ENDOTHELIAL-CELL SARCOMA OF LIVER FOLLOWING THOROTRAST INJECTIONS *

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As a pathological entity, a primary hemorrhagic endothelial-cell sarcoma of the liver is an unusual and interesting finding. When it is found in a patient who has received thorotrast, its presence may be of much greater significance. Thorotrast is colloidal thorium dioxide. It was first introduced into the practice of medicine 18 years ago when Blühbaum, Frik, and Kalkbrenner [1] described its use in roentgen visualization. As a diagnostic aid it has become widely adopted. It was first used in the field of gastroenterology, later in urology, and most recently in neurology. Its use has been condemned by some and extolled by others. Reeves and Stuck [2] have pointed out its disadvantages, and Yater [3] and McClure, Jankelson, and Osgood,[4] as recently as 1944, have championed its advantages.

REPORT OF CASE

The patient was a female who, at 40 years of age, had had a cholecystectomy. Ten years later she had experienced, over a 2-week period, attacks of paroxysmal pain under the costal margin. There was a history of considerable but vague abdominal distress during the subsequent 8 years. At the end of this period, when the patient was 58 years of age, a mass was described as filling the entire right half of the abdomen. A barium enema revealed displacement of the hepatic flexure and ascending colon to the left by a large mass in the right side of the abdomen. By pneumoperitoneum there were visualized one shadow filling the right half of the abdomen, interpreted as that of the liver, and a second shadow beneath the right diaphragm of undetermined origin. Repeated serological tests for syphilis at that time were strongly positive. Because of the uncertainty of the diagnosis a commercial preparation of thorotrast was given intravenously. Three daily doses of 25 cc. each were injected and very satisfactory contrast films were obtained. The liver was obviously rotated downward. The left lobe lay beneath the dome of the diaphragm and the right lobe filled the right half of the abdomen. The thorotrast also clearly revealed a sharply defined filling defect, measuring approximately 8 cm. in diameter. This lay in the right lobe. A diagnosis of gummatous syphilis of the liver was made and specific therapy was instituted. Following adequate intramuscular and intravenous antiluetic treatment, the patient became entirely free of symptoms. Subsequent roentgenograms taken over a 6-year period clearly demonstrated a progressive diminution in size of the liver and ultimate disappearance of the gumma. Ten years after the injection of thorotrast, the patient, then 68 years of age, was described as being in good health and very active physically and mentally. It is of interest that her blood pressure was subnormal for her age, averaging about 110/60 mm. Hg. Two years later she was admitted to the hospital as an emergency case. She had suddenly experienced weakness and pallor. On admission she was restless and her pulse was rapid. Laboratory studies revealed a hemoglobin of only 37 per cent and a red blood cell count of 1,760,000. Her condition

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was very poor. Blood pressure recordings were unobtainable. Treatment with transfusions was of no avail. She died a few hours after entrance with the clinical diagnosis of "shock, the result of internal hemorrhage."

AUTOPSY FINDINGS

At autopsy the body was found to be moderately well nourished and well preserved for 70 years of age. The skin and underlying tissues were pale and bloodless. The peritoneal cavity contained 2000 cc. of fluid and freshly coagulating blood. The *liver* was rotated and displaced to the right, and lay in an almost vertical plane. It was smaller than is normal and weighed only 1050 gm. It was composed of small and large lobes separated by deep and shallow furrows. It presented the picture of hepar lobatum. It was firm, reddish brown, and the surfaces of the individual lobes were smooth. In addition to this displacement and deformity there were three other unusual findings. First, the entire capsular surface showed a fine yellowish white, thread-like marking. Secondly, the right lobe was spotted with brilliant patches of red varying from 0.1 to 2 cm. in diameter. Thirdly, there was a ragged, friable, soft, spongy mass, 5 cm. in diameter, saturated with blood, that merged with the inferior surface of the liver. This was the source of the fatal hemorrhage and this was a primary tumor. Sections of the liver revealed that this soft blood-soaked mass of neoplastic tissue was embedded in its substance, that the many small hemorrhagic areas visible at the surface were equally numerous throughout the entire right lobe of the liver (these proved to be metastases), and that the yellowish white thready lines seen through the capsule traversed the whole liver. Adjacent to the hemorrhagic tumor these lines became broader and more numerous and converged on a solitary, firm, creamy yellow, gritty mass, 2 cm. in diameter. The *spleen,* which weighed 100 gm., was soft, reddish brown, and almost bloodless. Like the liver it showed, both on the surface and on section, innumerable delicate, yellowish white, interlacing thread-like lines throughout the parenchyma. *Lymph nodes* from the hilus of the liver, mesentery, and para-aortal area contained a yellowish white substance. The *bones* were fragile and could be cut easily with a knife. The *marrow* of the ribs, sternum, and vertebrae was red. The *heart* was small and moderately firm. The *lungs* showed one interesting finding grossly. There were several small, solitary, discrete hemorrhages in the right lower lobe which proved to be metastases.

Microscopical Examination

Liver. Before enumerating or describing the very extensive and unusual pathological changes within the liver, it is important to point out that a considerable portion was still well preserved. Three significant

histological lesions were demonstrable: (1) A primary malignant tumor with metastases, (2) a very heavy deposition of thorotrast with severe damage to the liver, and (3) scars of healed syphilitic hepatitis with gumma formation.

The most important of these three findings was the tumor with its regional metastases throughout the liver. There were several noteworthy features of this tumor (Fig. 1). It had originated in an area immediately bordering the largest concentration of thorotrast in the body. It was composed of a single type of cell resembling most closely the Kupffer cell. The cells varied considerably in size; the average was about as large as a liver cell. They varied in shape. Some were nearly round, others were elongated and narrow, still others were very irregular and showed grotesque vacuolated forms with large and small, clear, blistering projections of their cytoplasm. The average cell had very little cytoplasm and this stained mildly basophilic. The texture of the cytoplasm varied from ground glass to finely granular. The outer limits of the cells were poorly defined; often no cell membrane was demonstrable. The nucleus occupied most of the cell and its shape could be compared to that of a potato. The nuclear membrane was sharp, thin, and wire-like. The nucleus stained very lightly except for two or three coarse clumps of chromatin that were suspended in a very delicate web of reticulum. Mitotic figures were rarely seen and these were atypical. Some tumor cells showed degeneration, necrosis, disintegration, and lysis. Karyorrhexis with nuclear fragmentation was a conspicuous feature of this regressive change. Other tumor cells contained inclusions consisting of thorotrast, red blood cells, leukocytes, and hemosiderin. Tumor cells containing thorotrast seemed particularly susceptible to necrosis. While tumor cells appeared singly, they tended to arrange themselves in three common patterns, namely: (a) in clusters so close together that individual cell outlines could not be identified, (b) as walls of irregular blood sinuses, bearing the same relation to liver cells as Kupffer cells elsewhere, and (c) as walls of blood vessels replacing normal endothelium. Everywhere they showed a tendency to cling to pre-formed surfaces, whether cells, basement membranes, or reticulum. They invaded, destroyed by lysis, and crudely replaced normal sinus endothelium (Fig. 2). They invaded the trabeculae of liver cells, broke up lobules, and destroyed normal patterns (Fig. 3). Their most conspicuous characteristic was to break normal endothelial barriers and produce hemorrhages which showed no sign of coagulation (Fig. 4). They grew within the lumina of branches of the portal vein and metastasized freely throughout the liver (Fig. 5). The effect of the tumor in the liver was fourfold (Fig. 6). First, its very presence destroyed

liver tissue; secondly, the hemorrhages led to compression and atrophy of liver cells; thirdly, by interfering with local circulation there was infarction and necrosis; and lastly, by destruction and rupture of the capsule of the liver there was a fatal intra-abdominal hemorrhage.

The second significant finding was the extensive deposition of thorotrast. No portion of the liver was entirely free of it, but in some areas there was so little that the normal structure was well preserved. In other fields there was so much of this material that all structural detail was entirely lost and in such areas no living or necrotic cells were recognizable (Fig.7). The thorotrast appeared as tiny granules and globules closely packed together. It was rather colorless but at times acquired a faint eosinophilic tint. As the index of refraction was quite different from that of the tissues, it could be visualized very clearly in the tissues by controlling the amount of light. Much of this substance lay quite free in the tissues; the rest was taken up by histiocytes, Kupffer cells, and tumor cells. Some cells contained little, others were so distended with it that only the cell outline was recognizable. In fields where the cells were packed, it was impossible to distinguish one cell from another. Cells distended with this material died and their contents spilled into the surrounding space. The greatest concentration was in areas of old inflammatory scar tissue. Next in degree of concentration was the region about the central vein where it replaced the liver cells of the central zone, and at times of the midzones of the lobule (Fig. 8). In this area there was some condensation and hyalinization of the stroma, but there was no significant increase in fibrous tissue. A third site was in the capsule and portal connective tissue, but though the amounts here varied considerably, they were not to be compared with the larger quantities in the scars and central zones (Fig. 9). In many of the portal areas thorotrast was deposited in histiocytes or was free. In either case it lay embedded in an excess of dense, homogeneous, hyaline connective tissue. This increase in portal connective tissue was associated with an obliteration of lymphatics and a narrowing or occlusion of veins. Occasionally in such areas a vein was partially or completely occluded by a thrombus. The increase in collagen in association with thorotrast was much greater in the capsule and portal areas than in the central zones. Liver cells bordering collections of thorotrast showed several forms of degeneration, disintegration, and necrosis. One of these was characterized by the accumulation of lipids and hyalin in the cells (Fig. 10).

The third important finding in the liver was the presence of large and small, old healed inflammatory scars. These scars accounted for the gross nodular deformity. Some scars contained little thorotrast,

others were saturated with it. There was nothing in any of the sections to suggest an active syphilitic infection.

Spleen. There was a heavy deposition of thorotrast in fibrous tissue outside the splenic capsule, in the capsule, in and about the trabeculae, in the pulp, and in the follicles, but the greatest concentration was centered about the small vessels (Fig. 11). No part of the spleen was spared. As in the liver, thorotrast tended to collect in tracts and clusters. Sometimes it was confined to histiocytes, but often, and especially in fibrous tissue, it lay quite free. The detailed structure of the pulp was poorly defined, but almost everywhere there was a relative increase in supporting collagen. This was especially true of capsule and trabeculae. The follicles were small and relatively numerous. Each showed a small central core of primitive cells bordered by a loose ring of lymphocytes. Some of the sinuses contained developing blood cells, and in one or two areas in the pulp there were found clusters of primitive erythroblasts. There was a moderate deposition of iron pigment, and at times histiocytes contained both thorotrast and hemosiderin. An interesting observation was the complete absence of polymorphonuclear leukocytes in all sections.

Lymph Nodes. Thorotrast was deposited all through the nodes, but there was the same tendency here as in the spleen and liver for it to be concentrated in masses (Fig. 12). Thorotrast was found in circulating monocytes within the peripheral and traversing sinuses. Almost as conspicuous as the thorotrast was the diminution in the total number of lymphocytes (Fig. 13). The lymphoid tissue was confined to small scattered nodules embedded in a web of reticulum. There was some bleeding into the node and, although there was a moderate reticulum and endothelial cell hyperplasia, there was no suggestion of connective tissue proliferation or fibrosis.

Bone Marrow. Solitary histiocytes and large and small nests of histiocytes laden with thorotrast were scattered throughout the marrow (Fig. 14). There was a very uneven distribution and a very definite diminution in hematopoietic tissue. There was too much fat in the marrow, even for this age. The capillaries and sinuses were numerous and dilated, and capillary bleeding was common. Erythropoiesis was abnormal. There were small nests of erythroblasts and megaloblasts free of hemoglobin. There also were clusters of normoblasts, but many of these showed little tendency to exhibit normal maturation and some appeared to be undergoing disintegration. In many fields there were no myeloblasts, no myelocytes, and no cells of the myelocytic series. There were very few mature polymorphonuclear leukocytes, and eosinophils were entirely lacking. The number of megakaryocytes was

diminished, and of those present the majority were quite immature. There were loosely arranged nests of lymphocytes replacing normal marrow (Fig. 15). The over-all picture was one of too few cells, and of these, many were very primitive, many lacked evidence of normal maturation, and many, especially of the red cell series, showed premature death. There was no hemosiderosis and no erythrophagocytosis.

Bones. There was generalized osteoporosis and in many areas trabeculae had entirely disappeared (Fig. 17). The trabeculae were thin and delicate, and some showed patches from which all bone cells had disappeared. Their margins were ragged and rough, and the ground substance showed a linear marking with a tendency to split longitudinally and even to break up. Histiocytes laden with thorotrast often lay adjacent to bone, sometimes along the surface of trabeculae, at other times about capillaries along the haversian canals. It should be pointed out that no thorotrast was found within the ground substance of bone.

Adrenal Glands. There was little thorotrast in the adrenal medulla and in the endothelial cells of the sinuses throughout the cortex. Islands of medullary tissue were replaced by nests of lymphocytes and plasma cells, and by histiocytes laden with thorotrast (Fig. 16). There was degeneration, atrophy, and fibrosis of portions of the zona glomerulosa containing thorotrast (Fig. 18).

Kidney. The normal structural detail of the kidney was well preseved, but there were two changes worthy of description. In blood vessels (Fig. 19) there was a disappearance of stained cytoplasm from the smooth muscle fibers of the walls; the elastica was interrupted and and in places absent, and the lumina were abnormally wide. The second change was that an occasional glomerulus showed a deposition of thorotrast associated with focal collapse and hyalinization of the glomerular tuft.

Lungs. In sections of the lungs taken through areas of hemorrhage there were tumor cells lining alveolar spaces distended with blood. There was a disappearance of smooth muscle from the walls of blood vessels (Fig. 20) and bronchi, and a replacement with hyaline tissue. No thorotrast was found in sections taken from the periphery of the lung.

Heart. Beneath the endocardium the muscle fibers and their cross striations were well preserved but elsewhere the fibers were swollen and their cross striations were either lost completely or were cloudy and barely discernible. No thorotrast was found, but there was a light collection of lymphocytes and plasma cells about some of the small vessels in the interstitial tissue. Small arteries were dilated and their walls were hyalinized and devoid of smooth muscle.

Final Diagnoses

Fatal intra-abdominal hemorrhage, from an endothelial-cell sarcoma of the liver showing multiple regional metastases. Thorotrast deposition and irradiation, with degeneration of liver, spleen, lymph nodes, bone marrow, bones, adrenals, kidney, and blood vessel walls. Old healed syphilitic hepatitis (hepar lobatum).

Discussion

All four significant lesions in this patient—the fatal hemorrhage, the malignant tumor, the thorotrast deposition, and syphilis—were centered in the liver. The hemorrhage was very large and sudden, and the tumor was its obvious source. This was filled with blood even after its outer surface, which was formed by the liver capsule, had ruptured into the peritoneum.

A hemorrhagic sarcoma apparently having origin in sinus endothelium is a very rare primary tumor of the liver. In this tumor the cells resembled Kupffer cells in both structure and function. They had the property of phagocytosis and could build crudely constructed sinuses. They tended to retain the same intimate association with liver cells as is shown by normal sinus endothelium. Their most striking characteristic was to destroy normal endothelium and produce multiple hemorrhages.

The significance of the thorotrast in the liver must not be underestimated. Most important was the fact that the tumor had originated in immediate association with the largest single deposition of this material in the body. Secondly, thorotrast had severely damaged the liver cells by slowly progressive necrobiosis which at the time of death was still active. The almost negligible regeneration of liver cells may also be attributed to its presence. Thorotrast had led to fibrosis of portal areas with narrowing and occlusion of veins and lymphatics and subsequent interference with the portal circulation.

In respect to the original syphilitic lesion, all that remained were coarse scarring and contractures leading to the well known hepar lobatum. That the liver was much below normal in size and weight can be explained only by the scarring and by progressive destruction of liver cells without significant regeneration.

Thorotrast in the reticulo-endothelial system of bone marrow, spleen, liver, and lymph nodes had seriously affected hematopoiesis. Much of this material was confined to the fixed cells, much of it was free, but some of it was found in circulating histiocytes, clearly indicating that thorotrast was in a continual process of migration.

Grossly, the bones were fragile and could be cut or broken easily;

histologically, there was direct evidence of necrosis where thorotrast and bone lay side by side.

In addition to these changes which were associated with thorotrast in immediate contact with tissues, there was the possible remote effect that thorotrast might have had on the cardiovascular system. Histologically, three changes were repeatedly observed in vessels in different parts of the body. First, there was degeneration and disappearance of smooth muscle fibers from the walls of both veins and arteries. Secondly, there was degeneration and interruption of the elastica in the walls of smaller arteries. Thirdly, there was a tendency on the part of arterioles and capillaries to dilate and bleed. It is of interest to correlate these changes with the clinical observation that in later years the patient's blood pressure had been consistently low.

Thorotrast as an Injurious Substance

There can be little doubt from a study of this case that thorotrast can do harm. The observations of Jacobson and Rosenbaum [5] can attest to that, for they found fibrotic changes in liver, spleen, lymph nodes, and arteries in a patient who 5 years before had received 75 cc. of this substance. Thorotrast, or thorium dioxide, is distinctly radioactive. In this respect it closely resembles uranium and radium, the activity of which depends on the continual liberation of ionizing radiations known as alpha, beta, and gamma emanations. In the body it is the gamma ray which is known to cause most harm. The amount of thorotrast injected into the body for diagnostic purposes varies, but the maximum doses employed are known to have a gamma ray equivalent to about 1 to 3 μg. of radium. The general effects of irradiation injury in the body are well known and parallel very closely the findings in our patient. For example: Bone marrow shows hypoplasia, dysplasia, and a disappearance of eosinophils; capillaries dilate and show a tendency to bleed; lymphoid tissue shrinks through injury to lymphocytes; bones become atrophic and break; glandular tissue degenerates; and smooth muscle may disappear.

Because of the property of spontaneous disintegration possessed by radioactive substances, it was of interest to know whether thorotrast, after a period of 12 years in the body, was still radioactive. To answer this question, blocks of liver tissue that had been preserved in formalin as long as 12 months after the autopsy, were tested with a Geiger-Mueller counter. This is a comparatively simple electrical apparatus, named after its inventors, for measuring and observing cosmic emanations. Each piece of liver gave a positive recording and the highest reading was obtained from the area of greatest thorotrast concentration. This was also the site of the primary malignant tumor.

Thorotrast as a Sarcogenic Agent

In 1929 Martland and Humphries [6] were the first to report the appearance of osteogenic sarcoma, attributed to radium and mesothorium, in 2 of 15 girls employed at painting watch dials with luminous radioactive paint. This report was followed 3 years later by a paper by Sabin, Doan, and Forkner [7] who described the appearance of osteogenic sarcoma in 2 of 7 rabbits, surviving 11 and 19 months respectively, that had been injected intravenously with radium chloride and mesothorium. Ross,[8] in 1936, implanted a platinum tube containing 0.1 mg. of radium under the periosteum of the rib of a rabbit, and 2 years later the tube was found encased in a large, actively growing osteogenic sarcoma. More recently, Dunlap, Aub, Evans, and Harris [9] produced osteogenic sarcoma in 9 of 13 male Wistar rats after feeding each animal 100 μg. of radium. There is no longer any question about the appearance of malignant tumors in man and animals subsequent to the injection or ingestion of radioactive substances. It is apparent, however, that in each of these cases the primary tumor has been in bone. This might suggest tissue specificity, but there is another and much more probable explanation, for Martland [10] has shown that when radium salts are ingested orally, the distribution of radium in the body is like that of lead. After absorption, it is phagocytized by cells of the reticulo-endothelial system and then it enters the skeletal system where it is concentrated and, in part at least, may be permanently retained. This is important in skeletal tumors induced by radium, for it is in bone and from bone that the osteogenic sarcomas arise.

The significance of such factors as concentration and localization of this sarcogenic agent in respect to the site and type of tumor produced has been demonstrated again by Roussy, Oberling, and Guérin,[11] who successfully produced peritoneal and subcutaneous sarcomas in 8 of 15 surviving mice that had been given intraperitoneal and subcutaneous injections of thorium dioxide. In our patient the greatest concentration of thorotrast was in the liver and it was in this organ that the primary malignant Kupffer cell sarcoma arose.

Thorotrast as a Diagnostic Aid

The most widespread use of thorotrast has been in the field of gastroenterology in the detection of diseases of the liver. In urology it seemed at first to be an ideal substance for pyelography, but soon its use was discarded because it tended to cause exacerbations of existing infections, to damage collecting tubules, to lead to obstruction, and to obscure lesions within the kidney. In certain diseases of the central nervous system it has been used in both diagnosis and localization. Here it has been injected locally, into vessels and even into the ven-

tricles; but for cerebral angiography, encephalography, and ventriculography its use has been generally condemned. It is still used, however, with great advantage, in very small quantities, to outline a cyst or abscess of the brain. Its most recent use has been in a study by Davis and Potter [12] of intra-uterine respiration and gastrointestinal activity. After injecting thorotrast into the amniotic sac it soon appears in both lungs and intestines of the fetus.

SUMMARY AND CONCLUSION

A case is reported of a patient who had been given thorotrast for the visualization of the liver. With the aid of this diagnostic procedure, combined with positive serological tests, it was possible to make an accurate diagnosis of hepatic syphilis with gumma. Following specific therapy, the patient made a clinical recovery and for 12 years lived a reasonably normal life. At the age of 70, death came suddenly. Autopsy findings confirmed the diagnosis of syphilis and in addition revealed a primary hemorrhagic endothelial-cell sarcoma of the liver, the source of fatal hemorrhage, and very widespread irradiation injury affecting particularly the liver and hematopoietic system. Evidence is produced from a study of this case to support the debatable contention that thorotrast, in sufficient quantities, as a radioactive substance, is injurious. Evidence is also produced to show that thorotrast, like other radioactive substances, in sufficient time may act as a sarcogenic agent.

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[*Illustrations follow*]

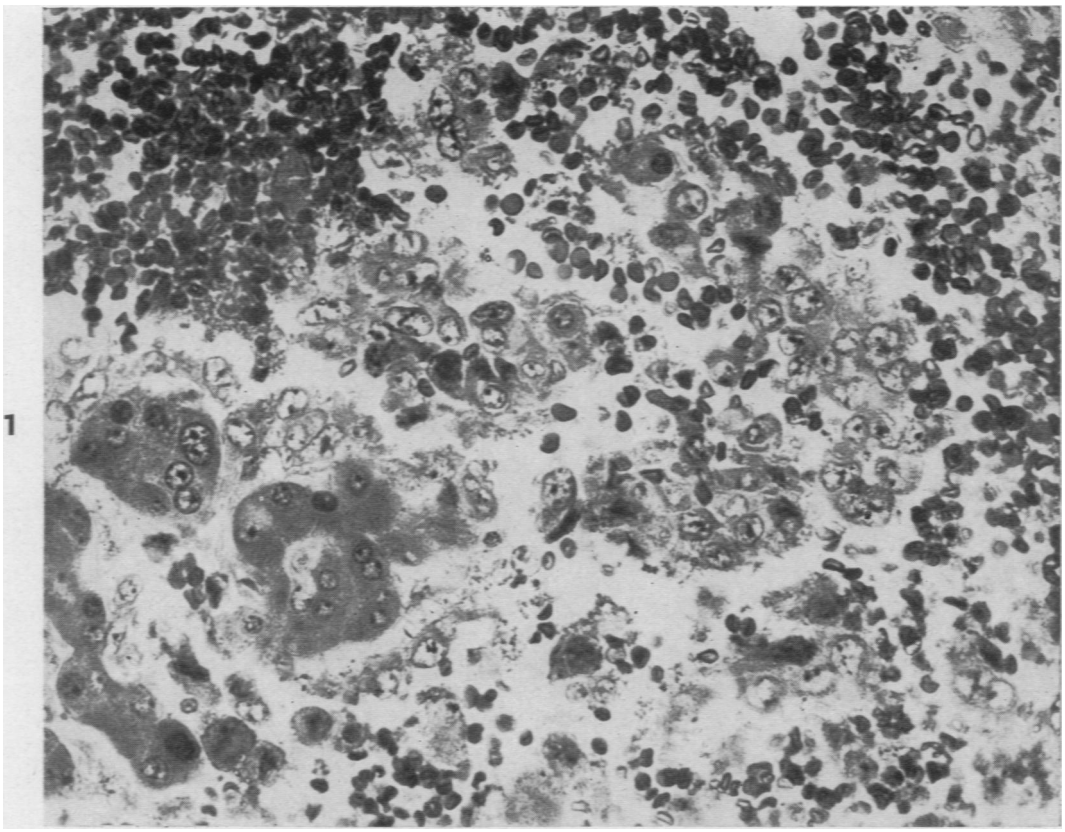
DESCRIPTION OF PLATES

All photomicrographs were made from sections stained with eosin and methylene blue.

PLATE 95

FIG. 1. Liver, showing nests of tumor cells bathed in blood. In the lower left-hand corner there are three groups of liver cells surrounded by tumor cells and blood. The tumor cells tend to group in clusters and to cover and surround liver cells with which they come in contact. The tumor cell is often as large as a liver cell; it has little basophilic cytoplasm, that varies from a ground-glass appearance to very finely granular. Its cell membrane is indistinct and when the cells are clustered it is impossible to see the lines separating one from another. The nucleus is large and occupies most of the cell. It is lightly stained. The nuclear membrane is sharp and wire-like. In shape, the nuclei resemble potatoes. There is little chromatin and this forms coarse clumps suspended in delicate interlacing threads. Mitotic figures are very seldom seen and then they are asymmetrical and hyperchromatic. × 275.

FIG. 2. Liver. In the lower right-hand corner there are trabeculae of liver cells showing compression atrophy. The remainder of the field is made up of loose tumor cells bathed on all sides by noncoagulated blood, and of a few small clumps of degenerating liver cells—all that remains of the lobule. × 140.



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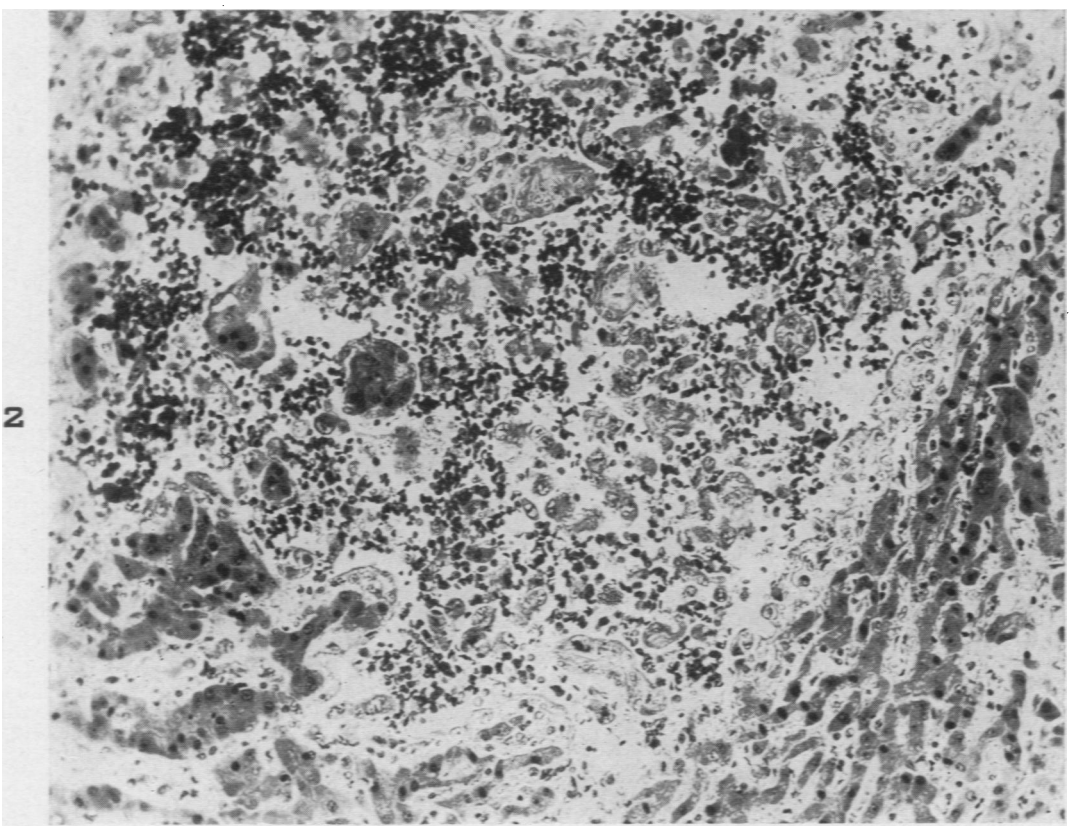

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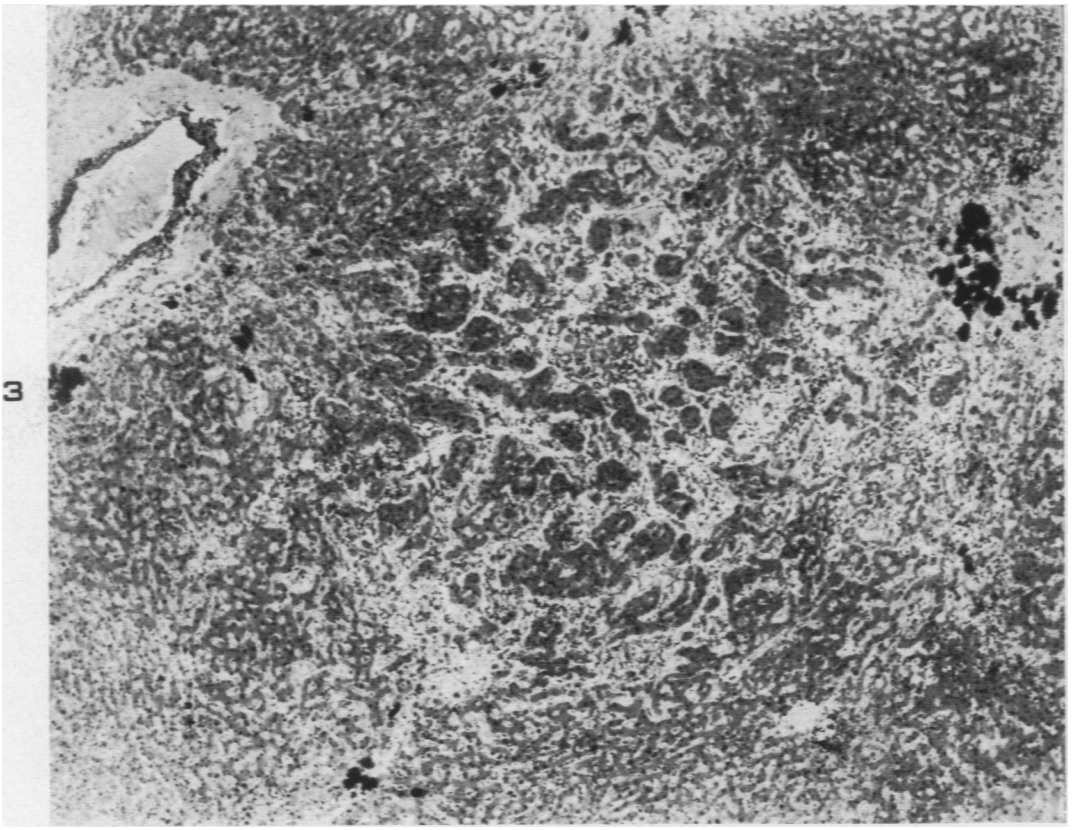
MacMahon, Murphy, and Bates Sarcoma of Liver Following Thorotrast

PLATE 96

FIG. 3. Liver, showing an area in which the normal trabecular pattern is broken up into small cords or islands of liver cells separated by spaces filled with blood and bordered in part by tumor cells. An occasional film of fibrin coats an island of degenerating liver cells. Small deposits of thorotrast are visible in the surrounding tissue. × 90.

FIG. 4. Liver, showing one of many hemorrhages. This hemorrhage lies very close to a portal area, below. The surrounding liver cells show compression. In the area of hemorrhage there are a number of tumor cells almost completely hidden by blood. A few necrotic and disintegrating liver cells are seen adjacent to the margin of the hemorrhage. There are small deposits of thorotrast, both to the right and left of the hemorrhage. × 140.



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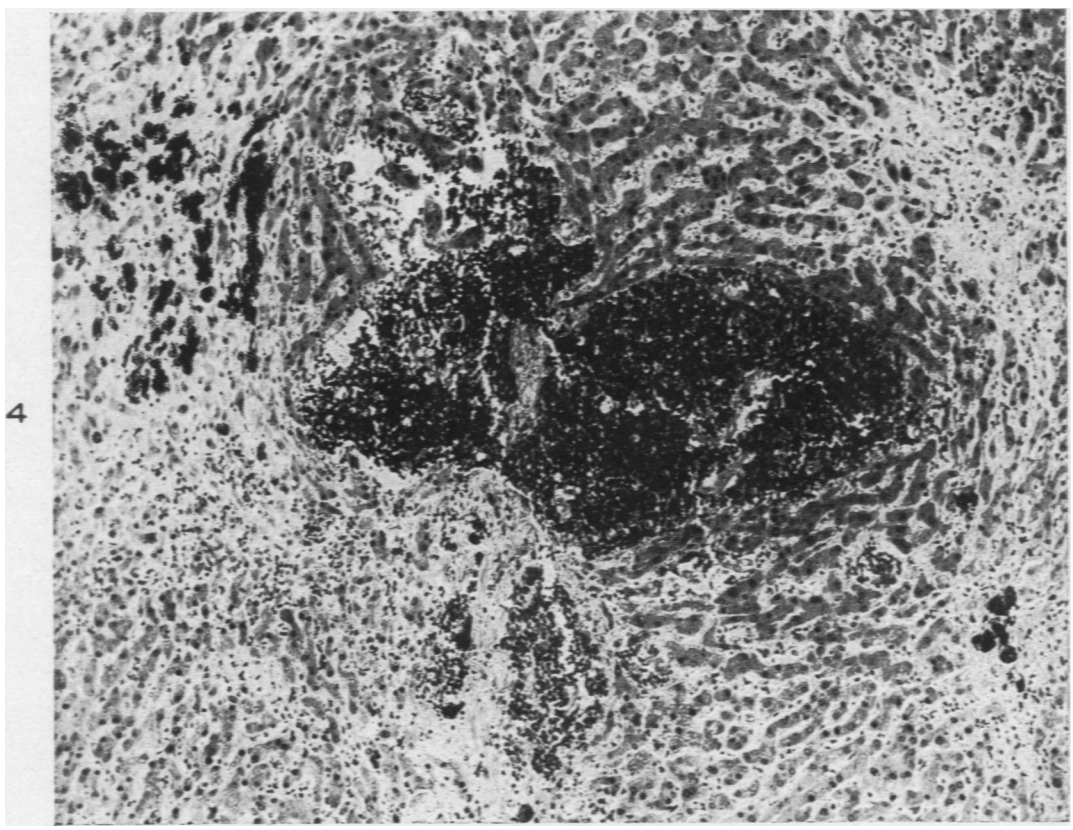

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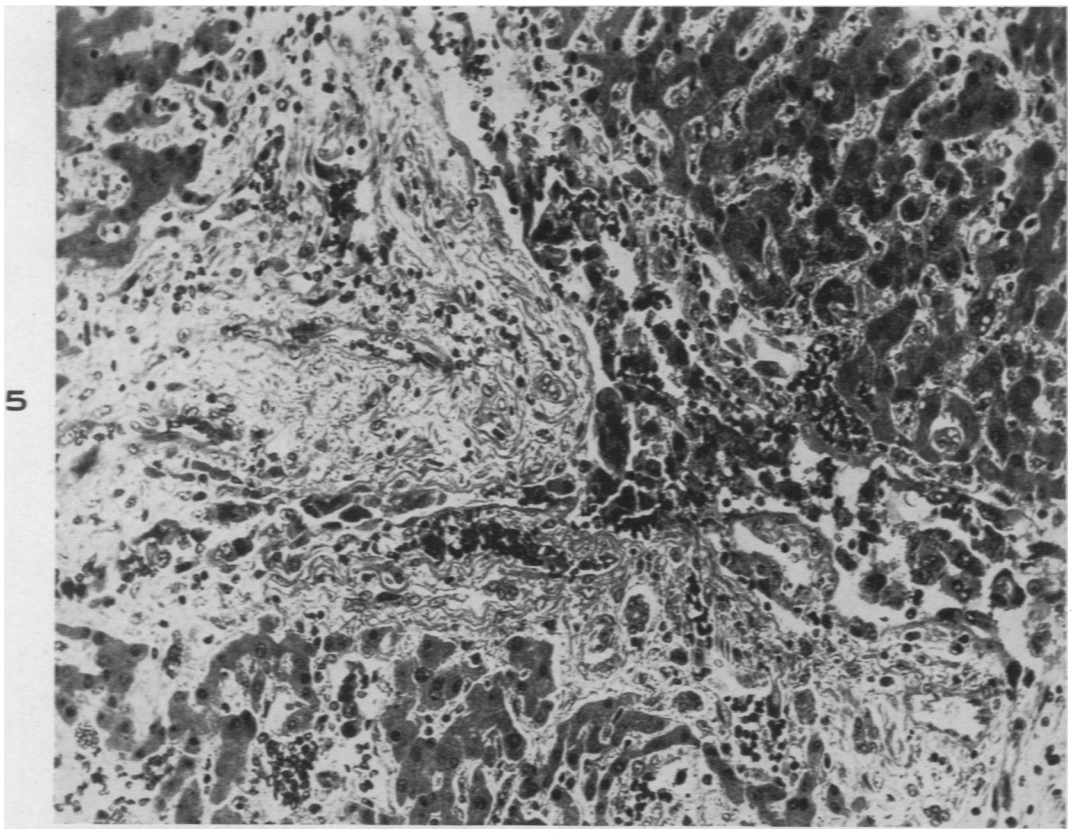
PLATE 97

FIG. 5. Liver, showing a portal area with some adjacent liver cells. A branch of the portal vein crosses and divides at about the center of the field. The lumen of the vein is dilated and almost obstructed by tumor cells. Some of these cells line the walls of the vessel, others lie free and are surrounded by blood. There is no fibrin deposition or coagulation. × 185.

FIG. 6. Liver at a very low power, showing in a single field several deposits of thorotrast, breaking up of the normal trabecular and lobular pattern of liver cells into small cords and islands, necrosis and lysis of liver cells, massive hemorrhage completely devoid of clotting, and a growth of tumor cells throughout the section. The over-all picture has a very superficial resemblance to placental tissue with its chorionic villi embedded in a sea of blood. × 45.



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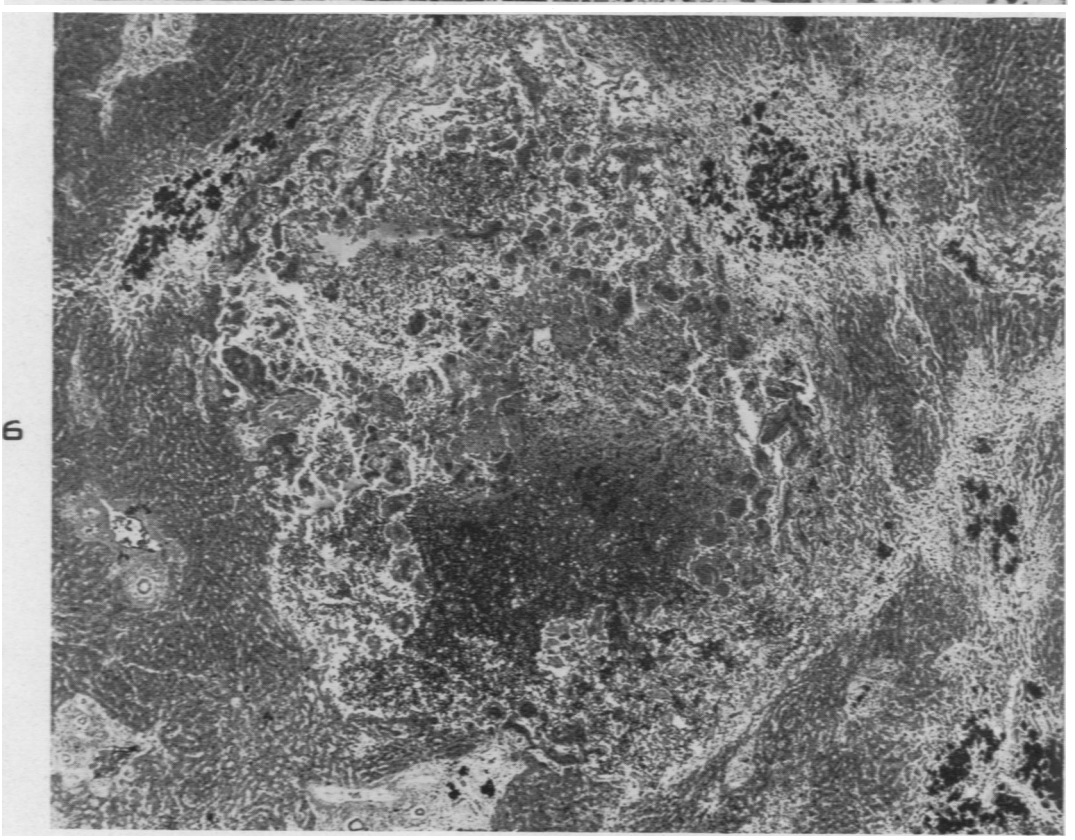

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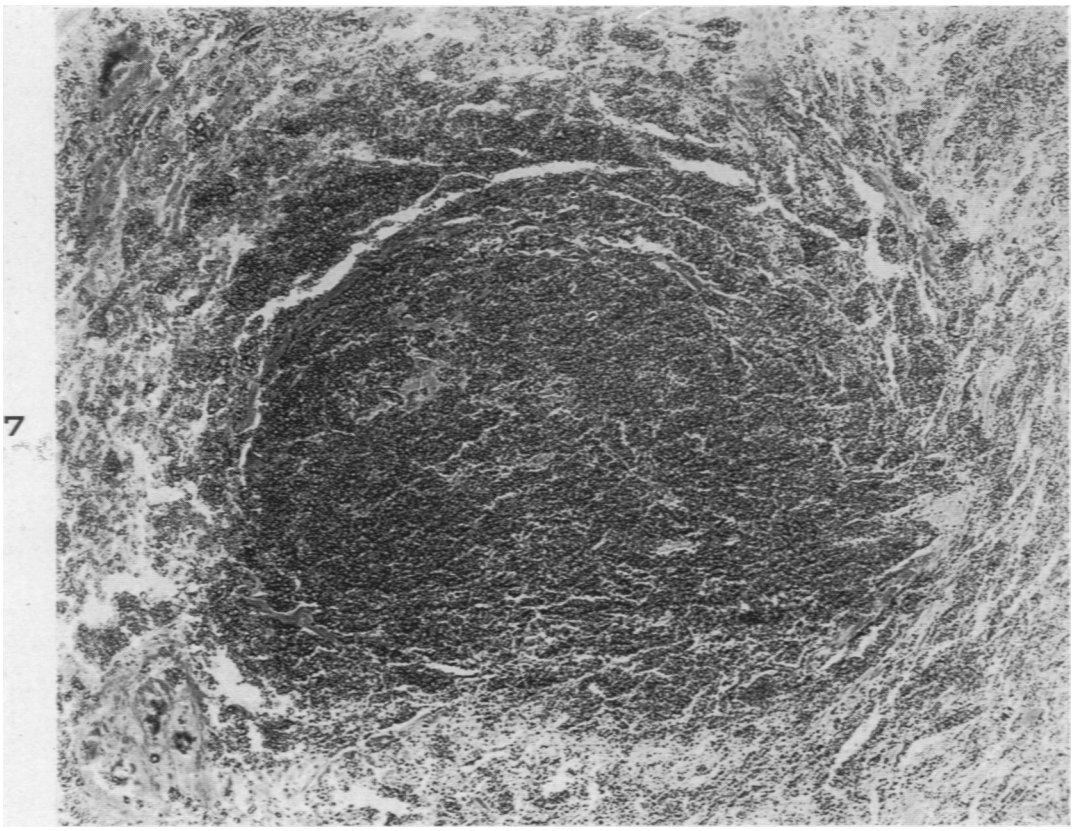
MacMahon, Murphy, and Bates Sarcoma of Liver Following Thorotrast

PLATE 98

FIG. 7. An area of the liver showing an unusually heavy deposit of thorotrast. All normal landmarks are lost and not a single hepatic cell is demonstrable. The thorotrast, like slush, lies enmeshed in poorly stained hyaline fibrous tissue. × 275.

FIG. 8. Liver, showing a central vein almost completely surrounded by a deposit of thorotrast and necrotic liver cells. This central zone is bordered by a mid-zone from which almost all liver cells have disappeared, leaving a reticulum framework infiltered with viable and necrotic histiocytes and plasma cells. Liver cells bordering this area of clearing show necrobiotic changes. There is no evidence of proliferation of liver cells in the outer peripheral zone. There is no increase in fibrous tissue or reticulum. The picture is one of destruction with little secondary resorption. × 140.



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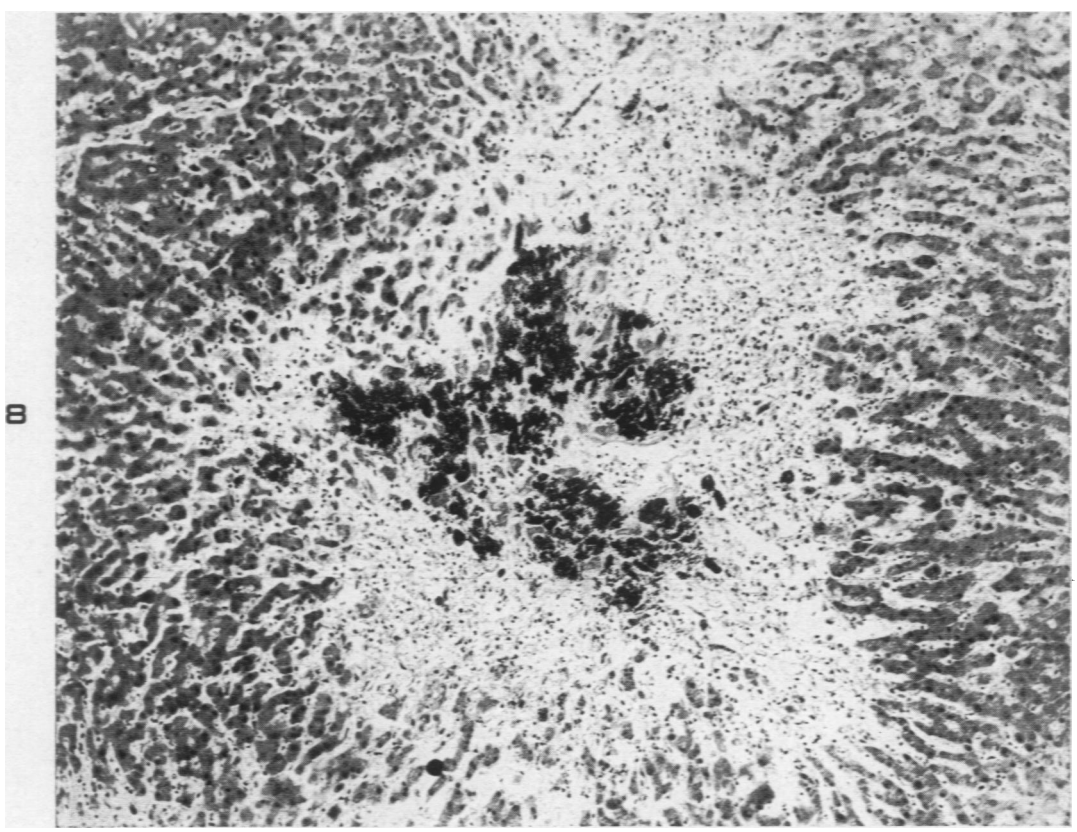

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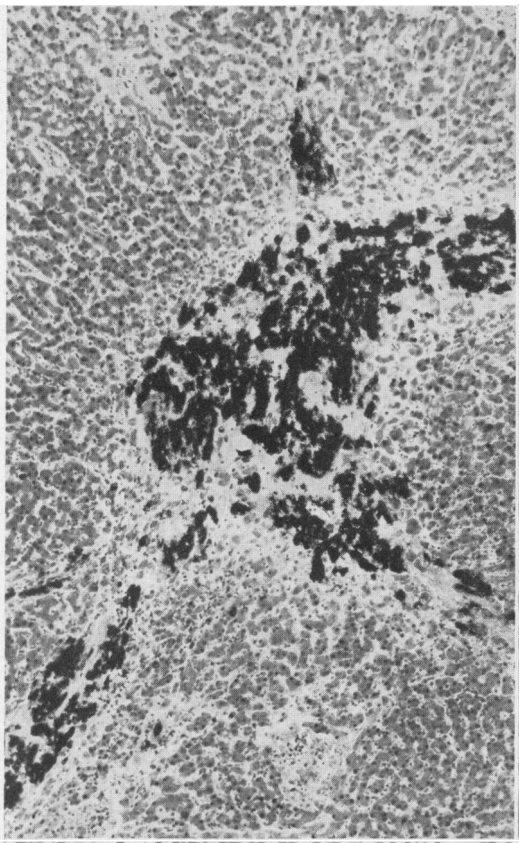
PLATE 99

FIG. 9. Liver, showing a heavy deposit of thorotrast in the central zone of a lobule and smaller deposits in adjacent portal areas. In the large central area both liver cells and endothelial cells have disappeared. Much of the thorotrast lies loosely enmeshed in a condensation of swollen reticulum. The bordering liver cells show regressive changes and necrobiosis. Their nuclei show karyorrhexis, and fragments of chromatin are scattered throughout these cells. × 90.

FIG. 10. Liver, showing a group of liver cells undergoing fatty degeneration, hyaline degeneration, necrosis, and disintegration. There is a sprinkling of thorotrast in this field but no tumor cells are demonstrable. In the upper portion there is a light condensation of stroma as well as a scattering of lymphocytes and plasma cells where liver cells have disappeared. × 370.

FIG. 11. Section of spleen. The central portion of the field is occupied by an accumulation of thorotrast. Most of it lies free; some is confined to the cytoplasm of histiocytes, the nuclei of which it is almost impossible to identify. Red blood cells are freely scattered throughout this mass. In the periphery there are lymphocytes, plasma cells, and, in one corner, a small arteriole showing hyalinization of its wall. × 275.

FIG. 12. Section of lymph node, showing a large deposit of thorotrast. Most of this is in cells—histiocytes. An examination of the individual histiocytes containing this material shows all stages of nuclear degeneration with pyknosis and ultimate lysis. For some time the thorotrast remains within the cytoplasm of the dead cell; then, with rupture of the cell membrane, it spreads into the surrounding area. In this field there are many plasma cells, some of which are giant forms with single and multiple nuclei. Although thorotrast is never found in these cells, they show active proliferation with typical and atypical mitotic figures. In the same area there are degenerating and disintegrating plasma cells, so that the over-all number remains about constant. In this field there is little hemosiderin in histiocytes. An occasional histiocyte contains both hemosiderin and thorotrast. × 90.



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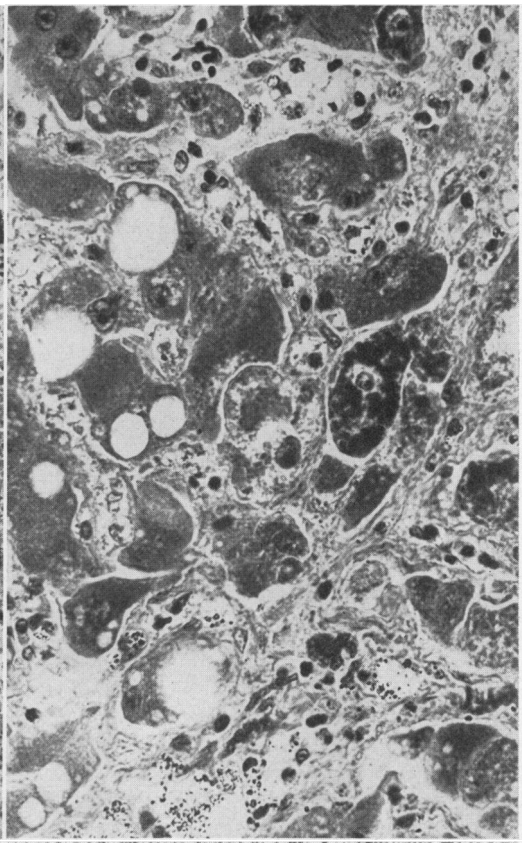

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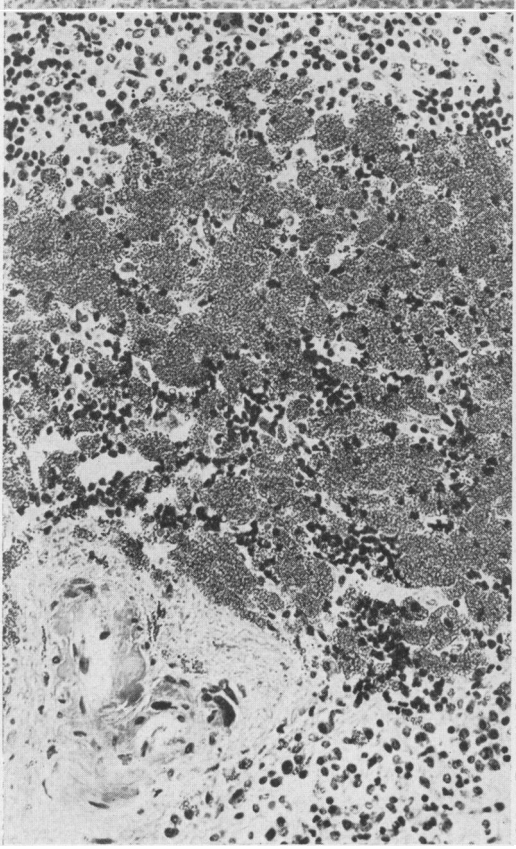

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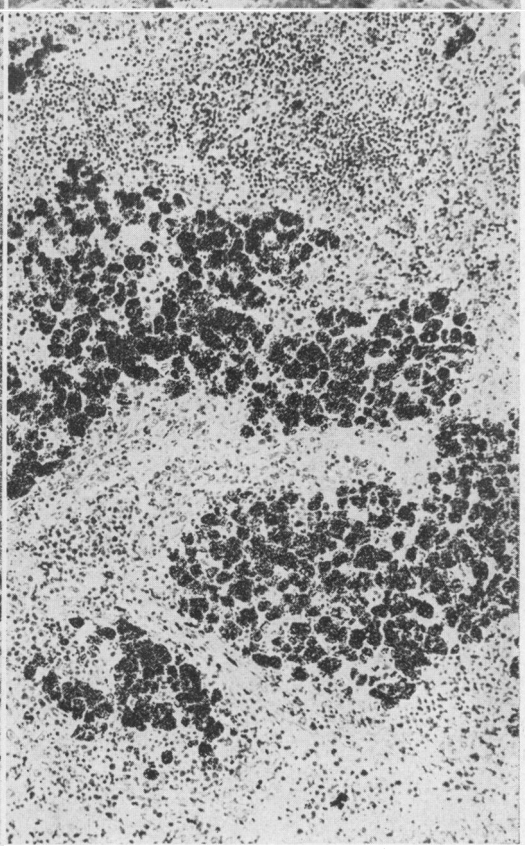

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PLATE 100

FIG. 13. Section of lymph node, showing several deposits of thorotrast. Most of this is in cells but some of it is free. Histiocytes containing very small quantities of thorotrast lie free in the sinuses, indicating a continual redistribution of this material. The lymph node shows atrophy of lymphoid tissue with an absolute increase in sinus endothelial cells. Red blood cells are freely scattered throughout the section and some of these are already phagocytosed by histiocytes. Plasma cells are unusually numerous in the capsule. There is no increase in fibrous tissue. × 90.

FIG. 14. Vertebral bone marrow, showing in the center of the field a number of histiocytes singly and in clusters, laden with thorotrast. Roughly 75 per cent of the surrounding cells are erythrocytes; the rest are erythroblasts, normoblasts, megakaryocytes, myelocytes, polymorphonuclear leukocytes, and fat cells. Fluid containing threads of fibrin lies in the intercellular spaces. × 275.

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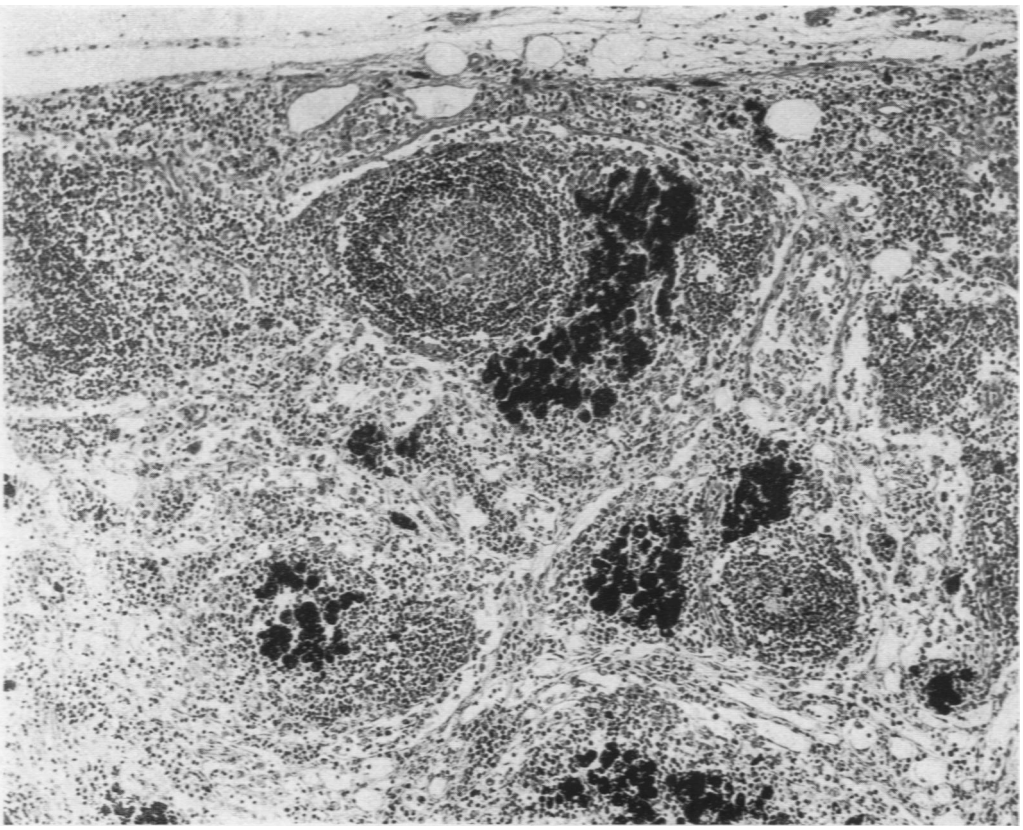

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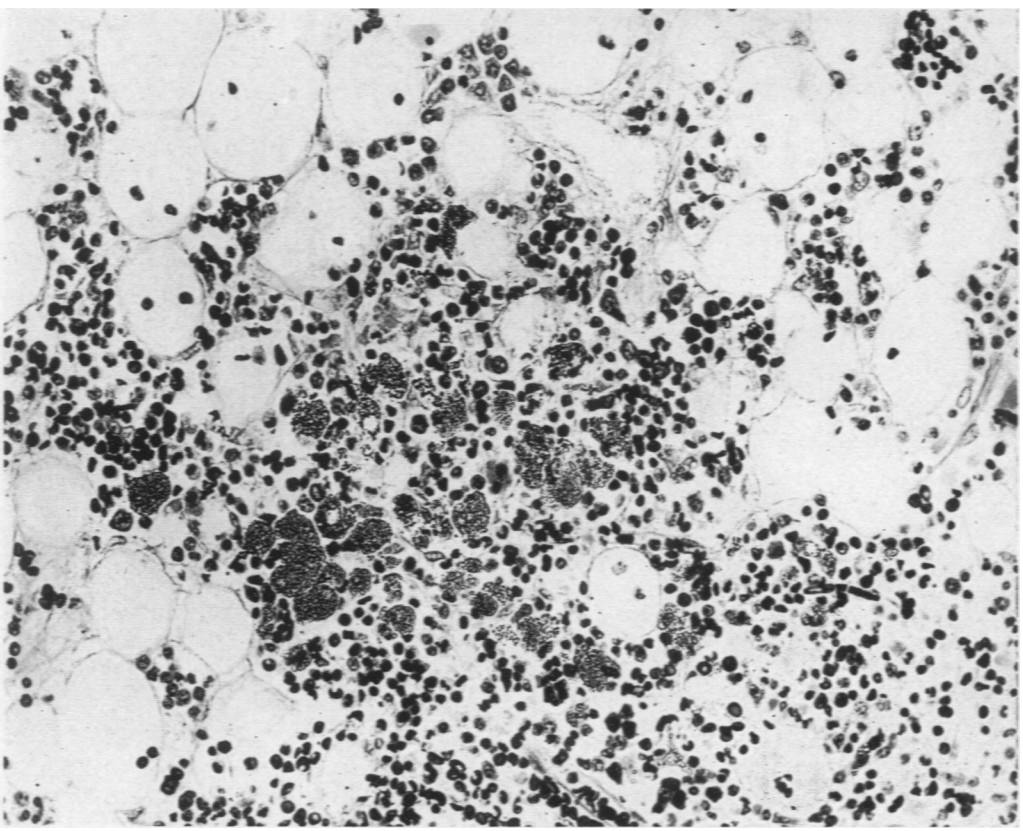
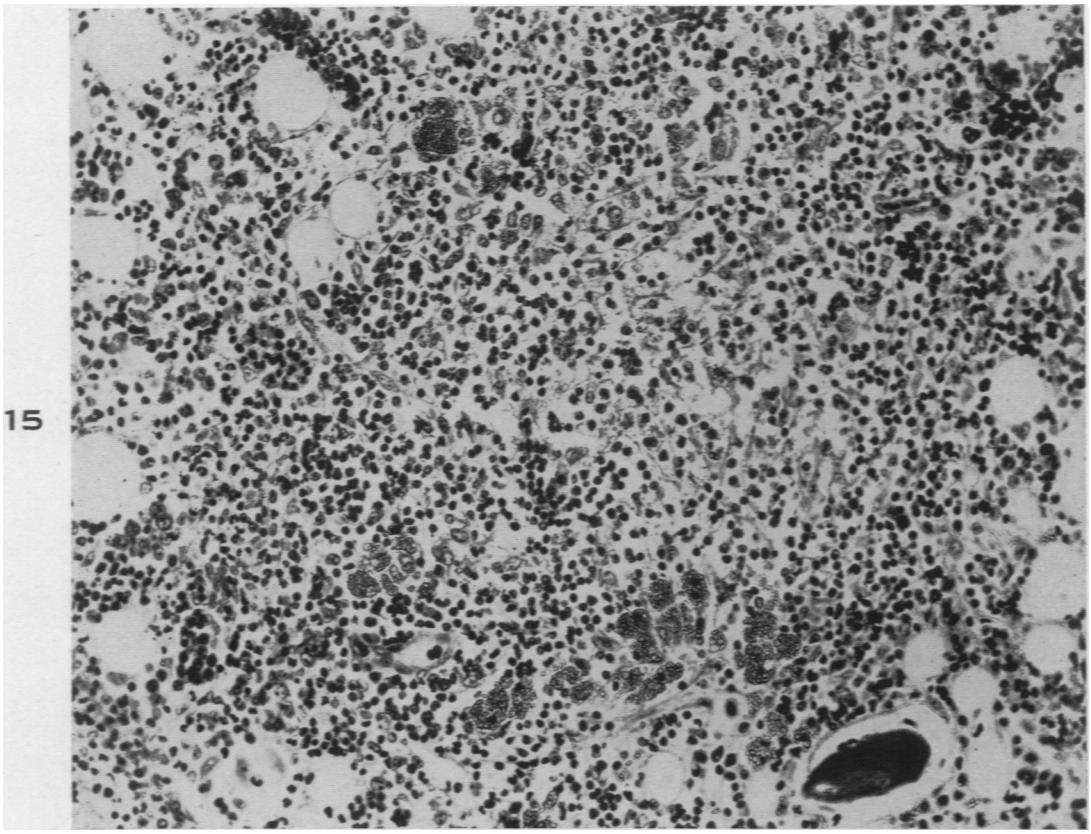


PLATE 101

FIG. 15. Vertebral bone marrow, showing in the center of the field replacement of normal marrow by an island of mature lymphocytes loosely held together by a poorly defined, somewhat hazy, reticulum web. Red blood cells are scattered freely throughout the field. In the lower right-hand corner there is a tiny fragment of bone. × 275.

FIG. 16. Section of adrenal, showing a field from the medullary area. The pheochromocytes here are almost completely replaced by lymphocytes and small deposits of thorotrast. The wall of the central vein is infiltrated with lymphocytes. × 275.



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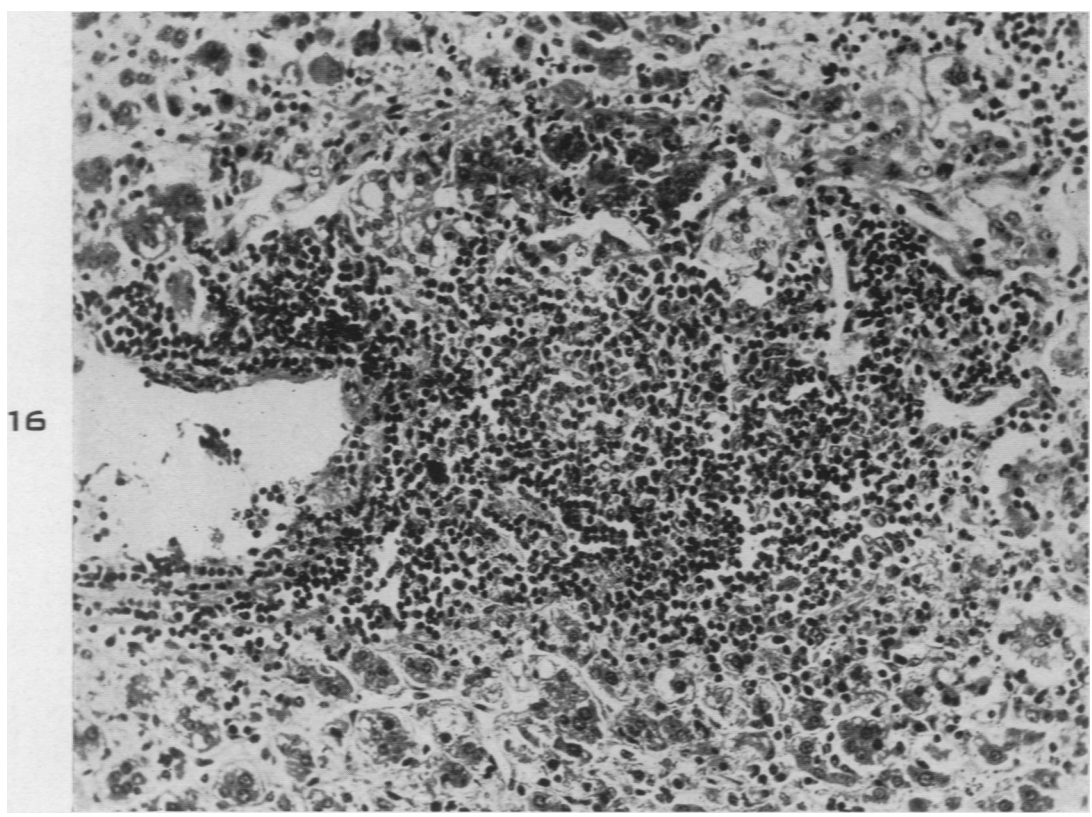

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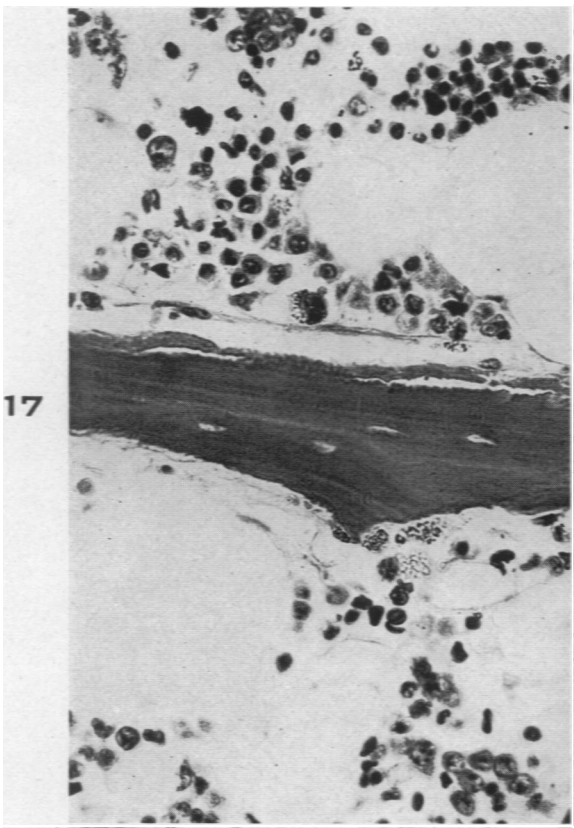
PLATE 102

FIG. 17. Section of vertebral bone marrow. A solitary trabeculum of necrotic bone crosses the center of the field. In it there are no osteocytes; the spaces, formerly filled with bone cells, are empty. The margins of the bone are rough and its ground substance shows linear longitudinal splitting and scaling. A few histiocytes, laden with thorotrast, lie in immediate apposition to this necrotic bone. On either side are fat cells, clusters of red blood cells, and small nests of both myeloblasts and erythroblasts. × 370.

FIG. 18. Section of adrenal, showing atrophy and fibrosis of the outer portion of the glomerular zone of the cortex. In this area of fibrous tissue there are small deposits of thorotrast. × 140.

FIG. 19. Kidney. A small lobular artery crosses the center of the field. The lumen of this vessel is abnormally wide and unevenly dilated. The intima is thin and composed of a single layer of endothelial cells supported by a poorly defined basement membrane. The media is composed of atrophic muscle fibers, each of which appears as a bare nucleus bordered by a narrow rim of scarcely stainable cytoplasm. There is little edema of the surrounding stroma. The glomerulus and tubules in this field show no abnormality. × 185.

FIG. 20. Lung, showing in the center of the field a medium-sized branch of a pulmonary artery. Muscle fibers, normally conspicuous in vessels of this order, are not recognizable. The wall is composed almost exclusively of hyalinized acellular fibrous tissue. The adventitia is made up of loosely arranged collagen. The adjacent alveoli are emphysematous. × 90.



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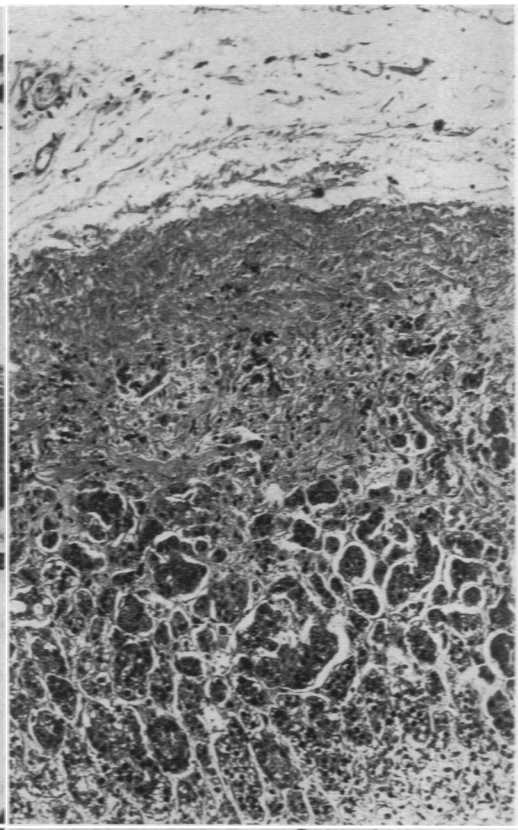

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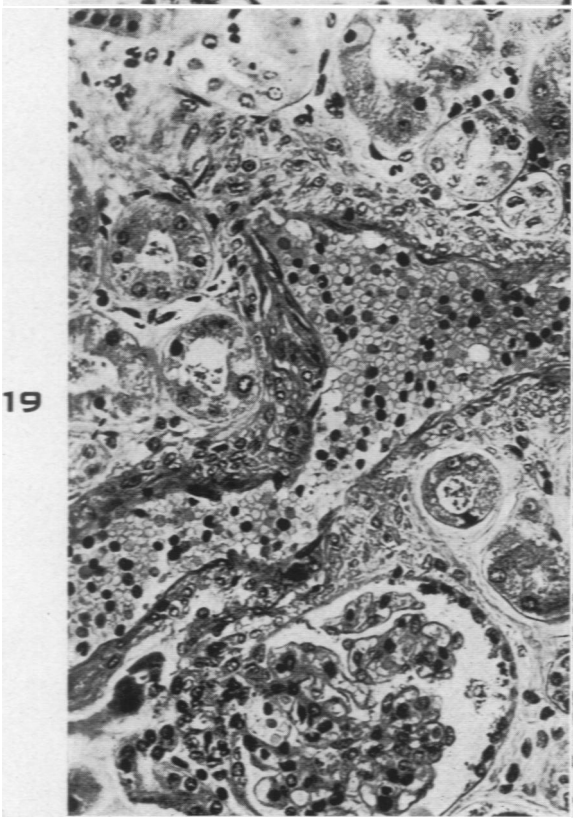

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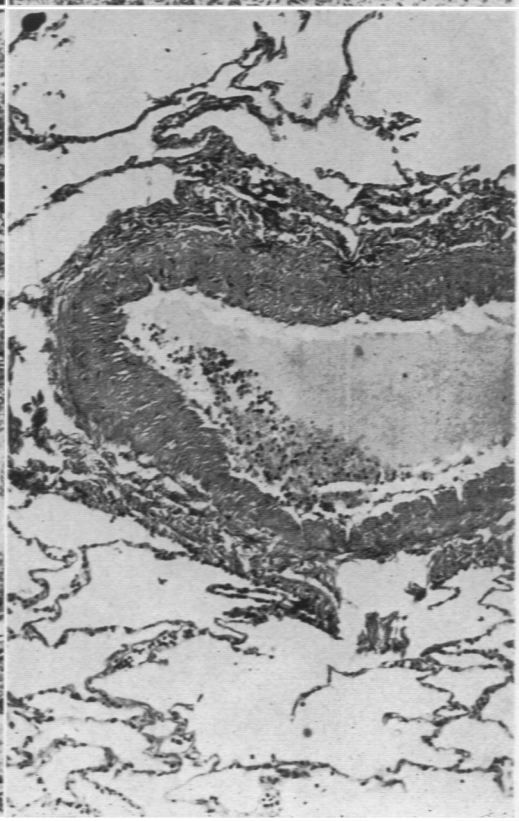

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