive tumor tissue into Paneth's cells suggested the duodenum rather than the stomach as the site of origin*.

Adenocarcinoma of the colon. - Path. No. 60526. Whole-body irradiation, 1,000 r, January 8, 1952. Pre-irradiation parabiosis. Separation 16 days after irradiation. Killed in moribund state, December 23, 1952, 350 days after irradiation. At autopsy bilateral bronchopneumonia was present. In the colon there was a small sessile polyp, about 5 mm. in diameter, consisting of irregular glands lined by hyperchromatic columnar epithelium without any differentiation into goblet cells (fig. 5). The muscularis mucosae was interrupted at the narrow base of the polyp and partly reflected at its edge. Irregular glandular structures extended down to, but did not invade, the muscularis proper.

Glioma. - Path. No. 59169. Whole-body irradiation, 800 r, on May 5, 1951. Postirradiation parabiosis for one month. This rat developed intermittent convulsive movements and was killed August 11, 1952. There was an extensive hemorrhage in the left frontal lobe, secondary to a tumor which was recognized only upon microscopic examination (fig. 6). The main mass of the tumor consisted of closely packed cells with ample cytoplasm of ill-defined outline and nuclei of fairly uniform size, varying from round or oval to kidney-bean and irregular shapes, with numerous mitotic figures. Beyond the main mass, tumor cells permeated the adjacent brain substance in which ganglion cells were still intact (fig. 7), and extended along perivascular spaces and beneath the meninges.

Adamantinoma. - Path. No. 57380. Whole-body irradiation, 700 r, October 12, 1951, following administration of PAPP. About 6 months later, a slowly enlarging tumor of the left side of the lower jaw was noted and the animal was killed on April 29, 1952, 200 days after irradiation. The left side of the mandible was partly replaced by a cyst measuring 2 cm. in diameter with a partly calcareous wall, lined with soft tissue, measuring up to 5 mm. in thickness. On section, the tumor consisted of cords and nests of epithelial cells with palisading of the marginal cell layers, the nuclei of which often stood away from the adjacent connective tissue stroma (fig. 12). Eccentrically situated in nests of tumor cells were spicules of homogeneous oxyphilic material that occasionally showed fine striations resembling those of dentin. More frequently, this material was perforated by capillaries and resembled dental cement. With Heidenhain's azan stain, this material was colored blue. Contiguous tumor cells often formed a layer of very tall columnar cells containing oxyphilic granules

*In a recent, still incomplete series of experiments, another intestinal adenocarcinoma of the same type, with extensive lymphatic spread, was found in a parabiotic rat 6 months after exposure to 900 r.

which stain brilliant red. A fine line of similarly staining material was often present on the adjacent cement- or dentin-like material (fig. 13). Rywkind (4) has described a similar tumor in man and has interpreted the secretory activity of the tumor cells as representing an unsuccessful attempt at enamel formation, which normally does not result in accumulation of secretory granules in the ameloblasts. Although the tumor formed dentin and cement, it has been classified as adamantinoma since the bulk of the tumor was epithelial and duplicated in structure the usual adamantinoma seen in man.

Renal carcinoma. - Path. No. 59170. Whole-body irradiation, 700 r, October 12, 1951, following administration of PAPP. An abdominal tumor was palpable and the animal was killed on August 25, 1952, 315 days after irradiation. The palpable tumor was located in the perirenal tissue and there were numerous tumor nodules in both kidneys, both lungs, and the mesentery. Solitary tumor nodules were present in the liver and the serosa of the jejunum. Both adrenals were invaded by tumor tissue. The masses in the kidney included circumscribed multicystic lesions that contained albuminous fluid with a varying admixture of red blood cells. The cysts were lined partly with a single or double layer of cuboidal epithelium and partly with stratified transitional epithelium devoid of intracellular bridges (fig. 8). Other cystic lesions showed multiple papillary projections lined with stratified epithelium of the transitional type, with superficial keratinization in one area. Elsewhere the kidney contained solid nests of round or oval cells resembling the cuboidal cell layer of some of the cystic lesions; and there was invasion of glomeruli or individual glomerular loops by similar tumor cells (fig. 9). The kidney pelvis was not invaded in any of the numerous sections examined and there was no pyelitis. The pulmonary nodules of tumor tissue consisted of cystic lesions with papillary projections lined with stratified epithelium and of similar papillary growth without cyst formation. The stratified epithelium of the tumor frequently showed extensive superficial keratinization. The papillary projections of epithelium covering a delicate connective tissue on cross section often simulated the concentric arrangement of pearl formation, but individual cell keratinization was not found. Portions of the epithelium of smaller bronchi were frequently replaced by stratified epithelium (fig. 10). Such partial replacement of the bronchial epithelium was always associated with adjacent extensive tumor growth, which often extended beneath well preserved bronchial epithelium. The metastatic lesions in the liver, the mesentery, and in the cervical lymph nodes (fig. 11), showed cystic and papillary tumor growth similar to that seen in the kidney. Cell keratinization was not seen in any of these lesions nor in the tumor nodule in the serosa of the jejunum which had invaded the muscularis, slightly elevating the well preserved mucosa.

The primary site of the lesion could not be established. The possible diagnosis of primary lung tumor was considered, but the multicystic lesions of the kidney with their partly cuboidal epithelial lining were quite unlike the structure of metastases of known lung tumors. A diagnosis of renal carcinoma was therefore made. The superficial keratinization in the pulmonary lesions was considered to be squamous metaplasia. This tumor was successfully transplanted subcutaneously in rats for three generations and maintained its cystic papillary growth pattern. No squamous metaplasia was present in any of the transplants. One of the subcutaneous transplants grew to 3 cm. in diameter over a period of two months, but failed to metastasize.

Sarcoma of subcutis. - Path. No. 59415. Whole-body irradiation, 700 r, October 12, 1951, following administration of PAPP. Killed September 6, 1952, when it was thought that a mild diarrhea observed in this rat may possibly have been caused by a tumor. No anatomic cause of the diarrhea was found. A subcutaneous tumor was present on the left flank, measuring 1 cm. in diameter and consisting of round or oval cells with fairly uniform nuclei with finely distributed chromatin and moderate numbers of mitoses. Although the cells formed a pavement pattern in some areas resembling the arrangement of epithelial cells, silver impregnation showed a fine and complete permeation of reticulum fibers between the individual tumor cells,

indicating mesenchymal rather than epithelial origin. The tumor invaded the striated muscle of the abdominal wall and the adipose connective tissue between the well preserved ducts of a mammary gland. There were no metastases.

DISCUSSION

The incidence of spontaneous tumors in rats varies from strain to strain. No detailed data are available on Sprague-Dawley rats but observations on a limited number of animals indicate that in this as in other strains, mammary fibroadenomas are the most common benign tumors (5) and that sarcomas greatly outnumber carcinomas among spontaneous malignant neoplasms. The occurrence of 8 tumors, other than fibroadenomas, in 21 animals that survived for 200 to 500 days after exposure to X radiation appears to be in excess of the spontaneous tumor incidence reported in several strains of rats (6). Moreover, six of the tumors were epithelial in origin. Four of these were adenocarcinomas of the intestinal tract, described only a few times as occurring spontaneously (7,8,9). The renal tumor of the present series is clearly distinct from the moderately common renal tumors with a sarcomatous component (7) which are generally classified as either embryonal carcinomas or adenosarcomas (10). Purely epithelial kidney tumors of tubular origin have been rarely reported (7,11,12). An adamantinoma has been described in the rat only once (13). Only one published report of a tumor of the central nervous system was traced and this referred to a ganglioneuroma of the optic nerve (7). A glioma, closely resembling the one here presented, was observed in a rat exposed to simulated high altitude by Dr. Highman in this laboratory. In contrast, the uterine sarcoma found in a nonirradiated litter mate is moderately common (7). Thus the spectrum of tumors observed in the irradiated rats deviated markedly from that of spontaneously occurring neoplasms, suggesting that the tumors in the present series were induced by irradiation.

The intestinal tumors are of particular interest since adenomatous proliferation of the epithelium of the small bowel have been described by Bond *et al.* (14) following simple local irradiation of the gut with 1,800 to 3,000 r.e.p. by a 190 Mev deuteron beam, doses comparable in biologic effectiveness to 1,800 to 3,000 r. At the time of their original report, the longest period of observation following irradiation was seven months. None of the lesions had metastasized, and the proliferative lesions described could not be classified as potentially malignant or even definitely neoplastic. Similarly irradiated animals have now been observed for 12 months, and in one case masses of mucoid tissue were found scattered over the peritoneal surface of the bowel and the diaphragm. These lesions consisted of aggregates of glandlike cysts of varying size, filled with mucus, occasionally containing numerous neutrophilic leukocytes lined with columnar epithelial cells, some of which produced mucus while others had a granular cytoplasm characteristic of Paneth's cells. In none of the sections did groups of such cysts or of individual cells directly invade the muscular wall of the bowel and the deposit of similar adenomatous structures on the diaphragm was well separated from the striated muscle of fibrous or granulation tissue (fig. 14). Lymph nodes adjacent to one of these lesions were not invaded. In view of the absence of direct invasion or lymph node metastases, a diagnosis of pseudomyxoma peritonei was made. In earlier lesions following local irradiation, ulcerations of the mucosa with fibrous replacement of the entire muscularis, proliferation of epithelium with formation of diverticula at the edge of the ulcers, and perforations at these sites had been observed. Rupture of pinched-off diverticuli is believed to account for the peritoneal dissemination of proliferating epithelium.

In contrast, two of the lesions of the gut following whole-body irradiation showed invasion of lymphatics, and there was destructive invasion of ovaries, lungs, and adipose tissue. In one of these tumors, the site of origin was clearly established and the primary lesion was sharply demarcated from the adjacent normal mucosa. The same was true of the two polypoid lesions, one of which showed invasion of the muscularis, the other extension into the mesentery. The diagnosis of adenocarcinoma appeared justified in these two instances, even in the absence of metastases, since taken together the four intestinal tumors represented

an apparent progression from the locally invasive to the metastasizing lesions. There was no evidence that an inflammatory process or proliferation of normal epithelium had preceded these lesions, and it may be inferred that these carcinomas take their origin from a change in the epithelium itself. It is noteworthy that even in the destructively invasive lesions, the normal appearance of the intestinal epithelium, including the differentiation into goblet and Paneth's cells, was occasionally faithfully reproduced, a feature of intestinal carcinoma of rats noted by Dunn (15).

The renal carcinoma of the present experiments may be similarly contrasted with a case of epithelial proliferation in a locally irradiated kidney. In a series of unpublished experiments Bond irradiated the spinal cord of rats by a single tangential exposure of the back of the rat to 3,000 r.e.p. of the 190 Mev deuteron beam. In most instances, one or both kidneys were in the field of irradiation. All of these animals developed necrosis of the spinal cord and most of them succumbed within a few months. Vascular changes and predominantly tubular damage were seen in all irradiated kidneys. The kidney of the single rat that survived irradiation for 12 months showed, in addition, epithelial proliferation apparently originating from the tubular epithelium (fig. 15). High-power views of individual fields were strikingly similar to the renal carcinoma here described. However, there was neither invasion of perirenal tissues nor distant metastases.

It is not suggested that the proliferating lesions of the intestinal epithelium following local irradiation could not ultimately have developed into malignant neoplasms. Such epithelial proliferations were strikingly similar to the adenomatous diverticuli produced in the glandular stomach of rats by methylcholanthrene implantation by Hare *et al* (16). They observed 273 lesions of this type and considered them precancerous, although none metastasized. Regardless of the merits of their argument, it appears warranted to conclude that the histogenesis of the malignant tumors of the intestine following whole body irradiation differs from that of the adenomatous lesions following local irradiation in that the former appear to be initially proliferative and the latter secondary to ulceration and dislocation of epithelium into scar tissue.

The findings in both the kidney and intestinal lesions point up the difficulties encountered in diagnosing proliferative epithelial lesions in the rat as malignant. It is well known that the intestinal mucosa of the rat is particularly prone to proliferation extending into preformed planes of separation between muscle bundles, thus simulating invasion (9). The present observations serve to re-emphasize that only the progression to organ invasion or metastasis can establish the diagnosis of malignancy in rat tumors with certainty, at least at the present state of our knowledge.

Protection from the immediate lethal effects of single whole-body irradiation does not ensure a restitution to the pre-irradiation state. Rats protected by anoxia have been shown to have a shortened life span (17), and the present experiments indicate that this is also true of rats given PAPP or GSH before exposure to X ray or joined in parabiosis following irradiation.

The 30-day LD₉₉ for Sprague-Dawley rats of weights and ages similar to those employed in the present experiment has been previously determined to be 660 ± 30 (3); 700 r may therefore be considered as close to uniformly lethal dose and the doses of 800 to 1,000 r as invariably fatal. Only treated animals survive these larger doses. They cannot, therefore, be directly compared with untreated irradiated controls. A comparison is possible, however, between animals exposed to these larger doses following administration of PAPP and similarly exposed animals protected by parabiosis or GSH. Such experiments may demonstrate some differences in the incidence of late effects in animals subjected to the various treatments and possibly some measure of protection by one or the other of the treatments against long-term radiation effects, such as the induction of tumors.

SUMMARY

1) Eight tumors, other than mammary fibroadenoma, occurred in 21 rats protected from lethal doses of radiation either by pretreatment with glutathione or *para*-aminopropiophenone, or by parabiosis before or after irradiation. Six of the eight tumors were epithelial in origin, and all were locally invasive. Three metastasized.

2) The high incidence of tumors in this small group of animals, and the incidence of tumor types that seldom occur spontaneously, indicate that these neoplasms were induced by whole-body irradiation.

3) The histogenesis of four adenocarcinomas of the intestinal tract in these animals differed from that of previously described proliferative epithelial lesions of the mucosa following single local irradiation.

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Table I

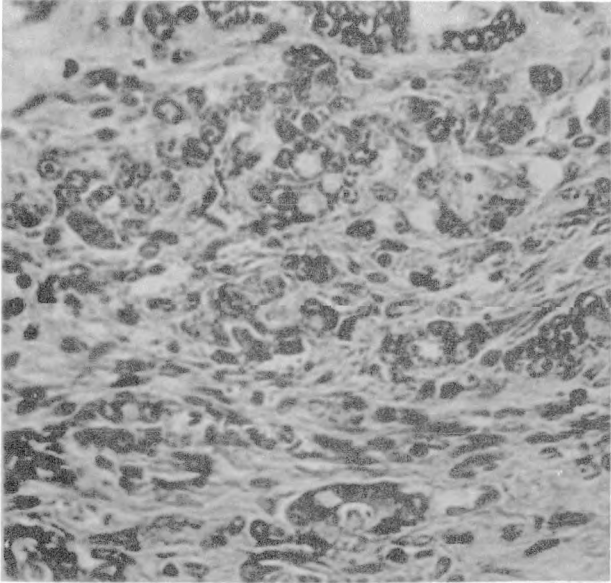
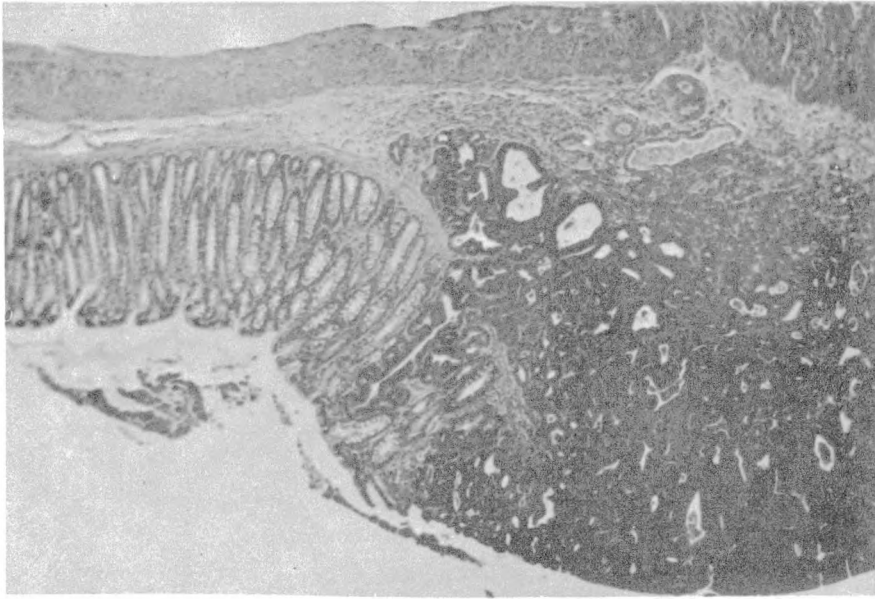
Tumors in Animals Surviving More Than Six Months
After Whole-Body Irradiation with 700 to 1,000 r

Dose in r	Treatment	No. of animals treated	No. of animals surviving 6 months or more	No. of animals with tumors	Type of tumors	Time between irradiation and autopsy
700	pre-irradiation <i>para</i> -aminopropiophenone	20	5	3	1 adamantinoma 1 renal carcinoma 1 subcutaneous sarcoma	6 months 10 months 11 months
700	pre-irradiation glutathione	18	4	0		
700	postirradiation parabiosis	11	3	1	adenocarcinoma of small intestine	16 months
800	postirradiation parabiosis	12	7	3	1 glioma 1 adenocarcinoma of small intestine 1 adenocarcinoma of duodenum	15 months 11 months 11 months
1000	pre-irradiation parabiosis	*8	2	1	adenocarcinoma of colon	12 months
none	parabiosis	10	10	1	Sarcoma of uterus	(16 months)†

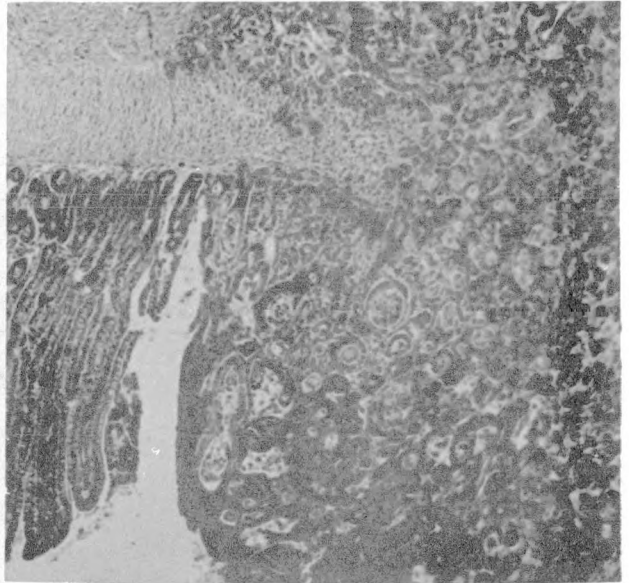
* 5 pairs were killed for histologic study within the first 5 days of irradiation.

† Time between irradiation of litter mates and autopsy.

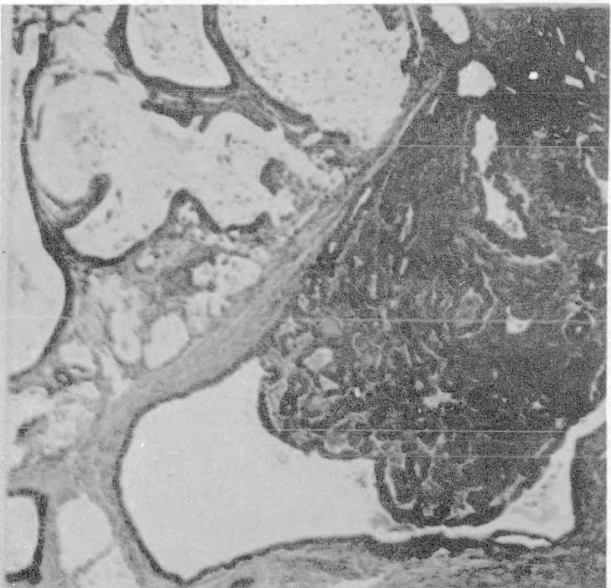
- Figure 1. Path. No. 57379. Edge of adenocarcinoma of jejunum in irradiated rat protected by parabiosis. Abrupt change to normal mucosa. X 80
- Figure 2. Same case as figure 1. Invasion of mesentery, partly with papillary growth, partly resembling mucoid producing adenomatous lesion following local irradiation (fig. 14). X 35
- Figure 3. Path. No. 57563. Adenocarcinoma of ileum, edge of primary lesion. X 30
- Figure 4. Same case as figure 3. Metastasis. X 350
- Figure 5. Path. No. 60526. Edge of polyp of colon with invasion of stalk. X 30



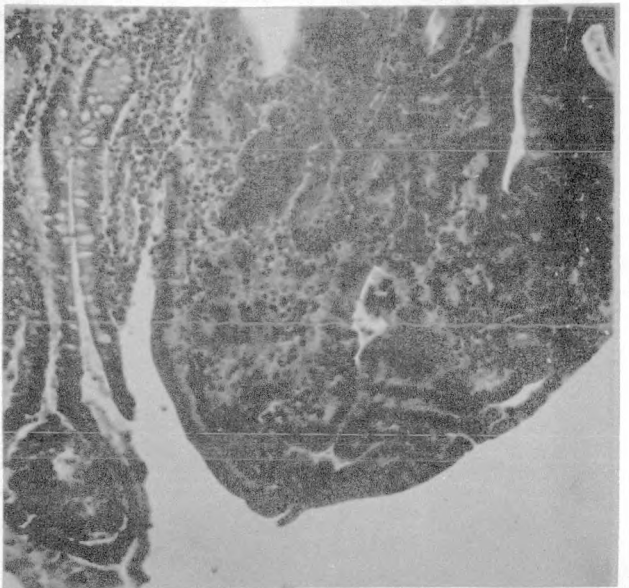
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3.



2.

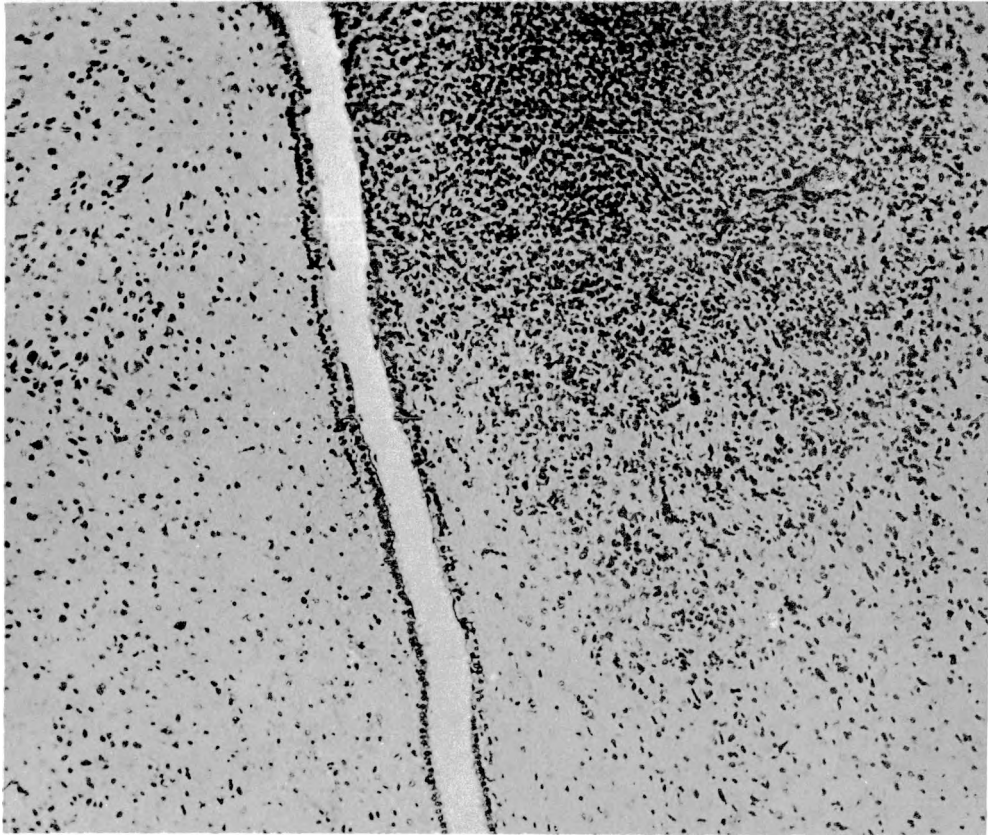


1.

Figure 6. Path. No. 59169. Glioma. X 30

Figure 7. Same case as figure 6. Edge of glioma with tumor cells spreading into normal brain tissue. X 400

6.



7.

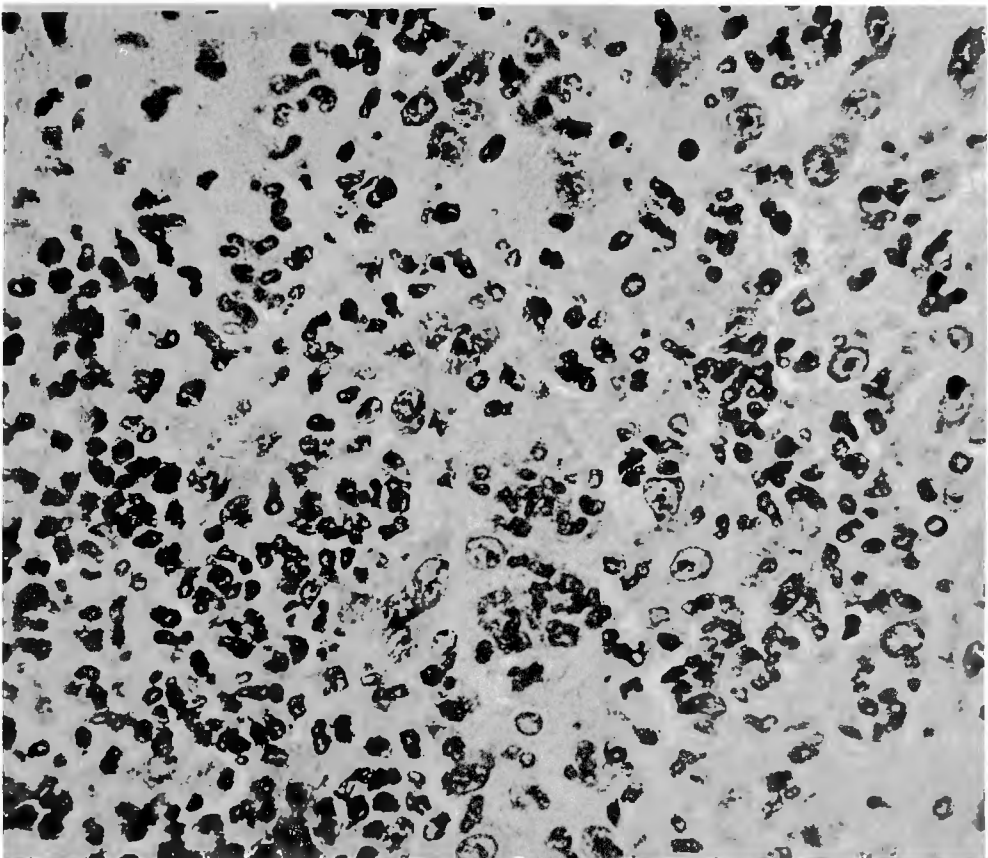
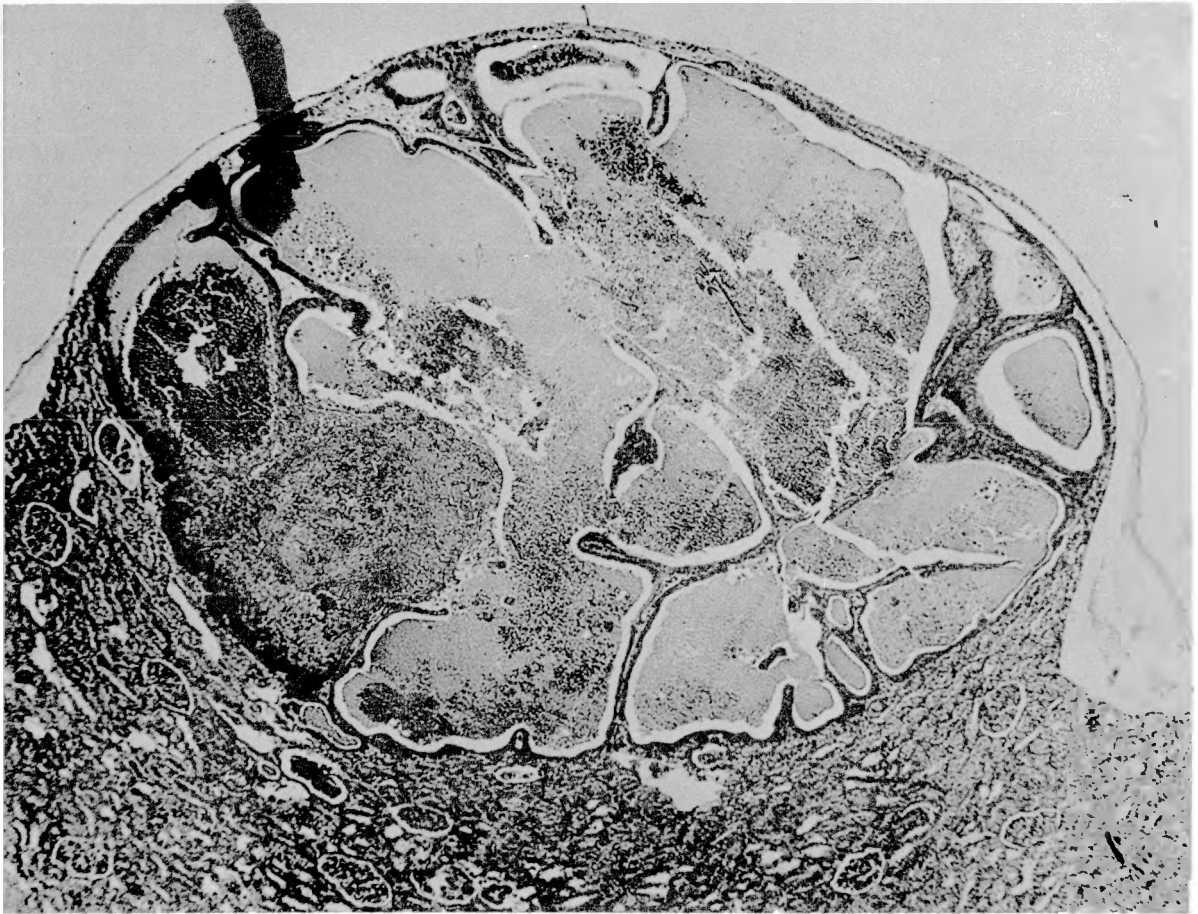


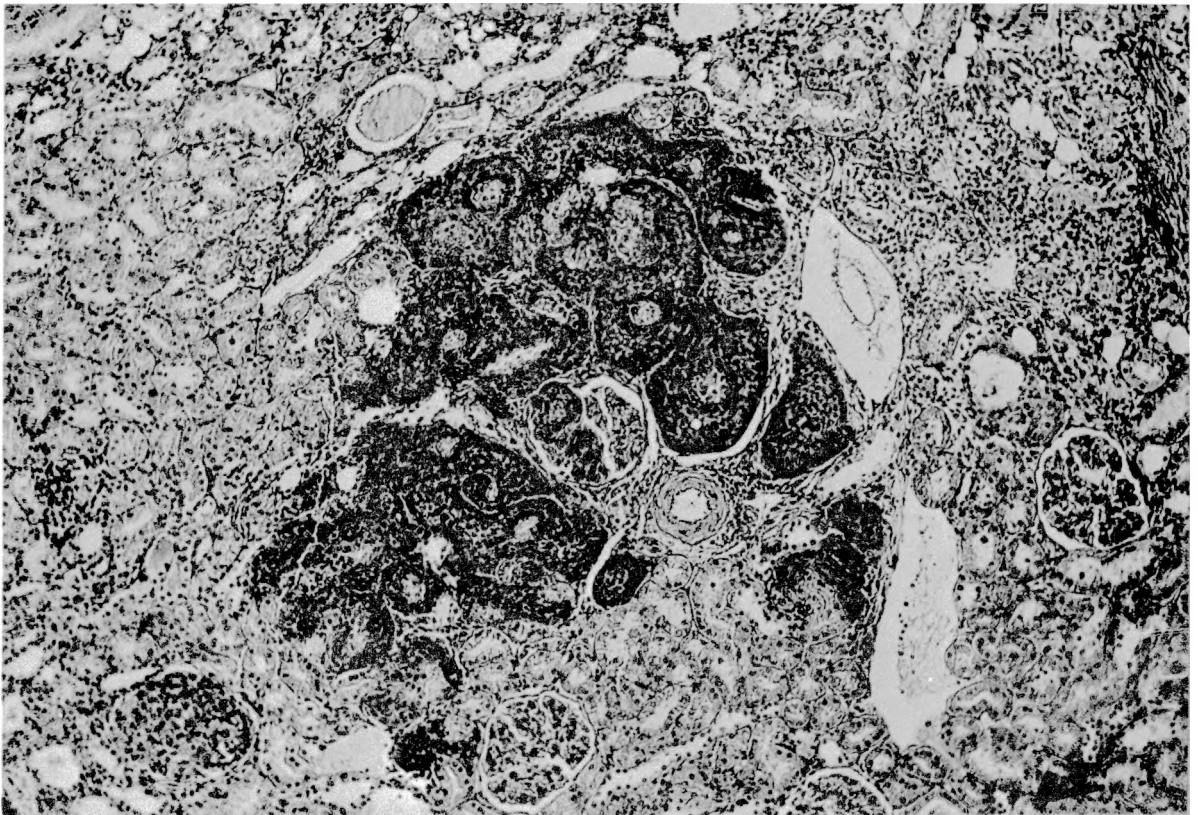
Figure 8. Path. No. 59170. Renal carcinoma. Cystic lesion. X 45

Figure 9. Same case as figure 8. Metastasis with solid growth and invasion of glomerulus.
X 90

8.

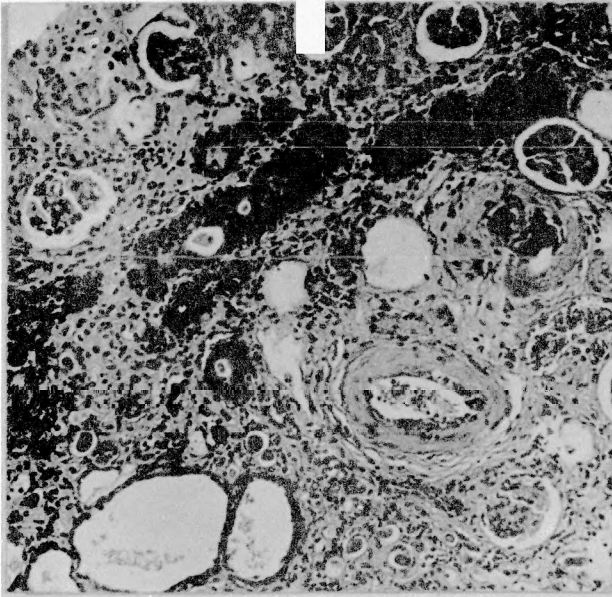


9.



- Figure 10. Same case as figure 9. Lung metastasis of renal carcinoma. Superficial keratinization. Invasion of bronchus. X 80
- Figure 11. Same case as figure 9. Metastasis in cervical lymph node. X 85
- Figure 12. Path. No. 57380. Adamantinoma. X 85
- Figure 13. Same case as figure 12. Secretory granules in palisaded tumor cells adjacent to cement-like material. X 500
- Figure 14. Adenomatous nodule on diaphragm (pseudomyxoma peritonei following local deuteron irradiation of gut). X 35
- Figure 15. Hyperplasia of tubular epithelium (following local deuteron irradiation of kidney). X 100

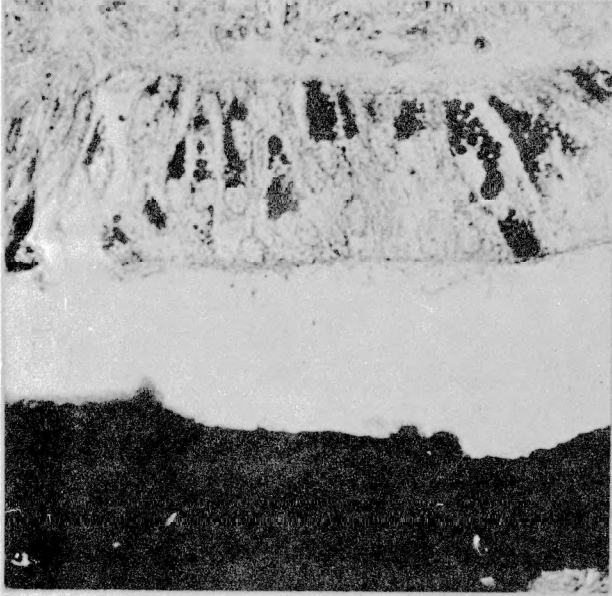
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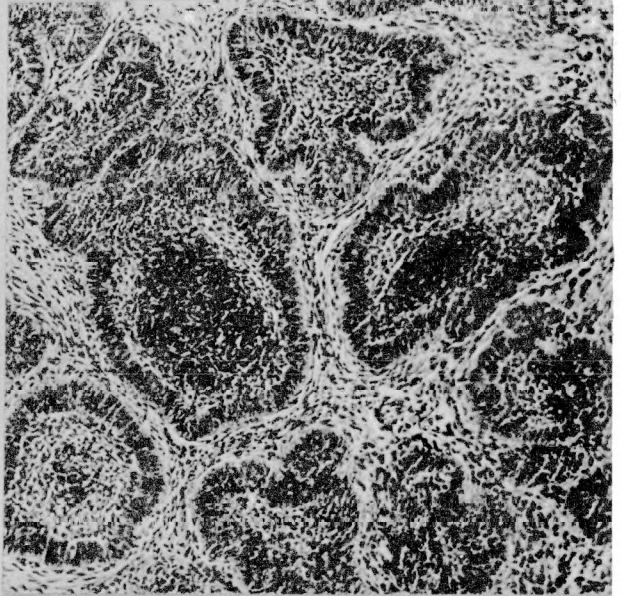
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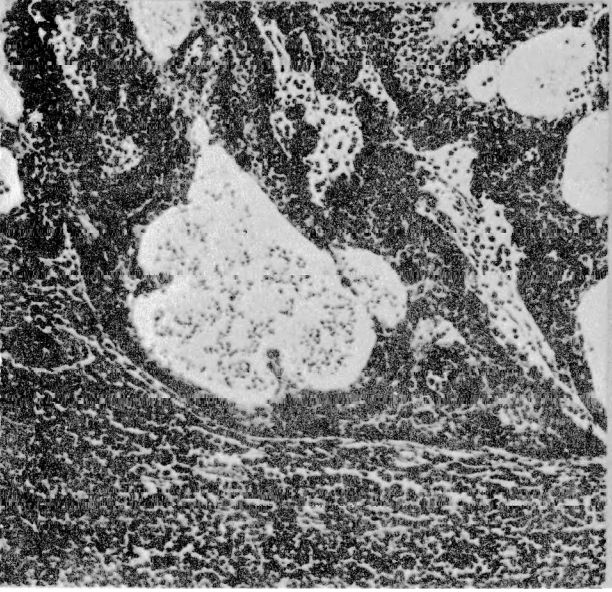
12.



13.



14.



15.

