Primary Neoplasms of the Liver in Infants and Children*

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PRIMARY NEOPLASMS OF the liver in children occur frequently enough to require consideration in the differential diagnosis of abdominal tumor. Nine cases were encountered at the Denver Children's Hospital during the past 14 years. Five of these were carcinomas, one was an angiosarcoma, two were benign hamartomas, and one was a non-neoplastic cyst. The individual case reports and discussion follow.

Case 1. C. E. L., aged 13 months, was admitted to the Denver Children's Hospital in 1941. He had been losing weight and color for about five months; his parents thought that he had been running a low grade fever. A mass in the upper abdomen, noticed by the parents 4 months earlier, had been growing steadily.

Examination revealed a thin, pale baby of 15 pounds (6.8 Kg.). A rounded, firm mass which moved with the liver occupied the right side of the abdomen. The mass extended into the right flank and reached the right iliac crest. The erythrocyte count was 3.6 million per cu. mm.; the hemoglobin was 65 per cent; and the leucocyte count was 12,600. A flat roentgenogram of the abdomen (Fig. 1) showed the mass displacing the intestines toward the left flank and pelvis.

At operation on January 2, 1942, a large rounded tumor was found protruding from, but deeply imbedded in, the right lobe of the liver. It was of firm consistency, and enclosed in a capsule containing numerous large blood vessels. The tumor was peeled out of the liver. Bleeding, though profuse, was controlled by deep encircling sutures and by a gauze pack covered with rubber dam.

Pathologic examination of the specimen revealed a completely encapsulated tumor mass 9.5 cm. in diameter, weighing 452 Gm. (Fig. 2). The capsule was thin but uninterrupted. Microscopically there was a preponderance of uniform cells resembling liver cells. The cytoplasm was reticulated or finely vacuolated, as though fat storage had occurred. The nuclei varied in size and architecture. Nowhere was there the normal lobulation of the liver parenchyma. Rather these cells were seen as large sheets. In some small areas, the cells were more crowded and contained no fat granules. Here the cells were polymorphic and some were extremely large, with distinctly atypical chromatin architecture and many mitotic figures, giving every evidence of anaplasia. No infiltration of the blood vessel walls by tumor cells was found (Fig. 3).

Diagnosis. Solitary hepatoma of the liver, with distinct malignant changes.

The patient made a slow recovery and was dismissed from the hospital 6 weeks after operation. Fifteen months after operation he had doubled his weight, was well nourished, and looked healthy. Seven months after this examination, in November 1943, the child was hospitalized in another state, where exploration was reported to show a normal right lobe of the liver but a left lobe full of tumor nodules. A biopsy taken there was diagnosed as carcinoma of the liver, hepatoma type. The tissue was considered, after comparison, to be very similar to that removed here in January 1942.

Comment. This case represents malignant hepatoma. Recurrence in the left hepatic lobe suggests that metastasis had occurred prior to the initial operation, though not then evident. The operative removal from the primary site was apparently adequate. Since a tumor was known to be present for 4 months prior to operation, it is interesting to speculate whether or not earlier operation might have been curative. The marked weight loss, the pallor, and the fever were certainly suggestive of cancer, and were present before surgical intervention.

Case 2. D. W. J., a 19-month-old male, entered the Children's Hospital on September 8, 1942, with abdominal enlargement of 2 months' duration. There had been no other symptoms. Weight gain had been normal. Except for the rounded abdomen which was so tense that palpation of any mass was precluded, the examination was negative. The ab-

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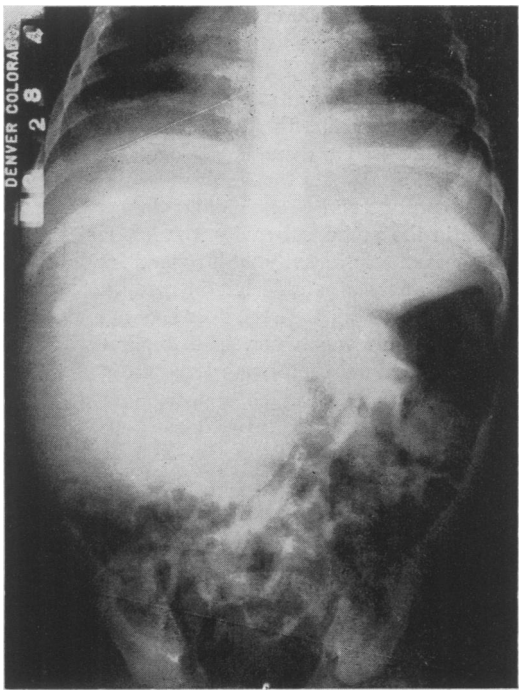

Fig. 1 (Case 1). Supine roentgenogram of the abdomen shows intestines crowded into the left flank and pelvis.

domen was dull to percussion throughout. Laboratory findings were not informative. The erythrocyte count was 4 million, the hemoglobin 78 per cent, and the leucocyte count 15,600.

Laparotomy 4 days after admission revealed a cystic tumor extending down from the right lobe of the liver and nearly filling the abdomen. It was shelled out, and the cavity was closed with deep catgut sutures. Recovery, a little stormy at first, was complete. Examination 2 years later revealed an apparently normal child.

In the pathologic report is described an ovoid mass measuring 20 x 15 x 14 cm. and weighing 1550 Gm. The cut surface presented a multicystic structure (Fig. 4). Although some of the loculi contained brownish watery fluid, the majority were filled with thick gelatinous material. Chemical tests for blood and for bile were negative. The fluid when hydrolyzed yielded a substance which reduced copper. These characteristics suggest the presence of a glycoprotein. The sections presented a varied structure, consisting primarily of proliferating tubules lined by cuboidal epithelium and surrounded by proliferating fibrous connective tissue. Where the tubules were greatly enlarged and cystic, the epithelium had become flattened and the resulting cyst contained mucin. In other places, the tubules

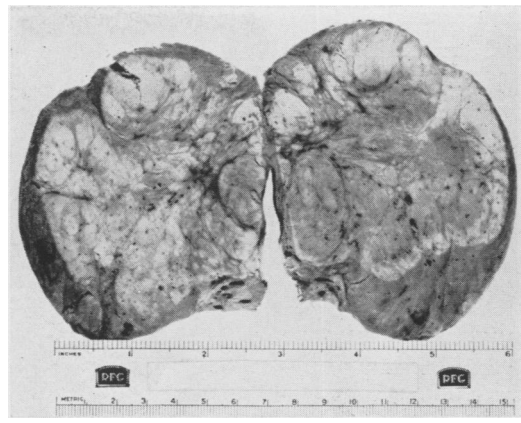

Fig. 2 (Case 1). Gross appearance of tumor.

were budding and forming new structures. The connective tissue about them was often embryonic in its characteristics. Small islands of liver cords separated by sinusoids were also present. There was no evidence of anaplasia (Figs. 5 and 6).

Diagnosis. Hamartoma of the liver.

Comment. This benign, congenitally dysplastic lesion was important because it endangered the baby's life from intra-abdominal pressure. This case illustrates that removal from the liver of a 1550 Gm. tumor can be safely accomplished in a 19-month-old baby.

Case 3. S. C., a girl aged 1 year, was admitted to the Denver Children's Hospital on June 23, 1943. The history was that of a mass in the right upper abdomen which had been increasing in size for 2 months. Pallor, fretfulness and vomiting on occasion had been noted. Except for pallor and a hard mass occupying most of the right abdomen, the examination was not remarkable. The erythrocyte count was 3.4 million; the hemoglobin, 55 per cent.

At operation on June 28, the right lobe of the liver was found to extend into the right iliac fossa; it was firm and hard and there were deep whitish areas located mostly over the dome. The left lobe was not involved, nor were metastases found elsewhere in the abdomen. Removal was not considered possible; a specimen was taken for biopsy.

Pathologic report is summarized as follows. The specimen was a small bit of grayish-white tissue. Sections showed cells closely resembling liver cells in a liver-like structure. The cells were growing in solid or tubular columns, in some places forming tubular spaces in which bile droplets were seen. The nuclei contained prominent nucleoli, some of

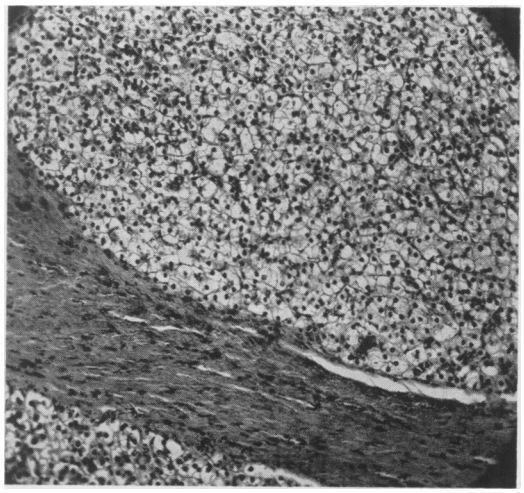

FIG. 3 (Case 1). Section of tumor showing a fibrous septum and solid masses of tumor cells with clear cytoplasm (x92).

which were greatly enlarged. Mitotic figures were seen in each low power field. It was considered that the histologic structure was that of a malignant tumor of the parenchymatous cells of the liver.

Diagnosis. Hepatoma (primary liver cell carcinoma).

When last seen in September, 1943, the patient was very pale and thin, and the abdominal wall was tight over the tumor. Death was reported in November of the same year.

Comment. The clinical features in this case, including the operative findings and postoperative course together with the histologic examination of the biopsied specimen, seem to limit the diagnosis to primary liver cell carcinoma. The pessimism expressed generally regarding treatment of this type of liver neoplasm is documented by this case.

Case 4. E. B., a girl aged 4 years, was admitted to Denver Children's Hospital on July 16, 1943. An abdominal mass had been discovered about 2 months earlier. Operation performed elsewhere one month before entrance had disclosed an enlarged left lobe of the liver. No attempt at removal had been made, but 60 ml. of bloody fluid was removed by needle aspiration. Examination revealed a poorly nourished and anemic child who had a prominent mass in the epigastrium. The erythrocyte count was 3 million; the hemoglobin, 55 per cent; the leucocyte count, 22,000. Roentgenograms showed a large soft tissue shadow which was apparently continuous with the left lobe of the liver. Exploration on August 2, 1943, revealed a huge mass involving the whole left lobe of the liver. Removal of the mass was attempted but was incomplete. The cavity was tightly packed with gauze in an effort to control bleeding, but death occurred 2 hours after operation, apparently the result of hemorrhage.

At postmortem examination there was free blood in the peritoneal cavity, the left lobe of the liver was mostly a cavity with ragged friable walls and with only a capsule left in many places. On microscopic examination the liver had normal architecture outside the tumor. The tumor tissue was very cellular, and there were large areas of necrosis. In the viable areas the tumor was made up of large polygonal cells arranged roughly in cords. The cytoplasm was acidophilic. The nuclei were oval, many were hyperchromatic, and mitotic figures were common. Giant cells were seen in all sections. The stroma was very delicate and consisted mostly of fine capillaries which ramified in a sinusoidal manner between the columns of tumor cells. Where the tumor was adherent to the stomach, sections showed actual invasion of the stomach wall. Lymph nodes were not involved, nor were there distant metastases.

Diagnosis. Primary liver cell carcinoma.

Comment. This is a late case of primary liver cell carcinoma. The tumor had been apparent for four months, during which time it had practically filled the left lobe, and even invaded the stomach wall and yet had not metastasized. The patient was in poor condition which even a child cancer patient reaches after blood loss and absorption of toxic material. A resection of the intact left lobe would seem by subsequent experience to have been the proper procedure, but the postmortem revelation of extension into the stomach wall makes it probable that this major operation would also have been unsuccessful.

Case 5. M. F., a girl baby of 7 months, was admitted to the Children's Hospital on September 19, 1949. Her history was not remarkable except that her mother had noticed a mass in the abdomen for 2 days. In addition the mother thought that the patient had been constipated for a month. Examination revealed a well developed and well nourished girl. The only positive finding was a large mass with an irregular surface, occupying the right upper and part of the left upper abdomen. It was not definitely separate from the liver. Neuroblastoma

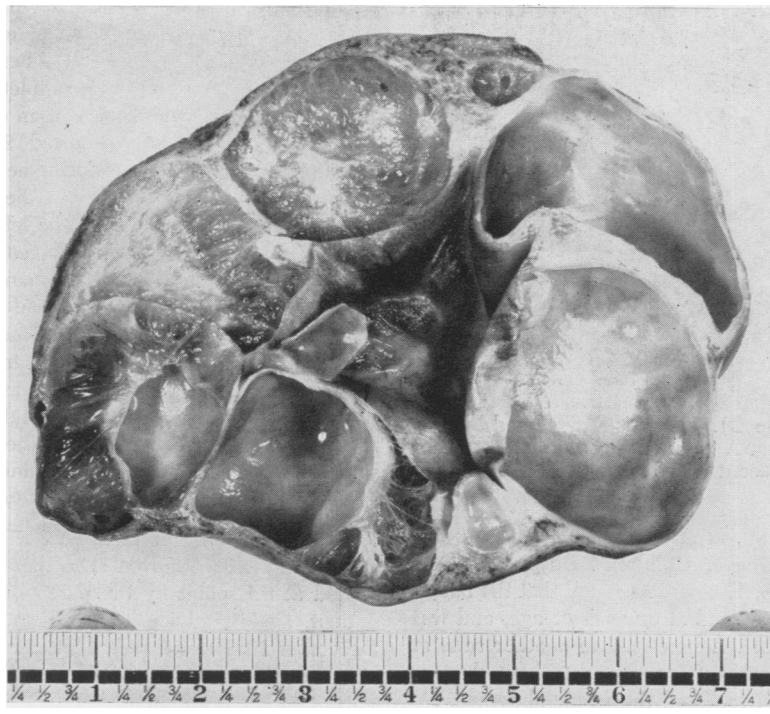

FIG. 4. (Case 2). Cut surface of gross specimen. The locules which contained watery fluid are empty; those above and to the left contain mucoid material. Scale is in inches.

was the tentative admission diagnosis, with Wilms' tumor and liver enlargement to be ruled out.

The erythrocyte count was 4.16 million; the hemoglobin, 10 Gm.; and the leucocyte count, 13,500.

Roentgenograms revealed a rounded mass, extending below the usual position of the margin of the liver in the anterior abdomen.

At operation a large, rounded, infiltrating tumor was found occupying part of the right lobe of the liver; no tumor tissue was found elsewhere in the abdomen; the left lobe was not involved. A wide wedge of the right lobe was removed well beyond visible tumor. The defect was closed with deep catgut sutures.

On the 14th day the patient was taking full feedings, had a normal temperature, and was dismissed from the hospital.

Pathologic report may be summarized as follows. The tumor mass weighed 258 Gm., had a thin capsule, and resembled liver. The cut surface presented a soft, yellow, lobulated pattern which was quite vascular throughout, and showed many necrotic and a few small cystic foci. The microscopic sections were made up of tissue which was predominantly neoplastic. There were some areas of normal liver cords fading into the neoplasm or separated from it by connective tissue septa. The tumor cells had scanty granular eosinophilic cytoplasm, and were generally larger than normal liver cells. They had vesicular or hyperchromatic nuclei; mitotic figures were numerous. The neoplastic cells were laid down in cords and pseudo-alveoli. A few giant tumors cells were seen (Fig. 7 A and B).

Diagnosis. Primary liver cell carcinoma (hepatoma).

In November 1949, the liver extended almost to the iliac crest, and there was a bulging hard mass in the abdominal wall. Roentgenogram of the chest indicated metastases. The patient died on the 25th of the same month. There was no autopsy.

Comment. This case illustrates again the bad prognosis of liver cell carcinoma. Local removal, even with a fair margin in this case, was obviously inadequate treatment and recurrence was prompt. While this patient gave the appearance of excellent health on first admission and the tumor had only just been discovered, it was very large and must have had extensions well into normal appearing liver.

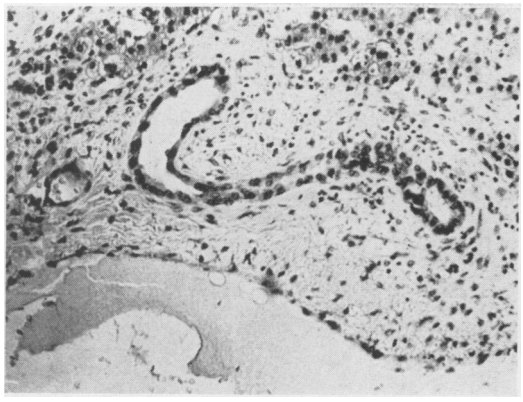

FIG. 5 (Case 2). Below is a cyst lined by flattened epithelium. A proliferating undilated duct is seen above adjacent to two small groups of liver cells.

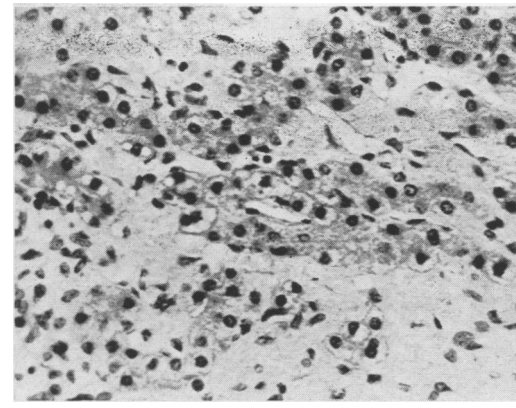

FIG. 6 (Case 2). Columns of vacuolated liver cells are seen in the central area separated by typical sinusoids and surrounded by cellular embryonic connective tissue.

Case 6. C. M., a girl aged 3 months, was admitted to the Denver Children's Hospital on November 29, 1949. The parents stated that the baby's abdomen was enlarged at 6 weeks of age, and was as hard as a table. Laparotomy in another state at the age of 2 months was reported to have demonstrated that the liver filled the whole abdomen. No specimen was taken.

Examination here revealed a markedly distended and very hard abdomen. A mass extended below the navel on the right, and three inches below the costal margin on the left.

Roentgenograms served only to confirm the physical findings; they demonstrated a soft tissue density filling the upper two-thirds of the abdomen; no metastases were seen in the skull or chest. The erythrocyte count was 3.4 million; the hemoglobin, 9.5 Gm.; the leucocyte count, 9,000.

Operative exploration revealed a very large liver which was diffusely studded with nodular masses. Those on the surface were whitish and of the same consistency as liver tissue. A small wedge including a nodule was removed.

Pathologic description of the sections is summarized as follows. Normal liver tissue faded into lobules, altered by wide bands of interlobular connective tissue and by foci of proliferating endothelial cells invading lobules and forming sinusoidal spaces. More centrally, the tissue was made up entirely of these proliferating endothelial cells, a few forming whorls but most forming capillaries, some of which contained blood. The stroma, as shown by Mallory's aniline blue stain, was a fine meshwork of connective tissue. Mitotic figures were occasionally seen. Invasion of liver tissue was evident at the periphery (Fig. 8).

Diagnosis. Angiosarcoma of the liver.

This patient received a course of roentgenotherapy to the liver area, consisting of 1700 r (measured in air) divided between three ports, 200 Kv HVL 0.9 mm. cu. The therapy was interrupted at this point by the parents, who took the patient, against advice, to her home in Texas on December 16, 1949. A recent letter from her physician some four and one-half years postoperative, states that she is apparently perfectly well. According to her physician her liver is not enlarged at this time. Dr. R. Parker Allen, roentgenologist at Denver Children's Hospital, who administered the therapy, states that this result may represent the same type of retrogression of blood vessel tumors that one sees in the angiomas of the dermis following subcarcinocidal dosage of roentgen-ray.

Comment. The presence at birth of malignant liver tumors has been reported on several occasions.[8, 16, 29] The large tumor found in this case at six weeks of age was probably congenital. It is an example of a primary neoplasm of the liver which does not arise from specific hepatic elements. Like the other primary tumors of this series it grew rapidly to large size. Angiomatous tumors, both benign and malignant, are rare in childhood. By contrast, benign hemangioma in adults is one of the commonest of liver tumors, and is not a precancerous process.

Case 7. R. S., a male aged 12 months, was referred to the Denver Children's Hospital on May 19, 1951. Nothing abnormal had been noted until 10 days before admission when his grandmother noticed his abdomen was unusually large. The baby weighed 18 pounds, 7 ounces (8.4 Kg.). General examination was negative except that the large abdomen was two-thirds filled with a firm but cystic-

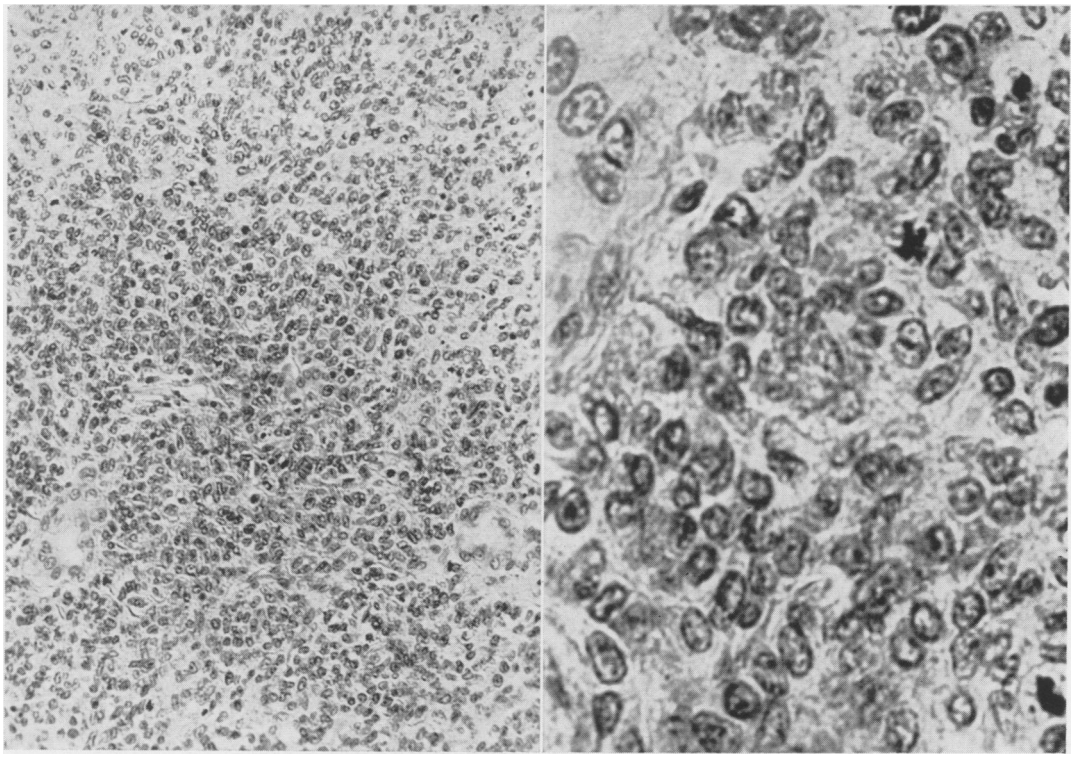

FIG. 7 (Case 5). (A) Photomicrograph x120. Solid cellular neoplasm showing considerable mitotic activity. (B) Photomicrograph x516. High power view giving the cellular characteristics of the neoplasm.

feeling tumor mass. By roentgenogram, all the intestine was in the left third of the abdomen; the pyelograms showed no distortion.

At operation a large, soft tumor was found arising from and involving the right lobe of the liver. It was possible to remove it with good margin, the defect being closed by mattress sutures over Gelfoam. The patient made a good recovery and left the hospital in 14 days.

Pathologic report is condensed as follows. The specimen was a mass of tissue weighing 1500 Gm. The surface was mostly mesothelial except for a 7 cm. width of liver tissue. The cut surface presented many cystic spaces measuring up to 10 cm. in diameter, with dense whitish walls. The tissue between the cysts had the color and gross appearance of liver tissue but was more indurated than the normal liver (Fig. 9). Sections demonstrated the tumor separated from the normal liver by a thin cleft composed of liver parenchyma lacking the normal architectural pattern. Instead, irregular masses of relatively normal appearing liver cells were arranged in cords, between which ran the sinusoids. However, the lobular pattern was entirely absent. Tubular structures of all sizes, some showing cystic dilatations, were scattered irregularly throughout, and resembled bile ducts in a general way. These duct-like spaces were lined with a simple cuboidal epithelium with normal appearing nuclei. They were surrounded by loose fibrous tissue similar to primitive mesenchyme. Central veins were absent, although venous channels were scattered irregularly throughout. Portal triads were missing. Small foci of leucocytes, predominantly lymphocytes, were present in the connective tissue. No evidence of malignancy was seen (Figs. 10, 11 and 12).

Diagnosis. Hamartoma of the liver.

Comment. Having successfully withstood surgical resection, this patient's prognosis is excellent. Hamartoma is a benign lesion. This case history, physical findings, and pathologic findings have a marked similarity to Case 2. The specimens weighed the same, and the description of the gross and microscopic features could be substituted one for the other. The case again emphasizes the

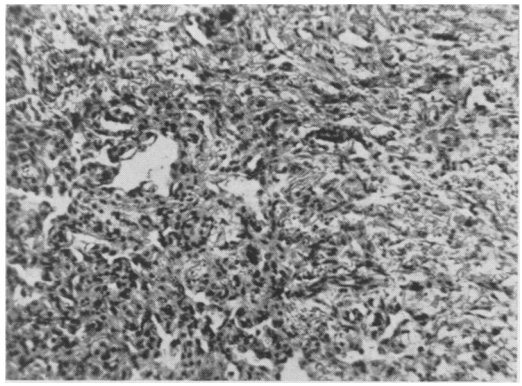

FIG. 8 (Case 6). Photomicrograph x84, revealing cellular vascular neoplasm.

necessity of exploration and resection of a liver mass in this age group.

Case 8. R. D., a boy aged 2 years, entered the Denver Children's Hospital October 8, 1952. He had been ill for 6 weeks, and just prior to this period he had received a possible but unobserved blow from a rolling automobile. Since the date of the suspected accident, his mother said, he wanted to lie down most of the time, would walk but had no energy, and would eat only sparingly. He had lost 8 pounds. For the 2 weeks prior to admission he had been particularly irritable, and a progressive abdominal enlargement had been observed.

Examination, otherwise unremarkable, revealed an enlarged protuberant abdomen, containing a mass which extended 10 cm. below the right costal margin, as well as across the midline to the left (Fig. 13). The erythrocyte count was 3.5 million; the hemoglobin, 9.5 Gm.; the leucocyte count, 7,800; and the sedimentation rate, 104 mm. in 60 minutes.

At operation on October 11 there was found adherent to the transverse colon and cecum a huge cystic mass in the right lobe of the liver, from which 1,000 ml. of bile-stained fluid was aspirated. After the roof of the cyst was removed, the appearance was that of a wide subcapsular defect extending up to the suspensory ligament. The defect was closed with layers of catgut. The child regained strength rather slowly, and went home 3 weeks later.

Pathologic examination revealed two strips of tissue which on section presented a cyst wall made up of dense collagenous fibrous tissue. There was no distinct lining membrane but rather the inner surface was sclerosing granulation tissue.

Diagnosis. Cyst of the liver following trauma.

Comment. This tumor is not a neoplasm, and should not be included under primary tumors, though the clinical findings were those of a mass in the liver. Exploration revealed its true identity to be a subcapsular rupture of the liver. The case does serve to point up a consideration in differential diagnosis of abdominal masses which are apparently of liver origin.

Case 9. R. G., a boy aged 2 years, admitted to Denver Children's Hospital February 2, 1953, had not seemed well for 3 weeks. Three days before entrance his mother noticed his abdomen was tight and hard. Examination of this 28-pound (12.5 Kg.) child showed an irregular, stony-hard mass filling the right abdomen and extending laterally into the flank and down to the iliac crest. The mass seemed to be continuous with the liver. The erythrocyte count was 3.2 million, the hemoglobin 9.5 Gm., and the leucocyte count 7,050.

Operation was performed by Dr. David Akers. When the peritoneum was opened bright blood welled from the abdominal cavity, issuing apparently from a 2 cm. rent in a greatly enlarged and tumor replaced right lobe of the liver. The bleeding was controlled with difficulty because the rent increased on manipulation. A biopsy specimen only could be removed. The operation was followed by radiation therapy.

The child was dismissed from the hospital on March 3. He was readmitted on June 11 and died on June 16.

At autopsy, there was found a neoplastic process of the liver with metastases to the lungs and to the brain. Tumor tissue occluded the inferior vena cava. The liver weighed 1510 Gm., the entire right lobe was replaced with very firm nodular tumor tissue, the left lobe was studded with numerous nodules of tumor. The multiple foci of neoplasm were composed chiefly of anastomosing cords of large polyhedral cells. Interspersed were more basophilic cells forming ducts, but no bile formation was seen. There was extension into the hepatic and portal veins. The lungs contained multiple metastatic nodules of the same microscopic picture, and tumor tissue was present in the arterial tree as emboli. The brain contained diffusely scattered hemorrhagic nodules of metastatic carcinoma similar in microscopic appearance to the primary liver tumor (Figs. 14 A and B).

Diagnosis. Primary hepatic carcinoma, mixed hepato-cellular-cholangitic type with extension into the portal, hepatic and inferior caval veins, metastatic to the lungs and brain.

Comment. Here again is found a primary liver cell carcinoma too advanced to permit

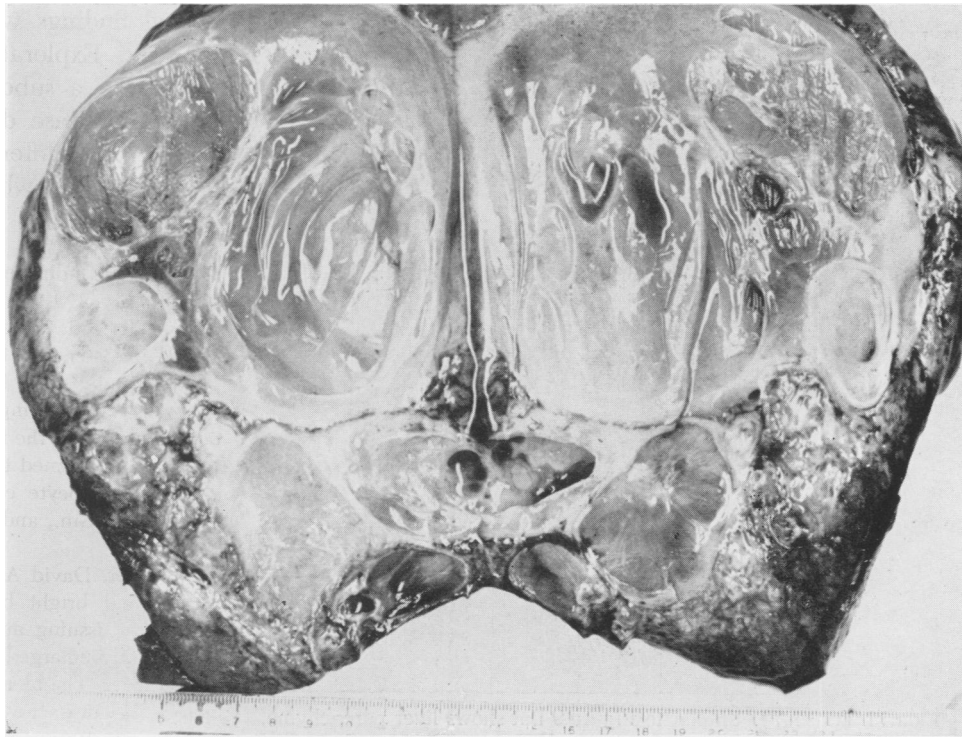

FIG. 9 (Case 7). Gross appearance of the cut surface of the specimen. Note the numerous cysts with contained viscid material.

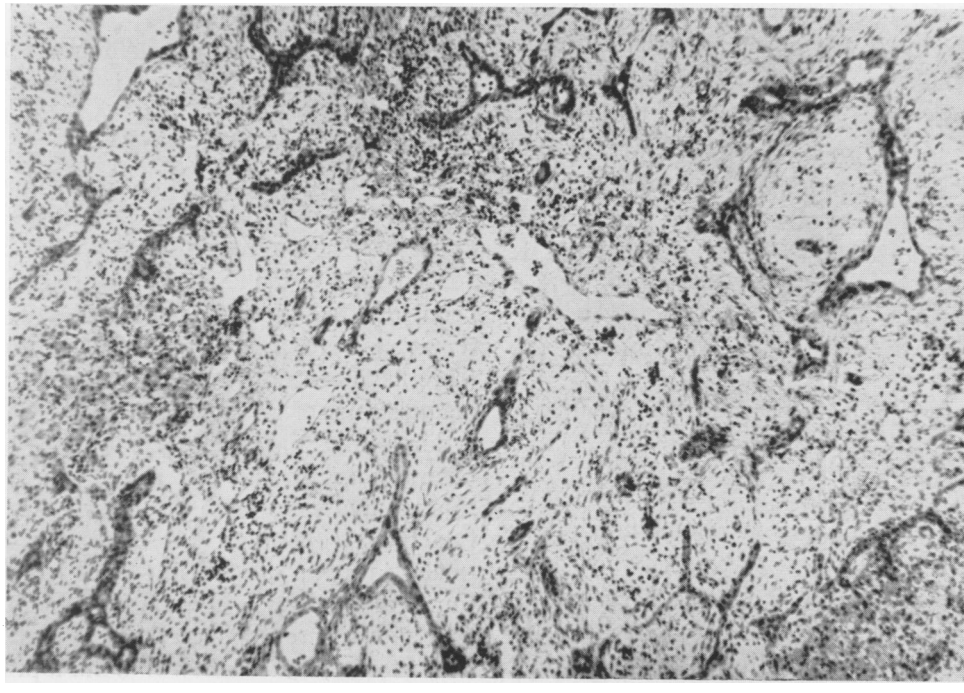

FIG. 10 (Case 7). Characteristic fields containing small cysts and proliferating mesenchyme.

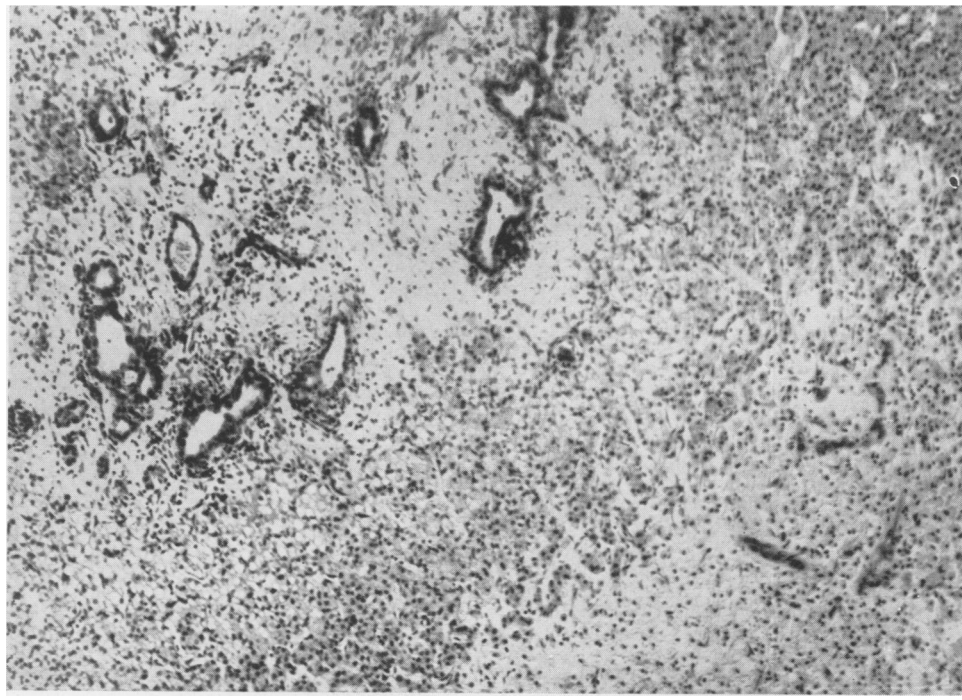

FIG. 11 (Case 7). Similar to Figure 9 but shows liver parenchyma.

possibility of removal. An additional event which has been reported elsewhere,[20, 23, 29] was spontaneous rupture of the liver when the abdomen was opened. In this case the rent tended to extend, and was most difficult to close. The replacement of nearly the whole right lobe of the liver by malignant neoplastic tissue emphasizes again the inoperability of many of these cases which reach an advanced stage before medical aid is sought. The case also illustrates the acuteness of many childhood neoplasms, the history of this child's illness dating back only three weeks, and the enlargement of the abdomen being noted by the mother only three days before admission. This two-year-old male child presents a rather classic example of malignant hepatoma in childhood. This tumor generally appears before two years of age, two-thirds of the cases occurring in males and without associated cirrhosis. In children the ratio of liver cell to bile duct type is 18:1. In this case there is an admixture of both. The extension into veins, with subsequent lung involvement is classic.

DISCUSSION

Primary liver neoplasm in children is obviously a rare tumor when it is considered that but nine cases have been found out of 126,000 admissions during 14 years at the Denver Children's Hospital. In order to cover briefly the nine primary liver tumors, histories have been necessarily greatly condensed, most of the laboratory findings have been omitted, practically no details of roentgenologic findings have been given, there has been no discussion of differential diagnosis nor of pre- and postoperative procedures, and the pathologic reports have been but briefly summarized. Of these nine tumors, five were liver cell carcinomas, all fatal though operative resection seemed adequate in two; one was a non-resectable tumor of blood-vessel type treated by radiation and apparently successfully; two were hamartomas; and one was a large cystic mass. The last three tumors were successfully

removed. This report gives a disappointing outlook for removal of malignant liver neoplasms though it may challenge the surgeon to attempt wider resection of these spreading tumors. At the same time it points to the necessity of exploration, since three of the patients with massive liver enlargements had benign lesions and are now well. A fourth case was successfully treated with roentgen ray, after biopsy.

Literature. It is not the purpose of this review to discuss the literature on primary liver neoplasm. Single case reports of primary malignant lesions and of the less frequent benign tumors are not uncommon. It is important to remember that benign neoplasms of liver cell or duct cell origin in children are almost non-existent, and that most of the reviewers deal with case material which is predominantly from the older age groups. Warvi,[27, 28] in two articles discussed in much detail the incidence and characteristics of both the malignant and benign types. Comprehensive reviews of primary carcinoma are those of Steiner,[25] Litman and Wells,[16] Rosenblatt and May,[24] Rosenberg and Ochsner,[23] and Bigelow and Wright.[5] Reports of the benign tumors, which are comparatively rare at any age, if small hemangiomas are omitted, include the designation of benign parenchymatous adenoma, benign adenoma of bile duct origin, benign mixed adenoma, solitary hyperplastic nodule and hamartoma.[3, 4, 6, 11, 13, 15, 17, 19, 22] It is of importance to note that different case reports show a considerable difference in the proportion of cell types and wide variance in structure at different areas in the tumor making single sections inadequate for exact classification.

Pathology. Any plan of management, including prognosis, must be based upon probabilities. Most of the classifications of liver neoplasms apply primarily to adult patients. In children such classification can be considerably simplified.

1. Hepato-carcinoma—primary liver cell neoplasms in children are almost always malignant. They may arise from the parenchyma cell or from the duct cell, or may be of combined liver cell-cholangitic origin. They occur characteristically without cirrhosis.

2. Malignant tumors primary in the liver but not arising from specific hepatic elements occur rarely. The angiosarcoma case in this series is an example.

3. Benign neoplasms in the liver in children are usually not of liver cell or duct cell origin. Benign hepatoma is not a childhood neoplasm. Hamartoma is the benign lesion which must be differentiated clinically from malignant lesions of the liver. The hamartoma probably represents an anomaly of development rather than a true neoplasm. The term, as originally used by Albrecht,[2] designates certain congenital tumors of a developmental nature which are made up of the tissue elements which normally comprise the organ but arranged in a disorganized and quantitatively disproportionate manner, so that they cause tumefaction. Hamartomas occur not only in the liver but are found with some frequency in the lungs, kidneys and intestinal tract. They vary greatly in size. Those in the kidneys and lungs are apt to be only a few millimeters in diameter, while those in the liver tend, as illustrated in the two cases in this series, to develop into enormous tumors. They are benign growths that cause symptoms only by pressure or disturbance of function. The characteristic features of the lesion, so far as the liver cases are concerned, are the embryonic nature of the tissue components, the inclusion of all liver elements arranged in a disorderly and disproportionate manner, and lack of all evidence of malignancy. To include these lesions with the adenomas or cystadenomas is wholly unjustified, since they are proliferations of several tissue elements and are probably not neoplastic. The term solitary hyperplastic nodule is neither descriptive nor accurate. The two cases of this series, because of a remarkable similarity of gross and microscopic structure, speak

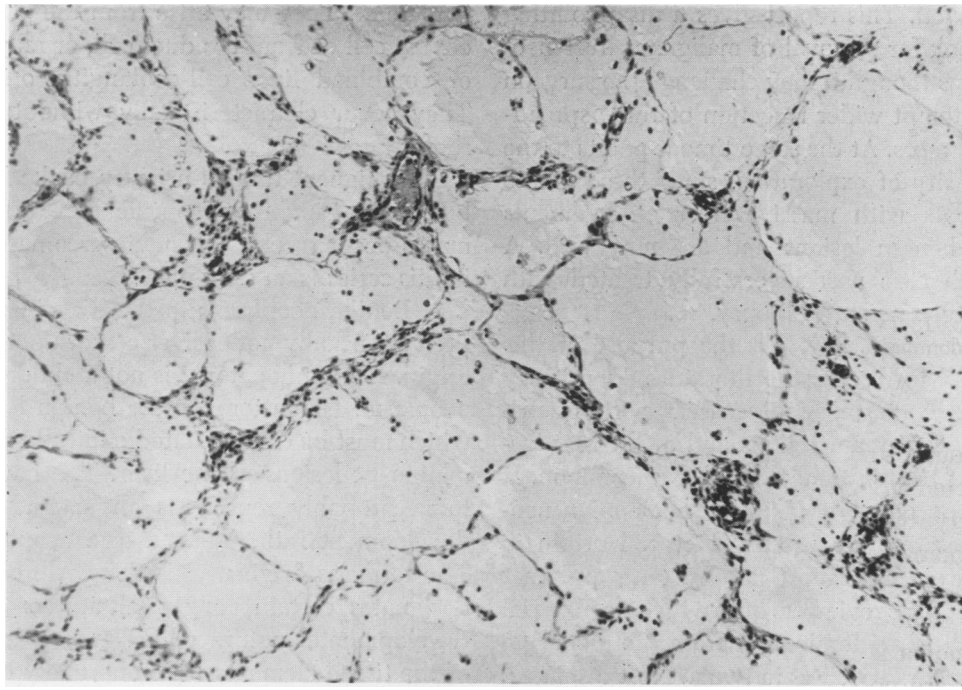

FIG. 12 (Case 7). Section from an area simulating lymphangiomatous structure.

for identity of origin and behavior—in other words, a clinicopathologic entity. Since differentiation from malignant lesions which appear to be encapsulated may not always be possible at time of operation, resection rather than biopsy should be attempted whenever possible.

Symptoms and Signs. There are no characteristic symptoms or signs indicating primary liver tumor preceding the discovery of a mass. In most cases, the tumor had expanded to a large size before it attracted attention. A short preliminary history of fussiness or poor appetite is often recalled but is not specific for this disease. In the benign cases, the mechanical effects of the mass may be responsible for many of the symptoms. In the malignant cases, anorexia, weight loss, and anemia occur as they do with malignant neoplasms elsewhere, jaundice and ascites appearing as terminal signs. Liver function is not disturbed until quite late. Earlier detection of liver tumors is hardly to be expected except on a careful well-baby examination. From the histories obtained, it would seem that tumor growth becomes rapid at some stage in its career. Some were apparently present at birth. Only one of our patients was over two years of age.

Diagnosis. Diagnosis is based primarily on the discovery of a tumor in the right upper abdomen which often extends into the right flank, and down to the iliac crest, or even across the midline. Differentiation from neuroblastoma and Wilms' tumor is based on continuity with liver dullness, its anterior position with displacement of the colon downward but not forward as shown on lateral roentgenogram, and by pyelogram. However, exploration, which is definitive, need not be delayed too long while other procedures are carried out, since it is indicated in all abdominal tumors of childhood without evidence of distant metastases.

Treatment. The treatment of primary liver tumors is surgical. Roentgeno-therapy of liver cell tumors is generally considered not only ineffectual but actually detrimental.[27]

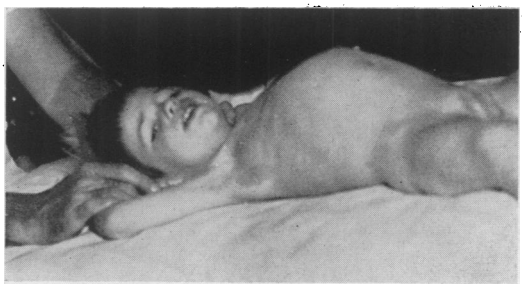

FIG. 13 (Case 8). Protuberance caused by intra-abdominal tumor.

Obviously 100 per cent mortality is to be expected in carcinoma of the liver without surgery. Since the average duration of liver carcinoma is four to six months from onset to death, it must be concluded that adequate, early removal may save some cases. If the carcinoma is multiple and not localized, if there are nodes, blood vessel or bile duct involvement at the hilum, if there is marked reduction in the liver function or if there are metastases, removal should not be attempted.

In the tumor of benign possibility, surgical therapy is perhaps even more positively indicated. It is often difficult to distinguish between benign and malignant neoplasm,[19] and biopsy may, at times, be inadequate in resolving this question. This leaves resection, when possible, the course of choice. Longmire[17] states that evidence supports the view that malignant hepatomas and malignant cholangiomas not infrequently have their origin in pre-existing adenomas, another argument for resection when possible of any liver tumor.

To consider in any detail at all the technic of liver resection is obviously impossible in this case review. The liver is a friable and vascular organ, and is often abnormally so when the site of a pathologic lesion. The fear of hemorrhage and the poor prognosis have deterred many surgeons from attempting what they considered a near futile procedure. A discussion of basic principles of liver tumor removal has been presented in a previous communication.[21] The literature has continued to contain single and multiple case reports of liver resection including, among many others, those of Hershey,[12] Duckett and Montgomery,[9] Patton,[22] and Rosenberg and Ochsner.[23] Warvi[27, 28] in 1945 attempted to collect all the reported cases of liver resection, found 223 fully reported and a probable additional 347 when those of limited description are included. Brunschwig[7] in 1953 reports a personal experience of 33 cases.

In brief, the use of exteriorization, of cautery and of packing has been largely discontinued in favor of the placement of a series of mattress sutures along the proposed line of division, with additional ties of main vessels. If ligatures do not entirely control the bleeding, a temporary gauze pack or a firm padding of Gelfoam may be used. Free drainage is of utmost importance. The entire left lobe has been removed several times[7, 9, 12] by transection just to the left of the falciform ligament, and successful removal of part or all of the right lobe has been reported and described.[3, 9, 24] Liver resection has become a standardized procedure, its success depending on proper exposure through a high abdominal or a thoraco-abdominal incision, on mobilization of the liver by division of supporting ligaments, and on a plan of control of hemorrhage by properly placed mattress sutures. Taking advantage of these principles, the surgeon should attempt excision of any solitary benign or primarily malignant hepatic neoplasm whenever possible, even when removal of a lobe is necessary.

Prognosis. Benign liver tumors, left alone, may grow to a size causing pressure on neighboring organs incompatible with life. Reports of successful removal are numerous. It would seem that the great majority are curable by surgery at some time during their growth. The benign tumors in this small series were removed without mortality.

Primary carcinoma of the liver, not too rare in infants and children and far more

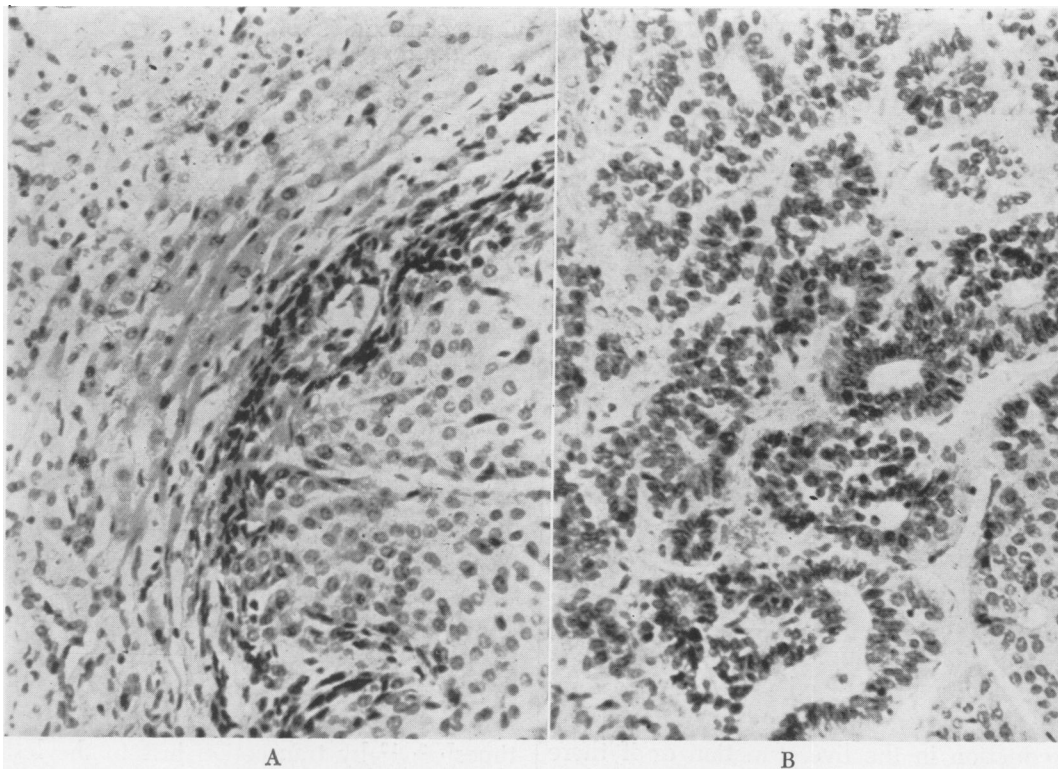

FIG. 14 (A) (Case 9). Photomicrograph x120. An area illustrating the hepatic cellular type of the lesion compressing normal liver. (B) (Case 9). Photomicrograph x516. An area illustrating the cholangitic cellular type.

common than the benign tumors, has a short course if untreated, the average duration of life from onset of symptoms being estimated as four to six months.[23] Our results in the primary carcinoma cases, like most others reported, have been most disappointing. This is true even in the minority of cases in which the tumor appeared to be resectable.[7, 10, 26] Some recent reviews[7, 10, 26] have been more encouraging, and include some apparent cures following operation, though in patients older than ours. If one considers that the mortality of primary liver carcinoma is 100 per cent without surgery, any salvage by better planned and more radical operation is a definite gain.

SUMMARY AND CONCLUSIONS

Nine cases of primary liver tumor in children are reviewed as to presenting signs, treatment and pathologic findings.

No case of primary liver cell carcinoma has survived over 22 months, although removal was considered adequate in two. All liver tumors should be considered primarily as surgical problems, and demand wide resection whenever this is possible. Three benign tumors of large size threatening life were successfully treated by surgery, and one malignant tumor of blood vessel origin apparently disappeared under roentgenotherapy. Thus, four of the nine patients are living and apparently well. These figures emphasize the fact that surgical removal of tumors of the liver in infants and young children is mandatory whenever possible and without regard to size of the tumor. When removal is not possible, biopsy is indicated in order that radio-sensitive neoplasms may be detected.

Limited biopsy may not give a true sample of the whole tumor structure. It must be

considered that some tumors may be removed in a premalignant stage, and it is even reasonable to suppose that some primary liver-cell carcinomas may be successfully removed, as has been reported in older patients.

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