A CASE OF PRIMARY MESENCHYMAL HEPATOMA: WITH NECROPSY *

NATHAN CHANDLER FOOT, M.D.

(From the Department of Pathology, College of Medicine, University of Cincinnati, Cincinnati, O.)

This case is of interest to both the clinician and the pathologist, for it presented obscure and misleading symptoms during life and was no less puzzling after a necropsy had been performed.

CLINICAL HISTORY

Present Illness: E. R., a white male baby of four months, was admitted to the pediatric service of the Cincinnati General Hospital on Aug. 23, 1926. The parents said that the child had become feverish and fretful a week prior to admission and that he had been somewhat constipated; no other symptoms were described.

Past History: A full-term, normally delivered baby, the child had been perfectly well since birth; he had never been exposed to contagion.

Family History: The father, mother and one brother were living and well; the mother had borne no other children besides these and there was no history of a miscarriage.

Physical Examination: The patient was a well developed, well nourished child, very restless, but apparently not acutely ill. The temperature was 101.6° F, the respiration 35 and normal, the pulse 140, irregular, but of good quality. Examination of the head, neck and chest failed to elicit anything abnormal; the abdomen protruded beyond the chest; bulging was present in the flanks. No abnormal pulsations were visible, there was no rigidity and but slight tenderness to palpation. A mass could be felt in the right upper quadrant, extending downward to just below the level of the umbilicus and to the left to within 3 cm. of it. It presented a notched, firm border, did not pulsate and the notch was felt just to the right of the umbilicus. Another mass occupied the left upper quadrant, extending downward to the iliac crest and to the right to within 3 cm. of the umbilicus. It had a sharply defined notch in its equally sharp border, felt just to the left of the umbilicus. These two masses were quite distinct, one from the other, the right being firmly fixed, the left one moving with respiration. There was an umbilical hernia and a double inguinal hernia. Aside from bowing of the legs, phimosis and slight icterus, nothing further could be determined.

Course in Hospital: The patient's condition grew steadily worse, despite continued breast feeding from its mother and six transfusions of blood from its father. Diarrhea developed and the temperature rose to 104° F, where it remained for a day or two before the child's death.

Laboratory Findings: A blood culture was negative.

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Urine: Albumen ++, otherwise negative.

Blood: 8/23/26. White blood cells, 30,000; polymorphonuclears 7 per cent; lymphocytes, 89 per cent; unidentified, 4 per cent. Anisocytosis, poikilocytosis, platelets absent.

8/28/26. Red blood cells, 1,784,000; white blood cells, 9,200; polymorphonuclears, 15 per cent; lymphocytes, 85 per cent.

8/29/26. Red blood cells, 1,790,000; hemoglobin, 50 per cent Sahli.

9/5/26. White blood cells, 10,400; polymorphonuclears, 4 per cent; lymphocytes, 89 per cent; mononuclears, 2 per cent; pathologic cells, 5 per cent; hemoglobin, 50 per cent Talquist. Occasional normoblast and megaloblast, few stippled cells, marked anisocytosis and poikilocytosis, platelets definitely diminished.

9/10/26. Red blood cells, 2,850,000; white blood cells, 11,700; platelets, 30,000 per cmm.; hemoglobin, 55 per cent Talquist.

Stool — Negative for parasitic ova.

Roentgenologic Examination: Heart outline somewhat enlarged, liver and spleen definitely so, otherwise negative. (Fig. 1.)

Clinical Diagnosis: Congenital lues, lymphoid leukemia, thrombocytopenic purpura and rachitis.

Necropsy Report

A necropsy was performed by Dr. Don F. Deeter, resident pathologist, seven hours postmortem. The child is definitely jaundiced, its skin lax and dry, the body somewhat emaciated. Nothing of note is observed previous to opening the abdomen.

Abdomen: Upon opening the peritoneal cavity, a rather large quantity of clear, amber fluid is evacuated. The liver reaches to the right anterior superior iliac spine and the spleen projects several centimeters below the left costal margin. The mesenteric lymphnodes are slightly enlarged.

Spleen: This weighs 35 gm. and is large, purplish, and shows several small grayish points on its surface. The section-surface is smooth, fairly firm and purplish red; it drips much blood. The follicles are so obscured by the pulp as to be practically invisible.

Liver: The liver is large and weighs 275 gm. Its surface is everywhere studded with small grayish yellow areas averaging 1 to 2 mm. in diameter and projecting slightly above the surface, beneath the capsule. On the section-surface, similar grayish yellow areas are set off from the dull, light brown parenchyma, whose markings are diffuse and obscure. These tubercles are often softened at their centers, as though necrotic. One of them, much larger than the rest, measures approximately 1 cm. in diameter. The gall-bladder is not remarkable.

Gastro-Enteric: There are a few superficial ulcerations or erosions in the gastric mucosa; they average about 1 to 2 mm. in diameter. There is some congestion of the lower ileum and its Peyer's patches are somewhat swollen and prominent.

Other Organs: Nothing remarkable is noted in the case of the kidneys, pancreas, testes, urinary bladder or ureters.

Diagnoses: Multiple gummata of liver, congestion of spleen, ulceration of gastric mucosa, ascites, jaundice, umbilical and double inguinal hernia and rachitis.

Microscopic Report

Technic: Sections of various organs were made in paraffin and stained by routine procedure with Harris' hematoxylin and eosin; in addition, liver and bone marrow sections were impregnated with silver-ammonium carbonate and counterstained by Van Gieson's method; sections of the liver were also stained with Mallory's phosphotungstic acid hematoxylin, carbol-fuchsin and Levaditi's silver method.

General Findings: In the case of the heart, pancreas, testes and suprarenals, nothing of interest is encountered; the kidneys show a well developed tubular nephritis, with marked granular and albuminous degeneration, limited to the convoluted tubules.

Thymus: This shows an unusual atrophy, in that it is composed chiefly of epithelial elements and there is a marked dearth of the normal cortical lymphocytes, with a corresponding prominence of the thymic reticulum cells. The thymic corpuscles are either rudimentary, or show marked degeneration with necrosis at their centers, without any cellular reaction. Many of them have been transformed into thin-walled epithelial vesicles containing a little granular débris.

Spleen: There is pronounced passive congestion that floods the venous sinuses and renders them very prominent, at the same time compressing the splenic corpuscles until they assume insignificant proportions. The sinuses and pulp spaces are thronged with many large, actively phagocytic cells whose cytoplasm is filled with hemosiderin, fragments of erythrocytes and leucocytes, and sometimes entire cells — chiefly polymorphonuclear leucocytes. So numerous are these phagocytes that the picture reminds one of typhoid fever,

but the distribution of the phagocytes, the type of cell they ingest and their general appearance, are quite different. There are masses of cells resembling myeloblasts and myelocytes that, for this reason, indicate myeloid metaplasia.

Lymph Nodes and Lymphoid Tissue: These, too, are atrophic and show a very noticeable reduction in the number of microlymphocytes present; in place of the normal lymphoid follicles, there are aggregations of macrolymphocytes, some of them in mitosis and many of them showing pathologic transformations into large, irregularly staining cells, often with lobulated nuclei and dark cytoplasm. Some of these are very reminiscent of the Dorothy Reed, or Sternberg, giant cells of the Hodgkins' nodes. The central lymph sinuses and the capillaries of the nodules are much dilated and contain large numbers of phagocytes; and fairly large numbers of pale, distorted erythrocytes are found in the vessels and scattered through the lymphoid tissue. Apparently, some process involving the destruction of microlymphocytes, together with a compensatory hyperplasia of their parent cells, has been at work. The lymphoid tissue of the Peyer's patches and intestinal submucosa, on the other hand, is hyperplastic and contains the usual, or a somewhat increased number of microlymphocytes.

Bone Marrow: Sections from the costal bone marrow show some fairly normal fields and, in contrast to these, others are encountered that are strikingly altered. There are sections that are almost entirely pathologic in their composition (Fig. 2) the marrow being invaded by large numbers of large, pale, irregularly outlined phagocytic cells that are, apparently, invading, devouring and replacing the bone marrow. These cells often contain fragments of leucocytes, erythrocytes, or pigment; they are polyhedral rather than of rounded outline, their cytoplasm is vacuolated, their nuclei tend to be vesicular and reniform. They are not only identical, at least in their morphology, with the cells to be described in the case of the liver, but they are imbedded in and intimately associated with a reticulum that is identical in its appearance with that of the tumors. Owing to unevenness of the bone sections, it is impracticable to photograph the silver impregnations.

Microscopic Findings in the Liver

General: The parenchyma of the organ is compressed and distorted by a growth of new tissue in the periportal areas, or "triads." There is a marked fibrous tissue reaction to the presence of this growth, with consequent interference with the secretion of bile, which is found dammed back in the bile capillaries and the liver cells. Many phagocytes show greenish brown, finely divided particles of pigment in their cytoplasm. The central areas of the lobules are markedly congested and somewhat degenerated.

The New Growth: In the periportal areas are collections of cells quite foreign to this situation (Fig. 3). They are of irregular size and shape, pale, often somewhat vacuolated and usually discrete, arranged either loosely, or in rambling cords, but not in epithelial complexes suggesting alveoli. Sometimes they rim spaces, but even then have very little resemblance to glands. Often they are merely aggregations of cells, each separate from its neighbor and presenting the appearance of the "epithelioid cells" of tuberculosis. In such cases, the aggregations are fairly sharply circumscribed and form spherical, somewhat encapsulated groups; they often show little delimitation and invade the liver parenchyma in their neighborhood by way of the sinusoids. Numbers of leucocytes are often intermingled with these cells, which frequently give the growth the appearance of some sort of granuloma.

The nuclei of the tumor cells are reniform, rounded, or squash- or club-shaped; they are vesicular and pale, with a well defined nuclear membrane and a very poorly defined, or no nucleolus; they are sometimes multiple, two or three presenting in a single cell. Very few mitotic figures are found after most careful and prolonged searching, but as they are in smaller cells it is questionable whether these are tumor cells, or elements of the stroma. A high power photomicrograph of the type cell is reproduced (Fig. 4).

One's first impression, while examining this tumor, is that it has an epithelial origin; for this reason careful observations were made to determine whether or not transitions between the tumor and the liver cords could not be found. Wherever the tumor invades the liver these cords become swollen and degenerated, their cells vacuolated and dissociated, but their nuclei retain their typical round outline and prominent nucleoli. Nucleoli are seldom observed in

the tumor cells. Furthermore, the only cells that resemble those of the tumor with any exactness are found in the walls of the sinusoids, or free in their lumina rather than associated with epithelium, and they are obviously Kupffer cells. Their nuclei are perfectly similar to those of the type cells and their hyaline, pale cytoplasm resembles that of the tumor, which is quite unlike the deeply staining, granular cytoplasm of the liver cords. The liver epithelium, moreover, is often bile-stained and contains large droplets of inspissated bile and encircles dilated bile capillaries; this is not noted in the tumor cells. Pigmented phagocytes lie isolated and included in masses of the tumor, but exactly similar cells are observed in the liver sinusoids; they are quite different in their appearance from the bile-stained epithelium. Where the tumor invades the liver, it does so by way of the sinusoids, rather than replacing liver cords.

As stated, there is a marked fibrous tissue reaction to the presence of the tumor, the stroma (or better, matrix) being chiefly composed of reticulum, although there is a great deal of collagenous connective tissue in the larger, more diffuse areas. This reticulum is so intimately associated with the type cells, not tending to demarcate alveoli, that the question as to whether it is not matrix, rather than stroma, is immediately raised (Fig. 5). In the writer's experience carcinomas very rarely and non-malignant tumors practically never show an invasion of their cell complexes by the stroma; such an invasion always suggesting mesodermal origin of the type cell (Foot and Day [1]).

Cell inclusions are frequently observed, although the frank phagocytosis exhibited by the strikingly similar cells in the bone marrow is not found. This might be explained by the firm, closely bound surrounding tissue in the one case and the loosely associated marrow elements in the second; it would be as easy for phagocytic cells to take up myeloid elements as it would be difficult and unusual for them to phagocytose fibers or liver parenchyma.

In order to rule out syphilis and tuberculosis, Levaditi and Ziehl-Neelson preparations were made and examined with quite negative results. Gram and methylene blue stains were equally unenlightening.

Microscopic Diagnoses: Primary mesenchymal hepatoma, probably metastatic to costal bone marrow; chronic passive congestion of liver, with bile stasis and cirrhosis; passive congestion of the

spleen, with myeloid metaplasia; atrophy of thymus and mesenteric lymph nodes.

Discussions

This is, then, a case of multiple tumors of the liver with an invasion of the neighboring bone marrow that strongly suggests metastasis, owing to the similarity of the cells in each instance. At first glance one is inclined to diagnose such a case as a granuloma of some sort, tuberculous or luetic. This was the provisional diagnosis at necropsy. But our microscopic examination throws us back upon a diagnosis of neoplasia. Having arrived there, with what type of tumor are we dealing? Primary adenoma of the liver is not uncommon in children, in a rather diffuse and multiple form; but can we consider this an adenoma? Can it, indeed, be considered to be of an epithelial nature? The type cell suggests epithelium, but it also suggests mesodermal origin.

Arguing against an epithelial origin we may point out that:

(*a*) There is no tendency for the cells to form glands or definitely coherent alveoli.

(*b*) There is great similarity between the cells of the tumor and the phagocytic interlopers in the costal bone marrow.

(*c*) There is a tendency for the cells to be multinuclear.

(*d*) They are usually discrete and very intimately associated and intermingled with reticulum, which is more typical of reticulo-endothelial, than it is of epithelial structures.

(*e*) They resemble Kupffer cells more closely than they do hepatic epithelium.

(*f*) They invade the liver tissue by way of the sinusoids, rather than replacing the liver cords.

In favor of an epithelial origin of the tumor the following points may be noted:

(*a*) Tumors corresponding to this type of neoplasm are usually epithelial.

(*b*) The cells of this tumor resemble epithelium closely enough to be termed "epithelioid," they show some tendency to form cords and a very slight one to line spaces.

(*c*) Ducts are occasionally seen in the tumor, but these could be construed as representing surviving bile ducts.

It is quite possible that there is no relationship between the cellular aggregations in the bone marrow and the tumor in the liver; the former are composed of much larger cells, as may be seen in the illustrations, which were taken at the same magnification. The increase in size, however, could be explained on the ground of compression in the dense tumor and lack of this in the loose marrow. Metastasis, in the absence of numerous mitoses, is not as readily assumed as it could be were there many of these; but the tumor has grown readily enough throughout the liver and could, therefore, set up subsidiary growths outside of that organ. That this tumor is malignant is indicated by the poor differentiation of its type cells, by their diffuse and infiltrating growth and the possibility of metastasis to the ribs; that it was clinically malignant is amply proved by the fact that it killed the patient.

The most comprehensive description of these tumors will be found in Ewing's Neoplastic Diseases.[2] He lists primary tumors of the liver under the following heads: (*a*) Solitary adenoma, (*b*) Primary massive liver cell carcinoma, (*c*) Multiple liver cell carcinoma or hepatoma, and (*d*) Carcinomatous cirrhosis; or, multiple adenoma, carcinoma, or hepatoma with cirrhosis. The tumor under discussion might fall into the last category, were we certain of its epithelial nature. Ewing mentions the fact that Geraudel considers some of these to be of mesodermal origin, but dissents from this view on the grounds that the liver "is derived from exactly the same endodermal bud as the bile ducts, and the only part of the parenchyma which is of mesodermal origin is the system of blood vessels."

If our tumors, then, be not of endodermal origin, they are probably derived from the vascular primordium of the liver, or from its appendages which produce the hepatic stroma. For the reasons already given, it seems to the writer that we are dealing with a primary mesodermal tumor of the liver which has grown diffusely, either arising simultaneously in many parts of the organ, or rapidly seeding itself out from the largest nodule discovered at necropsy and possibly metastasizing to the neighboring ribs. Such a diagnosis may seem presumptuous, in the face of tradition, but we have ample evidence that the Kupffer cells may form large aggregations in tuberculosis, and in other conditions. The experimental work on tuberculosis of the liver has shown this to be true (Evans, Bowman, and Winternitz,[3] Foot,[4] Kockel,[5] and others). Why should these cells

not be capable of undergoing somewhat similar changes under the influence of neoplastic stimulation and become transformed into actively growing tumor masses? This hypothesis will bear consideration; it is only by publishing such cases and inviting free criticism and discussion, that we can arrive at any definite conclusion as to their true nature.

NOTE: Personal correspondence with Dr. Ewing indicates unmistakably that he considers this case to be one of multiple adenoma of the liver. Although he examined the sections from the liver, he did not see those from the marrow, which attracted attention only after the liver sections had been studied and sent on to him.

SUMMARY

A case of multiple tumors, occurring in a boy of four, is described from the clinical and pathologic points of view, the latter being stressed. The tumors simulate multiple granulomata, possibly tuberculous or luetic, but when examined more closely are found to be neoplastic. They are rich in reticulum and are found to invade almost all the periportal tissue of the liver. Similar cells and reticulum are found in the neighboring costal bone marrow, which are probably metastases to that tissue, although this is not proved. The nature of the growth is discussed, and it is concluded that it probably had its origin in the mesodermal primordium of the liver; the possibility of its being of epithelial origin has not been overlooked.

Photomicrographs by Mr. J. B. Homan (Dept. Medical Art, College of Medicine, University of Cincinnati) and the author.

REFERENCES

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4. Foot, N. C. The endothelium in experimental general miliary tuberculosis in rabbits. *J. Exper. Med.*, 1921, xxxiii, 271.
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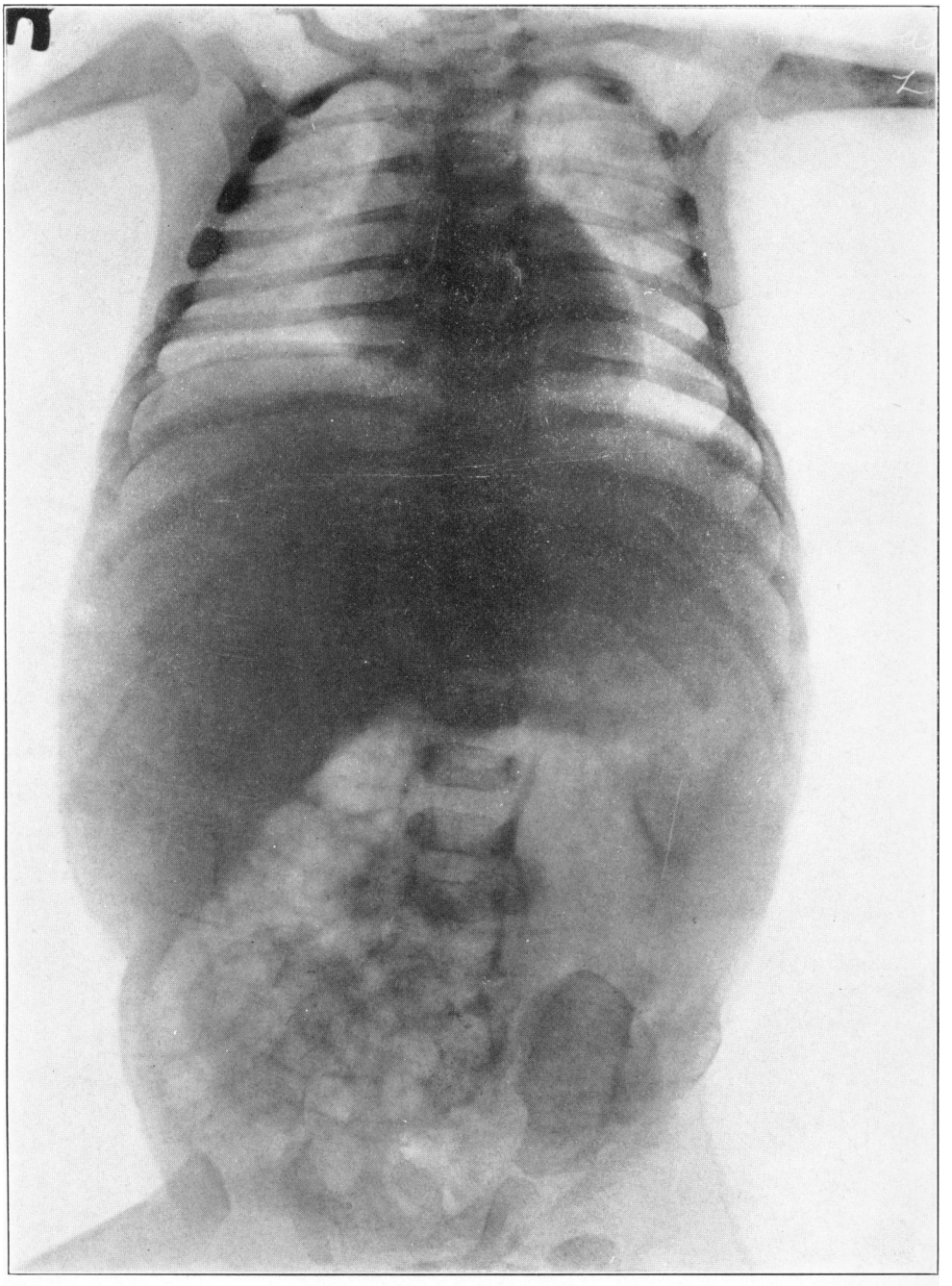
DESCRIPTION OF PLATES

PLATE 174

FIG. 1. Roentgenogram of the patient, showing enlarged liver, spleen and heart; no metastasis visible in ribs.



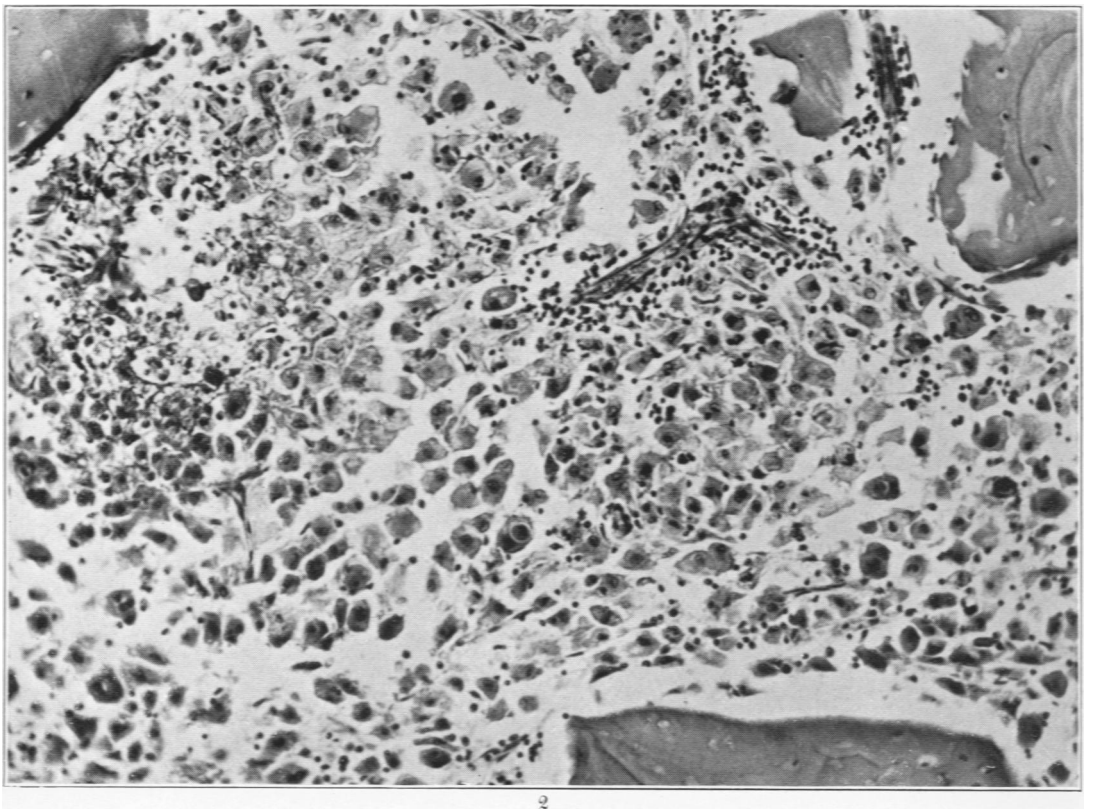
1

Foot Primary Mesenchymal Hepatoma

PLATE 175

FIG. 2. Photomicrograph of the bone marrow, showing invasion by large numbers of phagocytes, possibly a metastasis. Hematoxylin-eosin. × 200.

FIG. 3. Photomicrograph of the tumor and the liver tissue at its margin. Note the lawless distribution of tumor cells. Hematoxylin-eosin. × 200.



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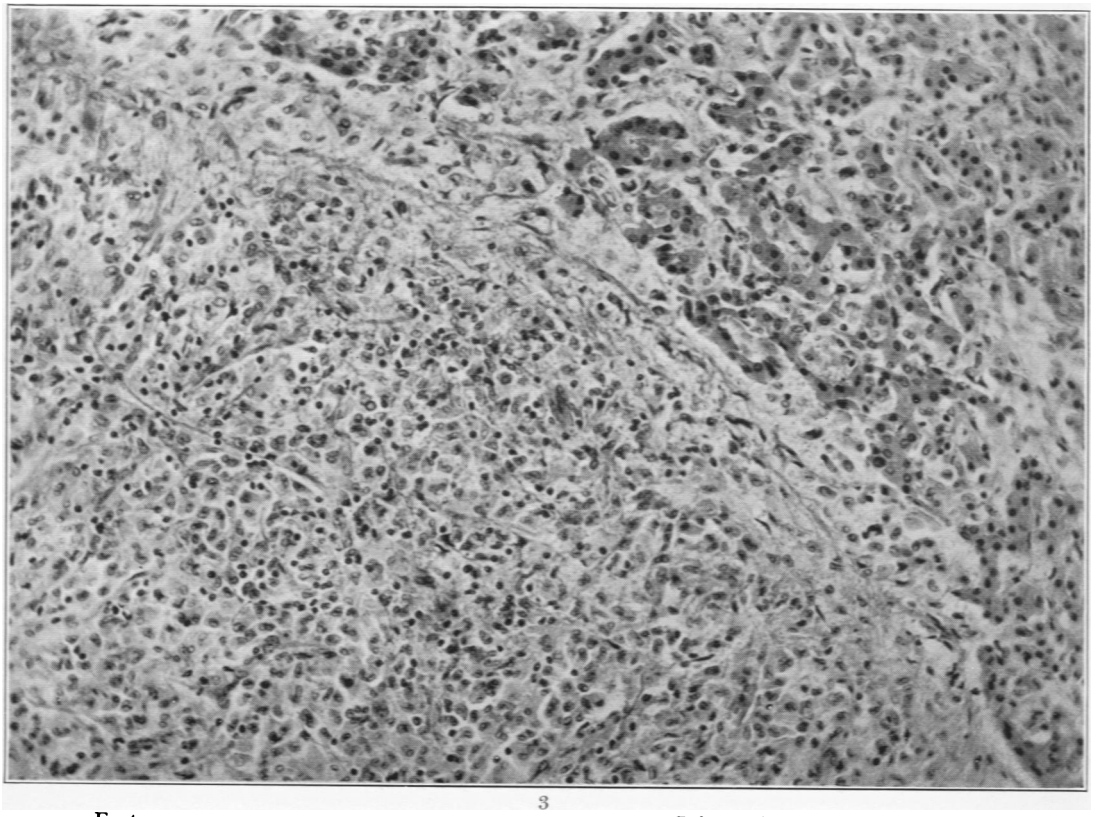


3

Foot

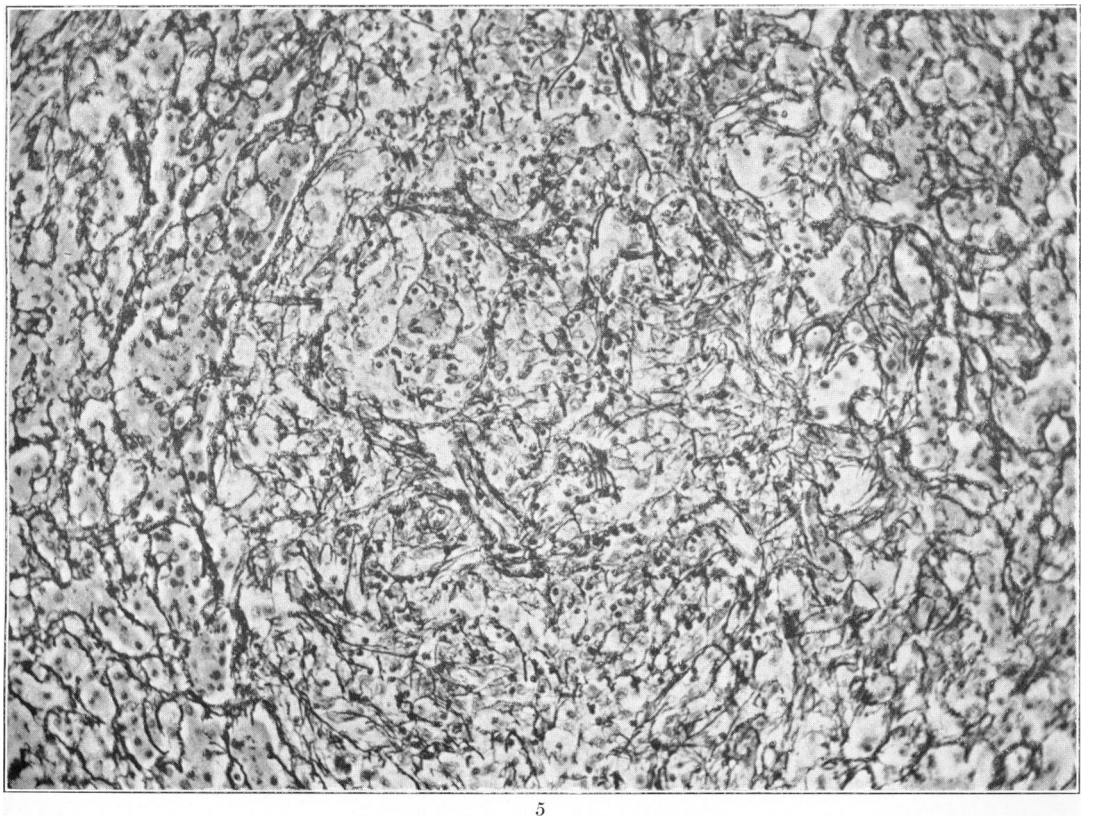
Primary Mesenchymal Hepatoma

PLATE 176

FIG. 4. Photomicrograph of a field in the tumor, to show the distribution of reticulum and the type cells. Silver-ammonium carbonate-Van Gieson technic. × 800.

FIG. 5. Photomicrograph of a portal area completely replaced by tumor tissue. Note distribution of reticulum and dissimilarity of the tumor and liver cells. Silver-ammonium carbonate-Van Gieson technic. × 200.

4



5

Foot

Primary Mesenchymal Hepatoma